NTP
National Toxicology Program
U.S. Department of Health and Human Services

NTP Technical Report on the Toxicology and Carcinogenesis Studies of Diisopropylcarbodiimide (CAS No. 693-13-0) in F344/N Rats and B6C3F$_1$ Mice (Dermal Studies)

NTP TR 523

FEBRUARY 2007

NTP TECHNICAL REPORT

ON THE

TOXICOLOGY AND CARCINOGENESIS

STUDIES OF

DIISOPROPYLCARBODIIMIDE

(CAS No. 693-13-0)

IN F344/N RATS AND B6C3F$_1$ MICE

(DERMAL STUDIES)

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

February 2007

NTP TR 523

NIH Publication No. 07-4473

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

FOREWORD

The National Toxicology Program (NTP) is an interagency program within the Public Health Service (PHS) of the Department of Health and Human Services (HHS) and is headquartered at the National Institute of Environmental Health Sciences of the National Institutes of Health (NIEHS/NIH). Three agencies contribute resources to the program: NIEHS/NIH, the National Institute for Occupational Safety and Health of the Centers for Disease Control and Prevention (NIOSH/CDC), and the National Center for Toxicological Research of the Food and Drug Administration (NCTR/FDA). Established in 1978, the NTP is charged with coordinating toxicological testing activities, strengthening the science base in toxicology, developing and validating improved testing methods, and providing information about potentially toxic substances to health regulatory and research agencies, scientific and medical communities, and the public.

The Technical Report series began in 1976 with carcinogenesis studies conducted by the National Cancer Institute. In 1981, this bioassay program was transferred to the NTP. The studies described in the Technical Report series are designed and conducted to characterize and evaluate the toxicologic potential, including carcinogenic activity, of selected substances in laboratory animals (usually two species, rats and mice). Substances selected for NTP toxicity and carcinogenicity studies are chosen primarily on the basis of human exposure, level of production, and chemical structure. The interpretive conclusions presented in NTP Technical Reports are based only on the results of these NTP studies. Extrapolation of these results to other species, including characterization of hazards and risks to humans, requires analyses beyond the intent of these reports. Selection *per se* is not an indicator of a substance's carcinogenic potential.

The NTP conducts its studies in compliance with its laboratory health and safety guidelines and FDA Good Laboratory Practice Regulations and must meet or exceed all applicable federal, state, and local health and safety regulations. Animal care and use are in accordance with the Public Health Service Policy on Humane Care and Use of Animals. Studies are subjected to retrospective quality assurance audits before being presented for public review.

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CONTENTS

SUMMARY

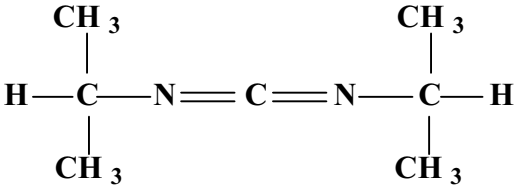
Background
Diisopropylcarbodiimide is used as a reagent in chemical reactions including peptide synthesis. We studied the effects of diisopropylcarbodiimide on male and female rats and mice to identify potential toxic or carcinogenic hazards to humans.

Methods
We applied solutions containing diisopropylcarbodiimide in ethanol to the backs of the animals five times per week for 2 years. Groups of 50 male and female rats and mice received 10, 20, or 40 milligrams of diisopropylcarbodiimide per kilogram of body weight. Similar groups of animals receiving just the ethanol solution served as controls. Tissues from more than 40 sites were examined for every animal.

Results
Survival by animals administered diisopropylcarbodiimide was the same as for the controls, but rats that received the highest concentrations weighed less than the controls. Male and female rats administered diisopropylcarbodiimide had increased rates of skin hyperplasia and lung inflammation, hyperplasia, or hemorrhage. Male rats had increased rates of brain hemorrhage.

Conclusions
We conclude that diisopropylcarbodiimide was not associated with any increase in cancer in male or female rats or mice. Lung and skin lesions occurred in male and female rats exposed to diisopropylcarbodiimide and male rats had increased rates of brain hemorrhage.

ABSTRACT



Diisopropylcarbodiimide

CAS No. 693-13-0

Chemical Formula: $C_7H_{14}N_2$ Molecular Weight: 126.20

Synonyms: 1,3-Diisopropylcarodiimide; *N,N′*-diisopropylcarbodiimide; *N,N′*-methanetetraylbis (2-propanamine)

Diisopropylcarbodiimide is used as a reagent for peptide syntheses and as a chemical intermediate. The National Cancer Institute nominated diisopropylcarbodiimide for study as a representative chemical in the alkylcarbodiimide class because of its acute toxicity; its use in chemical, pharmaceutical, and recombinant DNA industries; and the absence of data on potential health effects. Male and female F344/N rats and B6C3F$_1$ mice were administered diisopropylcarbodiimide (greater than 99% pure) dermally for 2 weeks, 3 months, or 2 years. Genetic toxicology studies were conducted in *Salmonella typhimurium,* rat and mouse bone marrow cells, and mouse peripheral blood erythrocytes.

2-Week Study in Rats

Groups of five male and five female F344/N rats were dermally administered 0.3 mL ethanol containing 0, 3, 9, 27, or 81 mg diisopropylcarbodiimide or 0.3 mL of the neat chemical containing 242 mg per animal, 5 days a week for 2 weeks. All rats in the 27, 81, and 242 mg groups died before the end of the study. Of the surviving groups, final body weights were similar to those of the vehicle controls. Clinical findings included convulsions/seizures, nasal/eye discharge, tremors, and comatose conditions in 81 and 242 mg rats and lethargy, ataxia, and abnormal breathing in 27 mg rats. The incidences of epidermal hyperplasia at the site of application in 9 and 27 mg males and 27 mg females were significantly greater than those in the vehicle controls; the incidences of hyperkeratosis in 3 and 9 mg males and 9 mg females were also significantly increased.

2-Week Study in Mice

Groups of five male and five female B6C3F$_1$ mice were dermally administered 0.1 mL ethanol containing 0, 1, 3, 9, or 27 mg diisopropylcarbodiimide or 0.1 mL of the neat chemical containing 81 mg per animal, 5 days a week for 2 weeks. All 9, 27, and 81 mg mice died before the end of the study. Final body weights of the surviving groups were similar to those of the vehicle controls. Clinical findings in 9, 27, and 81 mg mice included comatose conditions, convulsions/seizures, tremors, abnormal breathing, nasal/eye discharge, lethargy, and irritation at the site of application. Incidences of chronic active inflammation at the site of application in 9 mg

males and females were significantly greater than those in the vehicle control groups.

3-Month Study in Rats

Groups of 10 male and 10 female core study F344/N rats were dermally administered 0, 10, 20, 40, 80, or 160 mg diisopropylcarbodiimide/kg body weight in ethanol, 5 days per week for 3 months. Groups of 10 male and 10 female clinical pathology rats were administered the same doses for 22 days. All 160 mg/kg core study rats were sacrificed moribund or died within the first week of the study. All 80 mg/kg rats died or were found moribund by day 59. Significant decreases in body weight gain occurred in 40 mg/kg males and females, and a significant decrease in final mean body weight occurred in 40 mg/kg females. Clinical findings in groups administered 40 mg/kg or more generally included irritation of the skin at the site of application, seizures, ataxia, abnormal breathing, ruffled fur, thinness, and lethargy. Significantly increased incidences of skin lesions at the site of application included epidermal hyperplasia in all dosed groups of males (except 160 mg/kg) and 40 mg/kg or greater females, epidermal necrosis in 160 mg/kg males and females, and chronic active inflammation in 80 and 160 mg/kg males and females. Significantly increased incidences of nonneoplastic lesions occurred in the brain, lung, and liver (males only) of rats administered 80 or 160 mg/kg.

3-Month Study in Mice

Groups of 10 male and 10 female B6C3F$_1$ mice were dermally administered 0, 17.5, 35, 70, 140, or 280 mg/kg diisopropylcarbodiimide in ethanol, 5 days per week for 3 months. All mice in the 280 mg/kg group and nine males and nine females in the 140 mg/kg group died before the end of the study. The final mean body weight gain of 70 mg/kg males was significantly less than that of the vehicle control group. Clinical findings observed in 140 and 280 mg/kg mice included abnormal breathing, ataxia, comatose conditions, convulsions/seizures, irritation at the site of application, lethargy, ruffled fur, and thinness. Significant increases in kidney weights occurred in 17.5 and 35 mg/kg males. Significant decreases in total spermatid heads per testis and average spermatid count occurred in 17.5 mg/kg males. At the site of application, the incidences of epidermal hyperplasia in males and females administered 70 mg/kg or greater, chronic inflammation in 140 and 280 mg/kg males and 70 mg/kg or greater females, and sebaceous gland hyperplasia in 140 mg/kg males were significantly increased. Thymic atrophy was significantly increased in 140 and 280 mg/kg males and females.

2-Year Study in Rats

Groups of 50 male and 50 female F344/N rats were dermally administered 0, 10, 20, or 40 mg/kg diisopropylcarbodiimide in anhydrous ethanol 5 days per week for 2 years. Survival of 20 mg/kg males was significantly greater than that of the vehicle controls; survival of all dosed groups of females was similar to that of the vehicle controls. Body weights of 40 mg/kg rats were generally less than those of the vehicle controls after week 13. Clinical findings frequently observed in 40 mg/kg males included ataxia, excitability, impaired gait, low muscle tone, abnormal breathing, lethargy, vocalization, and seizures.

Because of severe neurological signs exhibited by the 40 mg/kg males, a neuropathological review of these animals was performed. The principal pathological findings of the brain included neuronal necrosis, hemorrhage, and/or fibrinoid arteriole necrosis.

Incidences of hemorrhage in the lung of 40 mg/kg males, chronic lung inflammation in 10 and 20 mg/kg females, and alveolar epithelium hyperplasia in 20 mg/kg females were significantly greater than those of the vehicle controls. At the site of application, the incidences of epidermal hyperplasia in all dosed groups of males and 20 and 40 mg/kg females and chronic inflammation in all dosed groups of males and 40 mg/kg females were significantly increased. There were no increased incidences of neoplasms related to diisopropylcarbodiimide administration.

2-Year Study in Mice

Groups of 50 male and 50 female B6C3F$_1$ mice were dermally administered 0, 10, 20, or 40 mg/kg diisopropylcarbodiimide in anhydrous ethanol, 5 days per week for 2 years. Survival of all dosed groups was similar to that of the vehicle control groups. Mean body weights of dosed groups of mice were generally similar to those of the vehicle control groups throughout the study. There were no increased incidences of neoplasms that were attributed to the administration of diisopropylcarbodiimide. Significantly increased incidences of epidermal hyperplasia and focal dermal inflammation of the

skin at the site of application occurred in 20 mg/kg male mice.

Genetic Toxicology

Diisopropylcarbodiimide was not mutagenic in *Salmonella typhimurium* strains TA97, TA98, TA100, or TA1535 with or without liver S9 activation enzymes. *In vivo*, the frequency of micronucleated normochromatic erythrocytes was significantly increased in male and female mice after 3 months of dermal exposure to diisopropylcarbodiimide. In addition, significantly elevated frequencies of micronucleated polychromatic erythrocytes (reticulocytes) and micronucleated normochromatic erythrocytes were seen in male mice during a 4-month dermal exposure to diisopropylcarbodiimide. Negative results were obtained, however, in an acute three-injection rat bone marrow micronucleus study. A three-treatment acute micronucleus test in male mice also showed no increase in micronucleated erythrocytes, but results of a single injection micronucleus test in male mice were concluded to be equivocal, due to an increase in micronucleated erythrocytes seen in peripheral blood but not in bone marrow preparations.

Conclusions

Under the conditions of these 2-year dermal studies, there was *no evidence of carcinogenic activity** of diisopropylcarbodiimide in male or female F344/N rats or $B6C3F_1$ mice administered 10, 20, or 40 mg/kg.

Clinical and histological signs of neurotoxicity in male rats were associated with diisopropylcarbodiimide administration.

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

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

	Male F344/N Rats	Female F344/N Rats	Male $B6C3F_1$ Mice	Female $B6C3F_1$ Mice
Concentrations in anhydrous ethanol	Vehicle control, 10, 20, or 40 mg/kg	Vehicle control, 10, 20, or 40 mg/kg	Vehicle control, 10, 20, or 40 mg/kg	Vehicle control, 10, 20, or 40 mg/kg
Body weights	40 mg/kg group less than vehicle control group	40 mg/kg group less than vehicle control group	Dosed groups similar to vehicle control group	Dosed groups similar to vehicle control group
Survival rates	20/50, 30/50, 32/50, 17/50	30/50, 32/50, 32/50, 25/49	39/50, 40/50, 38/50, 36/50	33/50, 33/50, 39/50, 40/50
Nonneoplastic effects	Brain: hemorrhage (1/50, 0/50, 3/50, 11/50); neuronal necrosis (0/50, 1/50, 0/50, 16/50); fibrinoid arteriole necrosis (0/50, 0/50, 0/50, 5/50) Lung: hemorrhage (6/50, 6/50, 7/50, 17/50) Skin: site of application, epidermis, hyperplasia (1/49, 10/50, 29/50, 19/50); site of application, inflammation chronic (0/49, 6/50, 12/50, 11/50)	Lung: inflammation chronic (10/50, 22/50, 19/50, 10/49; alveolar epithelium, hyperplasia (3/50, 4/50, 10/50, 1/49) Skin: site of application, epidermis, hyperplasia (1/50, 5/50, 16/50, 21/49); site of application, inflammation chronic (0/50, 0/50, 3/50, 10/49)	Skin: site of application, epidermis, hyperplasia (2/50, 3/50, 10/50, 1/50); site of application, dermis, inflammation, focal (2/50, 2/50, 9/50, 1/50)	
Neoplastic effects	None	None	None	None
Level of evidence of carcinogenic activity	No evidence	No evidence	No evidence	No evidence

Genetic toxicology

Salmonella typhimurium gene mutations:	Negative in strains TA97, TA98, TA100, and TA1535 with and without S9
Micronucleated erythrocytes	
Rat bone marrow *in vivo* (3 × IP):	Negative
Mouse bone marrow *in vivo* (3 × IP):	Negative
Mouse bone marrow/blood *in vivo* (1 × IP):	Equivocal
Mouse peripheral blood *in vivo* (3 months dermal exposure):	Positive
Mouse peripheral blood *in vivo* (4 months dermal exposure):	Positive

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 diisopropylcarbodiimide on September 28, 2005, 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 28, 2005, the draft Technical Report on the toxicology and carcinogenesis studies of diisopropylcarbodiimide 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. R.S. Chhabra, NIEHS, introduced the toxicology and carcinogenicity studies of diisopropylcarbodiimide by describing the nomination and rationale for the study of carbodiimides and the design and results of the 2-year dermal studies. The proposed conclusions were *no evidence of carcinogenic activity* of diisopropylcarbodiimide in male or female F344/N rats or male or female B6C3F$_1$ mice. Diisopropylcarbodiimide was associated with clinical signs of neurotoxicity and with brain hemmorrhage in male rats.

Dr. Roberts, the first principal reviewer, had no scientific criticisms of the study conduct and expressed his appreciation for the inclusion of toxicokinetic data. He did not feel the occasional background seizures affected the interpretation of neurotoxicity. He wondered if inhalation might have been another route of exposure given the low dermal absorption rate. He also inquired if alveolar/bronchiolar carcinomas in female mice were discounted as an effect because of comparison with historical values.

Dr. Sikka, the second principal reviewer, had no scientific criticisms and agreed with the proposed conclusions. He noted that although the chemical was negative for carcinogenicity in rats and mice, it did yield a positive response in the mouse micronucleus test.

Dr. Elwell, the third principal reviewer, inquired if a statement that animals could have tolerated higher doses was warranted.

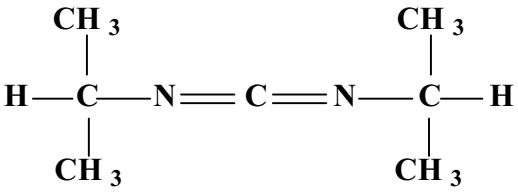
Dr. Chhabra explained that dermal exposure was chosen as the route of exposure in part because of reports of accidental human exposure that resulted in dermatitis. He also explained that the alveolar/bronchiolar carcinomas were discounted because there was no significant effect when adenomas and carcinomas were combined. Dr. Chhabra also defended the dose selection, noting that the high dose of 40 mg/kg was not far from the dose (70 mg/kg) that produced chronic necrosis and inflammation in the 3-month studies.

Dr. Crump noted that the historical control range for alveolar/bronchiolar carcinomas in female mice was somewhat misleading, with one study having six neoplasms being an outlier and 28 other studies having incidences less than half that and below the incidence in this study.

A revision making the second paragraph of the conclusions more general was presented. The new statement was: "Clinical and histological signs of neurotoxicity in male rats were associated with diisopropylcarbodiimide administration."

Dr. Roberts moved that the conclusions be revised as presented, and Dr. Elwell seconded the motion. The motion was accepted unanimously with five votes.

INTRODUCTION



Diisopropylcarbodiimide

CAS No. 693-13-0

Chemical Formula: $C_7H_{14}N_2$ Molecular Weight: 126.20

Synonyms: 1,3-Diisopropylcarodiimide; *N,N′*-diisopropylcarbodiimide; *N,N′*-methanetetraylbis (2-propanamine)

Chemical and Physical Properties

Diisopropylcarbodiimide is a colorless liquid, with a boiling point of 145° to 148° C, a flash point of 33° C (closed cup), a refractive index of 1.433, and a density of 0.806 g/mL (*Aldrich*, 1988). It is flammable; soluble in chloroform, methylene chloride, acetonitrile, dioxane, dimethylformamide, and tetrahydrofuran; and reacts with water to form 1,3-diisopropylurea. Diisopropylcarbodiimide is a member of the carbodiimide class of chemicals. Diisopropylcarbodiimide is available in purities ranging from 97% to 99% in quantities up to 1,000 kg. The main impurities are unreacted isocyanates and polymerized carbodiimides (*Janssen Chimica*, 1990; Kuney, 1990).

Production, Use, and Human Exposure

Diisopropylcarbodiimide is manufactured primarily by four processes. In the first process, diisopropylcarbodiimide is produced by extended or excessive heating of isopropyl isocyanate from 100° to 250° C under anhydrous conditions to condense the carbodiimide with elimination of carbon dioxide. A number of catalysts are effective in accelerating this reaction to the extent of making it a practical synthesis for this symmetrical carbodiimide. The phospholine oxides are particularly effective catalysts, although simple trialkylphosphine oxides or even triethyl phosphate may be used (Chadwick and Cleveland, 1979). Other organometallic catalysts, including tetraisopropyltitanate and tetraisopropylzirconate, are also used to produce diisopropylcarbodiimide (Budnick, 1968; Smeltz, 1969).

In a second process, *N,N′*-diisopropylthiourea is reacted with cyanuric chloride in dichloromethane to yield an oily product, which, when hydrolyzed with sodium hydroxide and heated, yields diisopropylcarbodiimide and trithiocyanuric acid (Furumoto, 1971a). Thirdly, diisopropylcarbodiimide can be obtained by treating *N,N′*-diisopropylthiourea in dichloromethane with dichlorodicyanobenzoquinone; the resultant mixture is evaporated and heated in sodium hydroxide to yield diisopropylcarbodiimide (Furumoto, 1971b).

In a fourth process patented by Celanese Corporation in 1967, a reaction mass consisting of diisopropylthiourea, lead oxide, and water is heated to refluxing temperature, the mixture is distilled, and diisopropylcarbodiimide is separated by decantation (White and Mullin, 1967).

Although carbodiimides were discovered in 1873, it was not until the early 1950s that they were used in industry. Reactivity of these compounds with free carboxyl groups made them valuable as stabilizing agents in elastomers, natural rubber, and many types of polyolefins, polyesters, resins, fibers, cellulose esters, and foam materials to protect against deterioration. In 1953, it was discovered that carbodiimides are potent condensing agents for mono- and diesters of phosphoric acid and for the corresponding di- and tetraesters of pyrophosphoric acid. Since then, these chemicals have been widely used in the synthesis of *ortho*- and pyrophosphate esters, nucleotides, cyclic phosphates, oligoribonucleotides, polynucleotides, nucleoside-5′-phosphoroamidates, and mixed anhydrides (Azzi *et al*., 1984).

Diisopropylcarbodiimide is a key chemical in the carbodiimide class. It is a useful reagent for peptide syntheses, especially solid-phase peptide synthesis. For example, diisopropylcarbodiimide is used as a peptide coupling reagent in the synthesis of protected peptide proteins of scorpion neurotoxin II, the *N*-hydroxysuccinamide active ester of diethylenetriaminepentaacetic acid (DTPA) (which is subsequently used in a process for conjugating DTPA to proteins), *N*-acyl ureas, and 2-alkoxyoxazolones from alkoxycarbonylamino acids, and as a condensing reagent in dipeptide synthesis (Bates *et al*., 1981; Orlowska *et al*., 1983; Izdebski and Pelka, 1984; Kricheldorf *et al*., 1985; Paxton *et al*., 1985; Sabatier *et al*., 1987). In addition, diisopropylcarbodiimide is used as a chemical intermediate in the synthesis of *N*-silylformamides (Ojima *et al*., 1974) and in the preparation of polyimide precursor coatings for electrophoretic image display fabrication (Minnema and Van der Zande, 1988).

There are numerous other proposed uses for diisopropylcarbodiimide. It has been reported that insoluble resin-bound diisopropylcarbodiimide, in the presence of 1-hydroxybenzotriazole, catalyzed the synthesis of the cyclic peptide gramicidin S (Nutt, 1978). Also, alpha, beta-dehydroamino acid derivatives can be made from serine, threonine, or cysteine using diisopropylcarbodiimide (Miller, 1980). Diisopropylcarbodiimide has been used as a stabilization reagent for a solution of *S*-(diisopropylaminoethyl)-*O*-ethyl methylphosphonothioate (Buckles and Lewis, 1977). In organic synthesis, diisopropylcarbodiimide has been used in cycloaddition reactions to form a number of heterocyclic compounds (*Aldrich*, 1988). Like most carbodiimides, diisopropylcarbodiimide has also been used in dehydration reactions for conjugated alkadienoic acid and anhydride preparations. In the presence of (dimethylamino)pyridinium toluenesulfonate as a catalyst, diisopropylcarbodiimide has been used to prepare polyester from hydroxyphenyl-terminated carboxylic acids (Moore and Stupp, 1990). Diisopropylcarbodiimide is used as a stabilizer for the military nerve agent, sarin (Nasr *et al*., 1988).

Potential human exposure to diisopropylcarbodiimide is based on its use as a stabilizer in sarin and the extensive handling of the compound that occurs during the synthesis of peptides and other compounds in the chemical, pharmaceutical, and recombinant DNA industries.

Absorption, Distribution, Metabolism, and Excretion

No studies on the absorption, distribution, metabolism, or excretion of diisopropylcarbodiimide in experimental animals or humans were found in a review of the published literature.

NTP conducted absorption and distribution studies via the dermal route in rats and mice (Appendix L). Data indicated that only a small percentage of the radiolabeled dose was absorbed (approximately 1% to 2%) due to the high volatility of diisopropylcarbodiimide. The majority of the dose was recovered in the charcoal-impregnated appliances used to cover the site of application. Approximately 90.7% of the dose was unabsorbed and 90.5% was contained in the appliance and skin wash. Less than 0.2% of the administered dose was recovered from any tissue site. The majority of the dose rapidly volatilized from the dose site and was not available for absorption.

Toxicity

Experimental Animals

The oral LD_{50} for diisopropylcarbodiimide in mice is 36 mg/kg (RTECS, 1991a). While the chemistry of diisopropylcarbodiimide and dicyclohexylcarbodiimide are virtually identical, interactions with biomolecules differ. Two cases in point involve ATPase. The Ca^{2+}-ATPase of sarcoplasmic reticulum vesicles is readily inactivated by diisopropylcarbodiimide (Murphy, 1981). Although the related chemical, dicyclohexylcarbodiimide, readily inactivates *Escherichia coli* BF1-ATPase at 0.05 mM, diisopropylcarbodiimide shows almost no inactivation at this concentration (Satre *et al*., 1979).

Humans

Delayed, temporary blindness has been reported in a worker following an acute occupational exposure to diisopropylcarbodiimide vapor (Moyer, 1990). The worker had cleaned up a 1 L spill of diisopropylcarbodiimide while wearing a respirator, laboratory coat, and impervious gloves. Approximately 12 to 18 hours later, the worker experienced hazy vision followed by mild pain that maximized 34 hours after the exposure. Damage to the outer layer of the cornea resulted in blindness that subsided over a 2-week period. Ellis (1991) noted that this injury resembled mild to moderate mustard gas injury, for which the postulated mechanism of action is alkylation of nucleophilic functional groups of intracellular components, occurring within minutes of exposure and leading to cellular dysfunction and even cell death. This author noted that it is reasonable to assume that all alkylcarbodiimides are capable of functioning as alkylating agents and are therefore potential vesicants and carcinogens.

A number of case reports have shown that dicyclohexylcarbodiimide, a chemical with a similar structure, is a contact irritant and causes dermatitis in humans (Zschunke and Folesky, 1975; Simpson, 1979; Davies, 1983; Hoffman and Adams, 1989).

Reproductive and Developmental Toxicity

Experimental Animals

No information on the reproductive or developmental toxicity of diisopropylcarbodiimide in animals was found in the literature, but a single oral reproductive study in rats of the related chemical carbodiimide has been reported (RTECS, 1991b). In this study, a dose of 2,450 mg carbodiimide/kg caused preimplantation mortality, 1,750 mg/kg caused paternal effects (testes, epididymis, sperm duct, prostate, seminal vesicle, Cowper's gland, and accessory glands), 208 mg/kg affected postimplantation mortality and the live birth index. In the same study, 2,600 mg/kg affected newborn rats (live birth index, growth statistics, and delayed effects).

Humans

No information on the reproductive or developmental toxicity of diisopropylcarbodiimide in humans was found in the literature.

Carcinogenicity

No data on the carcinogenicity of diisopropylcarbodiimide in animals or epidemiology studies or case reports associating diisopropylcarbodiimide exposure with cancer risk in humans were found in the literature.

Genetic Toxicity

Witt *et al.* (1999) described the results of a series of *in vivo* mutagenicity tests with diisopropylcarbodiimide. The chemical was shown to induce micronuclei in erythrocytes of male and female mice treated by skin painting for a period of 3 months. An additional subchronic micronucleus investigation was performed with diisopropylcarbodiimide in male mice, in which the chemical was administered by skin painting for 4 months and weekly or biweekly counts of micronucleated erythrocytes, as well as percent polychromatic erythrocytes (PCEs), were obtained. Results of this study confirmed the activity of diisopropylcarbodiimide that was observed in the 3-month skin painting study. However, short-term tests using a three-injection protocol with diisopropylcarbodiimide in rats and in mice showed no evidence of micronucleus induction in bone marrow PCEs. Results of a single-injection mouse micronucleus test with diisopropylcarbodiimide gave results that were concluded to be equivocal; frequencies of micronucleated PCEs were significantly increased in peripheral blood samples obtained 48 hours after injection, but in bone marrow, the frequency of micronucleated PCEs, although elevated at 24 and 48 hours in two of three trials, did not differ significantly from the control levels. The authors suggested that one interpretation of these results might be that diisopropylcarbodiimide induces chromosomal damage in erythrocytes soon after treatment, and that, due to the kinetics of erythrocyte maturation, this damage is detectable as micronucleated cells in blood but not bone marrow at the standard time points assayed for micronucleus induction. Alternatively, the spleen might be a target organ for diisopropylcarbodiimide, and damage to splenic cells might result in increased frequencies of micronucleated erythrocytes in the circulating erythrocyte population compared to the population of erythrocytes residing in the bone marrow.

Study Rationale

Diisopropylcarbodiimide and dicyclohexylcarbodiimide were nominated by the National Cancer Institute as representatives of the carbodiimide chemical class. The

results of the dicyclohexylcarbodiimide studies will be reported separately.

Diisopropylcarbodiimide has been used in industry as a stabilizing, coupling, and condensing agent. The potential for human exposure exists during the synthesis of polypeptides and other chemicals in the chemical and pharmaceutical industries and during protein synthesis in the recombinant DNA industry. Evidence on which to evaluate the potential for human carcinogenicity is lacking. No epidemiological studies or case reports associating diisopropylcarbodiimide with a cancer risk in humans have been reported. No information was found on the carcinogenicity in experimental animals, genotoxicity, teratogenicity, or metabolism of diisopropylcarbodiimide.

In the current studies, a dermal route of exposure was chosen to mimic the human exposure conditions based on the case reports. In addition to these studies, the NTP has also studied diisopropylcarbodiimide in Tg.AC hemizygous and p53 haploinsufficient genetically modified mouse models (NTP, 2007a).

MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION

Diisopropylcarbodiimide

Diisopropylcarbodiimide was obtained from Aldrich Chemical Company (Milwaukee, WI) in three lots. Lot 01207BG was used during the 2-week and 3-month studies; lot 13016JS was used during the 2-year studies. One additional lot (09330DR) was used solely for dose formulation stability studies and was not used in the animal studies. Identity and purity analyses were conducted by the analytical chemistry laboratory at Midwest Research Institute (Kansas City, MO) and by the study laboratories at Microbiological Associates, Inc. (Bethesda, MD; 2-week and 3-month studies), and Southern Research Institute (Birmingham, AL; 2-year studies); physical properties, moisture content, and stability of the bulk diisopropylcarbodiimide were determined by the analytical chemistry laboratory. Reports on analyses performed in support of the diisopropylcarbodiimide studies are on file at the National Institute of Environmental Health Sciences.

Lot 01207BG, a colorless liquid, was identified as diisopropylcarbodiimide by the study laboratory using infrared (IR) spectroscopy. Lot 13016JS was identified as diisopropylcarbodiimide by the study laboratory using IR and proton nuclear magnetic resonance (NMR) spectroscopy and by the analytical chemistry laboratory using IR, proton NMR, and ultraviolet/visible spectroscopy and gas chromatography (GC)/mass spectrometry. All spectra were consistent with the structure of diisopropylcarbodiimide and with literature references.

The purity of lot 01207BG was determined by the study laboratory using GC. The purity of lot 13016JS was determined by the study laboratory using GC and by the analytical chemistry laboratory using thin layer chromatography (TLC) and GC. The moisture content of lot 13016JS was determined by the analytical chemistry laboratory using Karl Fischer titration; the boiling point and relative density of this lot were also measured by the analytical chemistry laboratory.

For lot 01207BG, GC indicated a major peak and five impurity peaks with areas ranging from 0.05% to 0.27% of the total peak area. Fourteen minor impurities were present in the sample chromatograms. The overall purity of lot 01207BG was determined to be 99.35%.

For lot 13016JS, the boiling point and relative density were consistent with the literature values for diisopropylcarbodiimide. Karl Fischer titration indicated 0.06% water in the bulk chemical. TLC detected a major, a minor, and two trace spots. GC indicated a relative purity of 102% when compared to a frozen reference sample and a mean purity of 99.6% when calculated on area percentage. GC indicated a major peak and five impurity peaks with a combined area of approximately 0.5% of the total peak area; the purity of the test article was determined to be approximately 99.5%. The overall purity of lot 13016JS was determined to be greater than 99%.

The analytical chemistry laboratory conducted accelerated stability studies of lot 13016JS with samples stored for 2 weeks in amber vials with Teflon®-lined septa at approximately 5°, 25°, and 60° C compared to frozen samples from the same lot stored at –20° C. Analysis using GC indicated that the test article was stable when protected from light at temperatures up to approximately 60° C for 2 weeks. To ensure stability, the bulk chemical was stored at room temperature under nitrogen, protected from light as recommended by the manufacturer. Stability was monitored by the study laboratories during the 3-month and 2-year studies using GC; no degradation of the bulk chemical was detected.

Anhydrous Ethanol

Anhydrous ethanol was obtained in two lots from Aldrich Chemical Company for use during the 2-year studies. Identity and purity analyses of both lots were conducted by the study laboratory. The chemical, a clear liquid, was identified as ethanol using IR spectroscopy; the sample spectra were a good match for the reference spectrum of ethanol. The purity of each lot was determined using GC. No impurities were detected that exceeded a relative concentration of 0.1% in either lot.

Preparation and Analysis of Dose Formulations

Except for the 242 mg (rats) and 81 mg (mice) dose formulations, which were used neat in the 2-week studies, the dose formulations were prepared by mixing diisopropylcarbodiimide and anhydrous ethanol to give the required concentrations; formulations were prepared once for the 2-week studies and weekly, biweekly, or monthly for the 3-month and 2-year studies. The dose formulations were stored at room temperature (2-week and 3-month studies) or refrigerated (2-year studies) for up to 28 days.

Because the dose formulations were the neat test article or true solutions of the test article in ethanol, homogeneity studies were not performed. A stability study of a 10 mg/mL dose formulation of lot 01207BG was conducted by the study laboratory using GC; stability was confirmed for at least 28 days for the dose formulation stored at ambient temperature in sealed containers. In a subsequent 35-day dose formulation stability study of lot 09330DR (not used in the animal studies), the analytical chemistry laboratory utilized GC to determine that a 2 mg/mL dose formulation was stable for at least 21 days when stored refrigerated in sealed glass containers and for up to 3 hours when exposed to light at ambient temperature. The study laboratory conducted a stability study of 5.0 and 20.0 mg/mL dose formulations of lot 13016JS and determined that the formulations were stable for at least 35 days when stored refrigerated in sealed glass containers.

Periodic analyses of the dose formulations of diisopropylcarbodiimide were conducted by the study laboratories using GC. During the 2-week studies, the dose formulations were analyzed once; all five dose formulations for rats and mice were within 10% of the target concentrations. Animal room samples of these dose formulations were also analyzed; all five of the animal room samples for rats and mice were within 10% of the target concentrations. Dose formulations were analyzed at the beginning, midpoint, and end of the 3-month studies; animal room samples of these dose formulations were also analyzed. Of the dose formulations analyzed, all 14 for rats and 13 for mice were within 10% of the target concentrations; all 12 and 13 of the animal room samples for rats and mice, respectively, were within 10% of the target concentrations. During the 2-year studies, the dose formulations were generally analyzed every 8 to 12 weeks; animal room samples of these dose formulations were also analyzed. All 33 of the dose formulations analyzed and used for rats and mice were within 10% of the target concentrations. Of the animal room samples analyzed, 11 of 12 for rats and 10 of 12 for mice were within 10% of the target concentrations.

2-Week Studies

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Taconic Laboratory Animals and Services (Germantown, NY). On receipt, the animals were approximately 5 weeks old. Animals were quarantined for 11 (rats) or 13 (mice) days; rats were 6 weeks old on the first day of the study and mice were 7 weeks old. Before the studies began, two male and two female rats and mice were randomly selected for parasite evaluation and gross observation for evidence of disease. Groups of five male and five female rats received dermal applications of 0, 3, 9, 27, 81, or 242 mg diisopropylcarbodiimide per animal and groups of five male and five female mice received dermal applications of 0, 1, 3, 9, 27, or 81 mg per animal 5 days a week for 16 days. The high dose was applied neat as 0.3 mL (rats) or 0.1 mL (mice) of test chemical. All other doses were dissolved in ethanol to yield dosing values of 0.3 or 0.1 mL for application to rats or mice, respectively. Vehicle control rats and mice received ethanol only. Solutions or neat chemical were applied to the shaved dorsal surface of rats and mice. Feed and water were available *ad libitum*. Rats and mice were housed individually. Clinical findings and body weights were recorded on days 1 and 8 and at study termination. Details of the study design and animal maintenance are summarized in Table 1.

Necropsies were performed on all rats and mice. The heart, right kidney, liver, lung, right testis, and thymus were weighed and examined for gross lesions. Histopathologic examinations were performed on the 0, 3, 9, and 27 mg rats and 0, 1, 3, and 9 mg 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 diisopropylcarbodiimide 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 (Germantown, NY). On receipt, rats and female mice were 5 weeks old and male mice were 6 weeks old. Rats

were quarantined for 12 (males) or 13 (females) days and mice were quarantined for 14 (males) or 15 (females) days. Rats and female mice were 7 weeks old and male mice were 8 weeks old on the first day of the studies. Before initiation of the studies, five male and five female rats and mice were randomly selected for parasite evaluation and gross observation for evidence of disease. At the end of the studies, serologic analyses were performed on five male and five female control rats and sentinel mice using the protocols of the NTP Sentinel Animal Program (Appendix K).

Groups of 10 male and 10 female core study rats received dermal applications of 0, 10, 20, 40, 80, or 160 mg diisopropylcarbodiimide per kilogram body weight. Groups of 10 male and 10 female mice received dermal applications of 0, 17.5, 35, 70, 140, or 280 mg/kg. All doses were administered in ethanol, in volumes of 0.5 or 2.0 mL/kg for rats and mice respectively; vehicle control animals received ethanol only. Single daily doses were applied 5 days per week for 13 weeks to a shaved dorsal area posterior of the scapulae to the base of the tail. Additional groups of 10 male and 10 female rats designated for clinical pathology evaluations on days 3 and 22 received the same dermal exposures as the core study rats. Feed and water were available *ad libitum*. Rats and mice were housed individually. Body weights and clinical findings for rats and mice were recorded initially, weekly, and at the end of the studies. Details of the study design and animal maintenance are summarized in Table 1.

Blood was collected for hematology and clinical chemistry analyses from clinical pathology study rats on days 3 and 22 and from surviving core study rats at study termination. Blood was collected for hematology analyses from surviving mice at study termination. At all time points, the animals were anesthetized with a 70% CO_2/30% O_2 mixture and blood was collected from the retroorbital sinus. Blood for hematology analyses was placed in tubes containing EDTA as the anticoagulant. Erythrocyte, platelet, and leukocyte counts, automated hematocrit values, hemoglobin concentration, mean cell volume, mean cell hemoglobin, and mean cell hemoglobin concentration were determined using a Serono-Baker System 9010 hematology analyzer (Serono-Baker Diagnostics, Allentown, PA). Manual hematocrit determinations were performed using an Adams Microhematocrit Centrifuge, Model CT2900. Differential leukocyte counts and erythrocyte and leukocyte morphologies were determined microscopically from blood smears stained with a modified Wright's stain on a Hema-Tek slide stainer (Miles Laboratory, Ames Division, Elkhart, IN). Reticulocytes were stained with new methylene blue and counted microscopically. For clinical chemistry analyses, blood samples were placed into untreated serum separator tubes, centrifuged, and the serum samples were analyzed using a Hitachi 717 chemistry analyzer (Boehringer Mannheim, Indianapolis, IN) and commercially available reagents. The parameters measured are listed in Table 1.

At the end of the 3-month studies, samples were collected for sperm motility and vaginal cytology evaluations on core study rats in the 0, 10, 20, and 40 mg/kg groups and mice in the 0, 17.5, 35, and 70 mg/kg groups. 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.

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 5 to 6 µm, and stained with hematoxylin and eosin (H&E). Complete histopathologic examinations were performed on 0, 40, 80, and 160 mg/kg core study rats and 0, 70, 140, and 280 mg/kg mice. Table 1 lists the tissues and organs routinely examined.

2-YEAR STUDIES

Study Design

Groups of 50 male and 50 female rats and mice received dermal applications of 0, 10, 20, or 40 mg/kg. All doses were administered in ethanol, in volumes of 0.5 or 2.0 mL/kg for rats and mice respectively; vehicle control animals received ethanol only. Single daily doses were applied 5 days per week for 105 weeks to a clipped area in the interscapular region of the back using a positive displacement micropipetter.

Source and Specification of Animals

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Taconic Laboratory Animals and Services (Germantown, NY). Animals were quarantined for 12 days. Before initiation of the studies, five male and five female rats and mice were randomly selected for parasite evaluation and gross observation for evidence of disease. Rats were 6 weeks old and mice were 5 or 6 weeks old on the first day of the studies. The health of the animals was monitored during the studies according to the protocols of the NTP Sentinel Animal Program (Appendix K).

Animal Maintenance

Rats and mice were housed individually. Feed and water were available *ad libitum*. Cages were rotated weekly, and racks were rotated every 2 weeks. Further details of animal maintenance are given in Table 1. Information on feed composition and contaminants is provided in Appendix J.

Clinical Examinations and Pathology

Clinical findings were recorded every 4 weeks beginning week 5. Body weights were recorded initially, weekly for 13 weeks, at 4-week intervals thereafter, and at the end of the studies.

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 H&E 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 brain, eye, and skin of male and female rats and mice; the lung of male and female rats; the spleen and testis of male rats; the mammary gland of female rats; the mesentery and peritoneum of male mice; and the adrenal gland of female mice. Preceding the Pathology Working Group (PWG) report for the 2-year rat study, the primary and reviewing pathologists had identified focal brain hemorrhages in some animals, particularly in the 40 mg/kg males. These lesions were of an acute nature, probably occurring at or near the time of terminal sacrifice. Clinically, some of these animals had early-occurring seizures. In an effort to discover possible brain lesions related to seizure activity, a detailed post-neuropathological review was conducted by the PWG. The review for the 2-year study included an evaluation of the three standard H&E brain sections for all control, mid-dose, and high-dose male rats. Based on the 2-year neuropathology findings, the 3 month male and female rat brain slides were reevaluated and read to a no-effect level. In both the 2-year and 3-month studies, neuronal necrosis and fibrinoid arteriole lesions were identified which were sometimes associated with vascular hemorrhages. Fibrinoid arteriole necrosis was confirmed with the use of Periodic Acid Schiff staining on selected rats from the 2-year study.

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 Dermal Studies of Diiospropylcarbodiimide

2-Week Studies	3-Month Studies	2-Year Studies
Study Laboratory		
Microbiological Associates, Inc. (Bethesda, MD)	Microbiological Associates, Inc. (Bethesda, MD)	Southern Research Institute (Birmingham, AL)
Strain and Species		
F344/N rats $B6C3F_1$ mice	F344/N rats $B6C3F_1$ mice	F344/N rats $B6C3F_1$ mice
Animal Source		
Taconic Laboratory Animals and Services (Germantown, NY)	Taconic Laboratory Animals and Services (Germantown, NY)	Taconic Laboratory Animals and Services (Germantown, NY)
Time Held Before Studies		
Rats: 11 days Mice: 13 days	Rats: 12 days (males) or 13 days (females) Mice: 14 days (males) or 15 days (females)	12 days
Average Age When Studies Began		
Rats: 6 weeks Mice: 7 weeks	Rats: 7 weeks Mice: 7 (females) or 8 (males) weeks	Rats: 6 weeks Mice: 5-6 weeks
Date of First Dose		
Rats: June 6, 1994 Mice: June 8, 1994	Rats: September 6 (males) or 7 (females), 1994 Mice: September 8 (males) or 9 (females), 1994	Rats: April 24, 2000 Mice: May 8, 2000
Duration of Dosing		
16 days	13 weeks	105 weeks
Date of Last Dose		
Rats: June 21, 1994 Mice: June 23, 1994	Rats: December 5 (males) or 6 (females, 1994 Mice: December 7 (males) or 8 (females), 1994	Rats: April 25, 2002 Mice: May 13, 2002
Necropsy Dates		
Rats: June 22, 1994 Mice: June 24, 1994	Rats: December 6 (males) or 7 (females), 1994 Mice: December 8 (males) or 9 (females), 1994	Rats: April 22 to 26, 2002 Mice: May 6 to 14, 2002
Average Age at Necropsy		
9 weeks	Rats: 20 weeks Mice: 20 (females) or 21 (males) weeks	Rats: 110 weeks Mice: 109-111 weeks
Size of Study Groups		
5 males and 5 females	10 males and 10 females	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

TABLE 1
Experimental Design and Materials and Methods in the Dermal Studies of Diiospropylcarbodiimide

2-Week Studies	3-Month Studies	2-Year Studies
Method of Animal Identification		
Tail tattoo	Tail tattoo	Tail tattoo
Diet		
NIH-07 open formula pelleted diet (Zeigler Brothers, Inc., Gardners, PA), available *ad libitum*, changed weekly	Same as 2-week studies	Irradiated NTP-2000 open formula pelleted diet (Ziegler Brothers, Inc., Gardners, PA), available *ad libitum*, changed weekly
Water		
Tap water (Washington Suburban Sanitary Commission Potomac Plant) via automatic watering system, available *ad libitum*	Same as 2-week studies	Tap water (Birmingham municipal supply) via automatic watering system (Edstrom Industries, Inc., Waterford, WI), available *ad libitum*
Cages		
Polycarbonate, changed once weekly	Same as 2-week studies	Polycarbonate solid-bottom (Lab Products, Inc., Maywood, NJ), changed once weekly
Bedding		
Sani-chips® (P.J. Murphy Forest Products Corp., Montville, NJ), changed once weekly	Same as 2-week studies	Heat-treated irradiated hardwood chips (P.J. Murphy Forest Products, Inc., Montville, NJ), changed once weekly
Cage Filters		
Unknown	Unknown	Reemay® spun-bonded polyester (Andico, Birmingham, AL), changed weekly or as needed
Racks		
Stainless steel, changed and rotated once every 2 weeks	Same as 2-week studies	Stainless steel (Lab Products, Maywood, NJ), changed weekly
Animal Room Environment		
Temperature: 72° ± 3° F Relative humidity: 50% ± 15% Room fluorescent light: 12 hours/day Room air changes: at least 10/hour	Temperature: 72° ± 3° F Relative humidity: 50% ± 15% Room fluorescent light: 12 hours/day Room air changes: at least 10/hour	Temperature: 72° ± 3° F Relative humidity: 50% ± 15% Room fluorescent light: 12 hours/day Room air changes: at least 10/hour
Doses		
Rats: 0, 3, 9, 27, 81, or 242 mg per animal. The high dose was applied neat (0.3 mL test chemical); all other doses were dissolved in ethanol to yield 0.3 mL of solution applied to each animal daily, 5 days a week. Control animals received 0.3 mL of ethanol only. Mice: 0, 1, 3, 9, 27, or 81 mg per animal. The high dose was applied neat (0.1 mL of test chemical); all other doses were dissolved in ethanol to yield 0.1 mL of solution applied to each animal daily, 5 days a week. Control animals received 0.1 mL of ethanol only.	Rats: 0, 10, 20, 40, 80, or 160 mg/kg administered in 0.5 mL/kg ethanol per day, 5 days per week Mice: 0, 17.5, 35, 70, 140, or 280 mg/kg administered in 2.0 mL/kg ethanol per day, 5 days per week	Rats: 0, 10, 20, or 40 mg/kg administered in 0.5 mL/kg anhydrous ethanol per day, 5 days per week Mice: 0, 10, 20, or 40 mg/kg administered in 2.0 mL/kg anhydrous ethanol per day, 5 days per week

TABLE 1
Experimental Design and Materials and Methods in the Dermal Studies of Diiospropylcarbodiimide

2-Week Studies	3-Month Studies	2-Year Studies
Type and Frequency of Observation		
Observed twice daily; clinical findings were recorded and animals were weighed initially, on day 8, and at the end of the studies.	Observed twice daily; body weights and clinical findings were recorded initially, weekly, and at the end of the studies	Observed twice daily; body weights and clinical findings were recorded initially, then weekly for the first 13 weeks, monthly thereafter, and at the end of the studies; clinical findings were recorded at 4-week intervals beginning week 5
Method of Sacrifice		
Carbon dioxide asphyxiation	Same as 2-week studies	Same as 2-week studies
Necropsy		
Necropsies were performed on all animals. Organs weighed were heart, right kidney, liver, lung, right testis, and thymus.	Necropsies were performed on all core study animals. Organs weighed were heart, right kidney, liver, lung, right testis, and thymus.	Necropsies were performed on all animals.
Clinical Pathology		
None	Blood was collected from the retroorbital sinus of clinical pathology study rats on days 3 and 22 and from all core study rats and mice surviving to the end of the studies for hematology and clinical chemistry (rats only) determinations. *Hematology:* automated and manual hematocrit; erythrocyte, reticulocyte, nucleated erythrocyte, platelet, lymphocyte, and atypical lymphocyte counts; hemoglobin concentration; mean cell volume; mean cell hemoglobin; mean cell hemoglobin concentration; leukocyte count and differentials *Clinical chemistry:* urea nitrogen, creatinine, total protein, albumin, alanine aminotransferase, alkaline phosphatase, creatine kinase, sorbitol dehydrogenase, bile acid	None

TABLE 1
Experimental Design and Materials and Methods in the Dermal Studies of Diiospropylcarbodiimide

2-Week Studies	3-Month Studies	2-Year Studies
Histopathology		
Histopathology was performed on 0, 3, 9, and 27 mg rats and 0, 1, 3, and 9 mg mice. In addition to gross lesions and tissue masses, the following tissues were examined: brain, kidney, liver, lung, skin, and spinal cord.	Complete histopathology was performed on core study rats exposed to 0, 40, 80, or 160 mg/kg and mice exposed to 0, 70, 140, or 280 mg/kg. In addition to gross lesions and tissue masses, the following tissues were examined: adrenal gland, bone with marrow, brain, clitoral gland, esophagus, gallbladder (mice only), heart with aorta, large intestine (cecum, colon, rectum), small intestine (duodenum, jejunum, ileum), kidney, liver, lung, lymph nodes (mandibular and mesenteric), mammary gland, nose, ovary, pancreas, pancreatic islets, 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. In the remaining groups, the skin of rats and mice and the brain, heart, spleen, and thymus of rats were examined.	Complete histopathology was performed on all rats and mice. In addition to gross lesions and tissue masses, the following tissues were examined: adrenal gland, bone with marrow, brain, clitoral gland, esophagus, eye, gallbladder (mice only), harderian gland, heart with aorta, large intestine (cecum, colon, rectum), small intestine (duodenum, jejunum, ileum), kidney, liver, lung, lymph nodes (mandibular, mesenteric), mammary gland, nose, ovary, pancreas, pancreatic islets, parathyroid gland, pituitary gland, preputial gland, prostate gland, salivary gland, sciatic nerve (rats only), skin, spinal cord (rats only), 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, core study rats from the 0, 10, 20, and 40 mg/kg groups and mice from the 0, 17.5, 35, and 70 mg/kg groups were evaluated for reproductive parameters. The following parameters were evaluated: spermatid heads per testis and per gram testis, spermatid count, and epididymal spermatozoal motility and concentration. 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. Estrous cycle length and the relative frequency of estrous stages were measured.	None

STATISTICAL METHODS

Survival Analyses

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

Calculation of Incidence

The incidences of neoplasms or nonneoplastic lesions are presented in Tables A1, A5, B1, B4, C1, C4, 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, only to site-specific, lesion-free animals that do not reach terminal sacrifice.

Analysis of Neoplasm and Nonneoplastic Lesion Incidences

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

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

Tests of significance included pairwise comparisons of each dosed group with controls and a test for an overall dose-related trend. Continuity-corrected 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 dosed and control groups in the analysis of continuous variables. Organ and body weight data, which have approximately normal distributions, were analyzed with the parametric multiple comparison procedures of Dunnett (1955) and Williams (1971, 1972). Hematology, clinical chemistry, spermatid, and epididymal spermatozoal data, which have typically skewed distributions, were analyzed using the nonparametric multiple comparison methods of Shirley (1977) (as modified by Williams, 1986) 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 (1957) 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 current NTP historical database contains all studies that use the NTP-2000 diet with histopathology findings completed up to the present. A second potential source of variability is route of administration. In general, the historical database for a given study will include studies using the same route of administration, and the overall incidences of neoplasms for all routes of administration are included for comparison. Because the only dermal studies using an ethanol vehicle in the current historical database are the studies presented in this Technical Report, only overall incidences for all routes of administration have been used for historical comparison in this Technical Report.

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 diisopropylcarbodiimide was assessed by testing the ability of the chemical to induce mutations in various strains of *Salmonella typhimurium,* micronucleated erythrocytes in rat and mouse bone marrow, and increases in the frequency of micronucleated erythrocytes in mouse peripheral blood. Micronuclei (literally "small nuclei" or Howell-Jolly bodies) are biomarkers of induced structural or numerical chromosomal alterations and are formed when acentric fragments or whole chromosomes fail to incorporate into either of two daughter nuclei during cell division (Schmid, 1975; Heddle *et al.*, 1983). 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

No toxicity data about diisopropylcarbodiimide were available in the literature. Therefore, the high dose group in this study received 0.3 mL of neat diisopropylcarbodiimide (242 mg/animal). For the lower dose groups, diisopropylcarbodiimide was diluted with ethanol and administered in concentrations of 3, 9, 27, or 81 mg/animal; each animal received a total volume of 0.3 mL. The vehicle controls were administered 0.3 mL of ethanol only. Doses of 3, 9, 27, 81, and 242 mg/animal were approximately equal to 20, 60, 230, 690, and 2,100 mg diisopropylcarbodiimide/kg body weight to male rats and 25, 80, 270, 830, and 2,400 mg/kg to female rats.

All rats in the 27, 81, and 242 mg groups died before the end of the study (Table 2). Of the surviving groups, final body weights were similar to those of the vehicle controls. Clinical findings included convulsions/seizures, nasal/eye discharge, tremors, and comatose conditions in 81 and 242 mg rats, and lethargy, ataxia, and abnormal breathing in 27 mg rats. There were no significant differences in organ weights between surviving dosed groups and the vehicle control groups (Table G1).

TABLE 2
Survival and Body Weights of Rats in the 2-Week Dermal Study of Diisopropylcarbodiimide

Dose (mg/animal)	Survival[a]	Mean Body Weight[b] (g)			Final Weight Relative to Controls (%)
		Initial	Final	Change	
Male					
0	5/5	114 ± 6	207 ± 7	93 ± 7	
3	5/5	117 ± 4	198 ± 5	81 ± 2	96
9	5/5	118 ± 5	201 ± 5	83 ± 2	97
27	0/5[c]	117 ± 6	—	—	
81	0/5[d]	117 ± 4	—	—	
242	0/5[e]	114 ± 4	—	—	
Female					
0	5/5	99 ± 2	131 ± 4	32 ± 2	
3	5/5	99 ± 3	133 ± 4	34 ± 4	101
9	5/5	97 ± 1	128 ± 3	31 ± 2	98
27	0/5[f]	99 ± 2	—	—	
81	0/5[g]	98 ± 3	—	—	
242	0/5[e]	100 ± 1	—	—	

[a] Number of animals surviving at 2 weeks/number initially in group
[b] Weights and weight changes are given as mean ± standard error. Subsequent calculations are based on animals surviving to the end of the study. Differences from the vehicle control group are not significant by Dunnett's test.
[c] Day of death: 5, 5, 5, 6, 6; [d] Day of death: 1, 1, 2, 2, 2; [e] Day of deaths: 1; [f] Day of deaths: 5; [g] Day of death: 1, 1, 1, 1, 2

The incidences of epidermal hyperplasia at the site of application in 9 and 27 mg males and 27 mg females were significantly greater than those in the vehicle controls; the incidences of hyperkeratosis in 3 and 9 mg males and 9 mg females were also significantly increased (Table 3).

TABLE 3
Incidences of Skin Lesions at the Site of Application in Rats in the 2-Week Dermal Study of Diisopropylcarbodiimide

	Vehicle Control	3 mg/animal	9 mg/animal	27 mg/animal
Male				
Number Examined Microscopically	5	5	5	5
Epidermis, Hyperplasia[a]	0	0	5** (1.2)[b]	5** (1.8)
Epidermis, Necrosis	0	0	0	3 (2.0)
Hyperkeratosis	0	5** (1.2)	5** (1.6)	2 (1.0)
Inflammation, Acute	0	0	0	3 (1.3)
Female				
Number Examined Microscopically	5	5	5	5
Epidermis, Hyperplasia	0	1 (1.0)	2 (1.0)	5** (1.8)
Hyperkeratosis	1 (1.0)	4 (1.0)	5* (1.0)	4 (1.0)

* Significantly different ($P \leq 0.05$) from the vehicle control group by the Fisher exact test
** $P \leq 0.01$
[a] Number of animals with lesion; histopathologic examinations were not performed on 81 or 242 mg/animal groups due to early mortality.
[b] Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked

3-MONTH STUDIES

All 160 mg/kg male and female rats were sacrificed moribund or died within the first week of the study (Table 4). All 80 mg/kg males and females died or were found moribund by day 59. Significant decreases in body weight gain occurred in 40 mg/kg males and females, and a significant decrease in final mean body weight occurred in 40 mg/kg females (Table 4). Clinical findings in groups administered 40 mg/kg or more generally included irritation of the skin at the site of application, seizures, ataxia, abnormal breathing, ruffled fur, thinness, and lethargy.

The hematology and clinical chemistry data are listed in Table F1. Scattered changes occurred in the hematology and clinical chemistry variables. In general, the changes were sporadic and minimal and were not considered toxicologically relevant. At the end of the 3-month study, the absolute liver weight of 40 mg/kg females was significantly less than that of the vehicle controls (Table G2). All other organ weights were similar to those of vehicle controls. There were no significant differences in reproductive tissue parameters or estrous cycle characterization between treated and vehicle control groups (Tables H1 and H2).

TABLE 4
Survival and Body Weights of Rats in the 3-Month Dermal Study of Diisopropylcarbodiimide

Dose (mg/kg)	Survival[a]	Mean Body Weight[b] (g)			Final Weight Relative to Controls (%)
		Initial	Final	Change	
Male					
0	10/10	121 ± 2	323 ± 5	203 ± 4	
10	10/10	121 ± 3	317 ± 10	197 ± 8	98
20	10/10	121 ± 3	321 ± 9	201 ± 6	99
40	10/10	122 ± 3	297 ± 8	175 ± 6**	92
80	0/10[c]	123 ± 2	—	—	
160	0/10[d]	122 ± 3	—	—	
Female					
0	10/10	103 ± 2	193 ± 3	90 ± 2	
10	10/10	103 ± 2	193 ± 4	91 ± 3	100
20	10/10	103 ± 2	191 ± 3	88 ± 3	99
40	10/10	104 ± 2	180 ± 3**	76 ± 1**	93
80	0/10[e]	102 ± 2	—	—	
160	0/10[d]	104 ± 2	—	—	

** Significantly different ($P \leq 0.01$) from the vehicle control group by William's test
[a] Number of animals surviving at 3 months/number initially in group
[b] Weights and weight changes are given as mean ± standard error. Subsequent calculations are based on animals surviving to the end of the study.
[c] Week of death: 3, 3, 3, 4, 4, 4, 4, 4, 5, 7
[d] Week of deaths: 1
[e] Week of death: 4, 5, 5, 5, 5, 6, 6, 6, 6, 9

Significantly increased incidences of skin lesions at the site of application included epidermal hyperplasia of minimal to moderate severity in all dosed groups of males (except 160 mg/kg) and 40 mg/kg or greater females, epidermal necrosis in 160 mg/kg males (moderate severity) and females (mild severity), and minimal to marked chronic active inflammation in 80 and 160 mg/kg males and females (Table 5). In the brain, the incidences of minimal focal edema and focal necrosis in 80 mg/kg males and females and minimal focal hemorrhage in 80 mg/kg females and 160 mg/kg males and females were significantly greater than those of the vehicle controls.

Dose Selection Rationale: Based on mortality and body weight changes, 40 mg/kg per day was selected as the high dose for male and female F344/N rats in the 2-year study of diisopropylcarbodiimide.

TABLE 5
Incidences of Selected Nonneoplastic Lesions in Rats in the 3-Month Dermal Study of Diisopropylcarbodiimide

	Vehicle Control	10 mg/kg	20 mg/kg	40 mg/kg	80 mg/kg	160 mg/kg
Male						
Skin (Site of Application)[a]	10	10	10	10	10	10
Epidermis, Hyperplasia[b]	0	5* (1.0)[c]	7** (1.0)	10** (1.6)	10** (2.0)	3 (2.3)
Epidermis, Necrosis, Focal	0	0	0	0	0	9** (2.9)
Inflammation, Chronic Active	0	0	0	1 (1.0)	7** (1.7)	10** (2.8)
Brain	10	10	10	10	10	10
Edema, Focal	0	0	0	0	5* (1.0)	1 (1.0)
Hemorrhage	0	0	0	0	1 (1.0)	4* (2.3)
Arteriole, Necrosis, Fibrinoid	0	0	0	0	0	1 (1.0)
Neuron, Necrosis, Focal	0	0	0	0	8** (2.6)	0
Female						
Skin (Site of Application)	10	10	10	10	10	10
Epidermis, Hyperplasia	1 (1.0)	2 (1.0)	3 (1.0)	5* (1.0)	10** (1.4)	10** (2.8)
Epidermis, Necrosis, Focal	0	0	0	0	0	10** (1.6)
Inflammation, Chronic Active	0	0	0	0	7** (1.0)	10** (3.7)
Brain	10	10	10	10	10	10
Edema, Focal	0	0	0	0	5* (1.0)	2 (1.0)
Hemorrhage	0	0	0	0	5* (2.2)	6** (2.0)
Arteriole, Necrosis, Fibrinoid	0	0	0	0	1 (1.0)	0
Neuron, Necrosis, Focal	0	0	0	0	8** (2.4)	2 (4.0)

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

2-YEAR STUDIES

Survival

Estimates of 2-year survival probabilities for rats are shown in Table 6 and in the Kaplan-Meier survival curves (Figure 1). Survival of 20 mg/kg males was significantly greater than that of the vehicle controls; survival of all dosed groups of females was similar to that of the vehicle controls.

TABLE 6
Survival of Rats in the 2-Year Dermal Study of Diisopropylcarbodiimide

	Vehicle Control	10 mg/kg	20 mg/kg	40 mg/kg
Male				
Animals initially in study	50	50	50	50
Moribund	18	12	10	23
Natural deaths	12	8	8	10
Animals surviving to study termination	20	30	32	17
Percent probability of survival at end of study[a]	40	60	64	34
Mean survival (days)[b]	670	678	696	539
Survival analysis[c]	P=0.056	P=0.135N	P=0.025N	P=0.141
Female				
Animals initially in study	50	50	50	50
Other[d]	0	0	0	1
Moribund	13	8	10	14
Natural deaths	7	10	8	10
Animals surviving to study termination	30	32	32	25
Percent probability of survival at end of study	60	64	64	51
Mean survival (days)	671	672	690	680
Survival analysis	P=0.415	P=0.838N	P=0.710N	P=0.562

[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 vehicle control column, and the results of the life table pairwise comparisons (Cox, 1972) with the vehicle controls are in the dosed group columns. A lower mortality in a dosed group is indicated by **N**.
[d] Inadvertently removed from study; censored from survival analysis

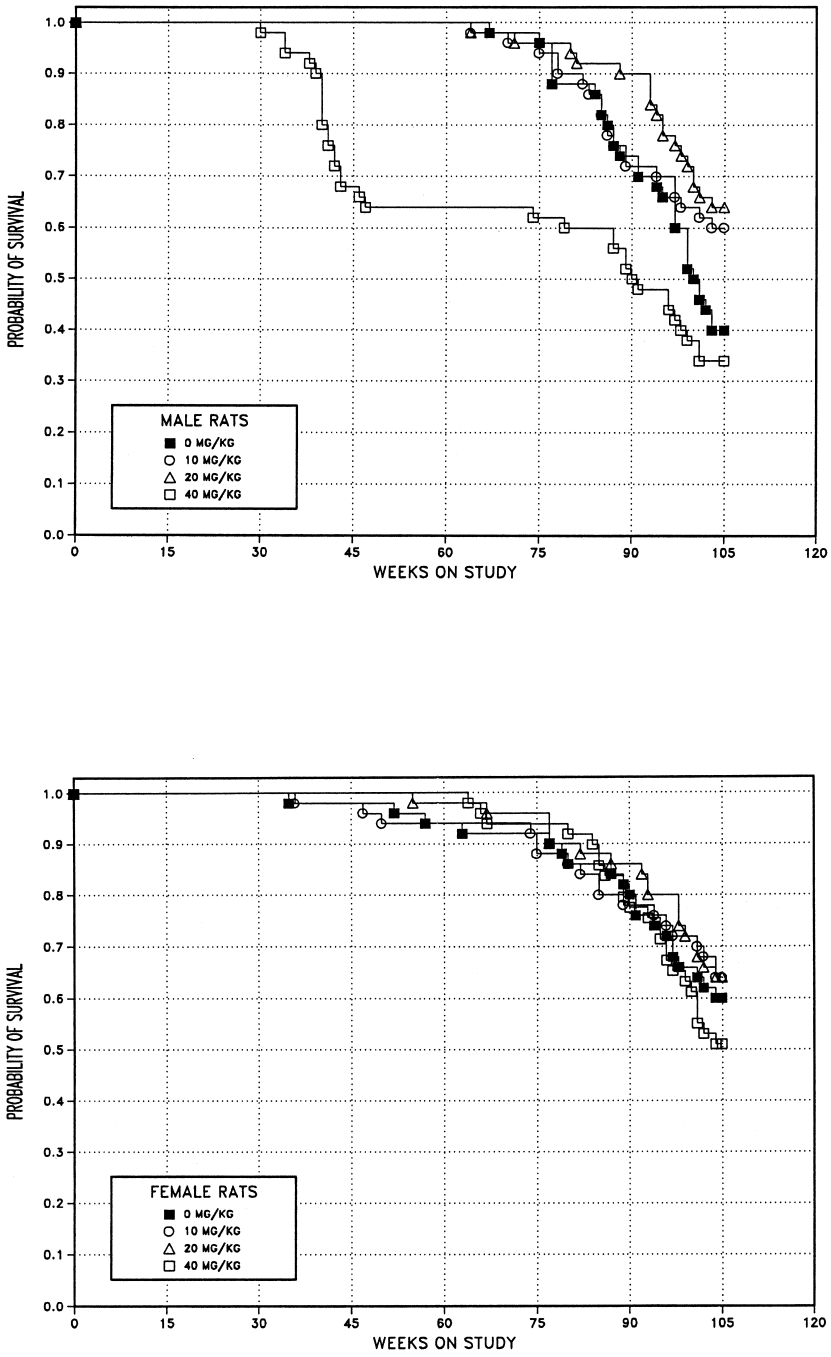


FIGURE 1
Kaplan-Meier Survival Curves for Male and Female Rats Administered Diisopropylcarbodiimide Dermally for 2 Years

Body Weights and Clinical Findings

Body weights of 40 mg/kg males were markedly less than those of vehicle controls after week 13 and 40 mg/kg females were slightly less after week 17 (Tables 7 and 8; Figure 2). At the end of the study, body weights of 40 mg/kg males and females were 79% or 88% of those of the vehicle control groups, respectively. Clinical findings frequently observed in 40 mg/kg male rats included ataxia, excitability, impaired gait, low muscle tone, abnormal breathing, lethargy, and vocalization (Table 9). Few clinical findings were recorded for females.

Primarily during the second year of the study, seizures were observed sporadically in some male and female rats from each dose group, including the vehicle controls. More females were affected than males (females: vehicle controls, 7/50; 10 mg/kg, 9/50; 20 mg/kg, 17/50; 40 mg/kg, 6/50; males: 4/50, 4/50, 9/50, 11/50), and the first onset was earlier in males (week 28) than in females (week 60). Most seizures were mild, characterized by an abnormal hunched posture and chewing movements sometimes accompanied by clonic spasms of alternate muscle contraction and relaxation, lasting approximately 30 seconds with a rapid recovery. Uncommon seizures of greater severity produced more pronounced jerking lasting up to 60 seconds with a recovery time of 2 minutes. Most seizure-prone animals had multiple episodes (two to 13). Eleven 40 mg/kg males experienced seizures; of these, seizures in six were considered related to chemical administration because of early onset (weeks 36 to 44) and other neurological signs concurrently observed (Table 9). The incidences and number of episodes per rat did not appear related to dose in any other rats.

Similar, sporadic seizures have been observed in F344/N rats in six other NTP inhalation or dermal exposure studies conducted at three different laboratories. In all of these studies, the single common factor was that animals were housed individually. No such episodes have been observed in concurrent dosed feed, gavage, or drinking water studies in which rats from the same lineage were group housed. In the individually housed animals, most seizures were observed early in the day, when technical and maintenance activities were commencing following the animals' dark cycle period. No deaths were associated with seizures, and no correlations with body weight, diet, feed consumption, or histopathologic lesions were noted in this or other studies. These transient events were not considered to have affected the toxicologic or carcinogenicity evaluations of this 2-year study.

TABLE 7
Mean Body Weights and Survival of Male Rats in the 2-Year Dermal Study of Diisopropylcarbodiimide

Weeks on Study	Vehicle Control		10 mg/kg			20 mg/kg			40 mg/kg		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	101	50	100	99	50	101	100	50	102	101	50
2	126	50	123	98	50	125	99	50	124	99	50
3	155	50	151	97	50	153	99	50	153	99	50
4	182	50	177	97	50	179	98	50	179	98	50
5	208	50	200	96	50	201	97	50	203	98	50
6	230	50	224	97	50	223	97	50	226	98	50
7	248	50	241	97	50	241	97	50	242	98	50
8	266	50	258	97	50	252	95	50	257	97	50
9	278	50	270	97	50	271	98	50	266	96	50
10	291	50	283	97	50	282	97	50	280	96	50
11	302	50	295	98	50	294	97	50	291	96	50
12	312	50	304	98	50	303	97	50	299	96	50
13	322	50	315	98	50	313	97	50	308	96	50
17	356	50	347	98	50	343	97	50	332	93	50
21	378	50	368	97	50	365	97	50	349	92	50
25	395	50	386	98	50	381	96	50	363	92	50
29	412	50	400	97	50	395	96	50	366	89	50
33	425	50	413	97	50	408	96	50	365	86	49
37	432	50	420	97	50	415	96	50	367	85	47
41	439	50	429	98	50	421	96	50	365	83	39
45	450	50	437	97	50	430	96	50	362	81	34
49	456	50	446	98	50	436	96	50	366	80	32
53	463	50	451	97	50	444	96	50	378	82	32
57	469	50	455	97	50	447	95	50	378	81	32
61	475	50	461	97	50	451	95	50[a]	385	81	32
65	480	50	464	97	49	459	96	49	384	80	32
69	480	49	464	97	49	459	96	49	389	81	32
73	475	49	463	98	48	465	98	48	390	82	32
77	482	45	467	97	47	468	97	48	394	82	31
81	480	44	463	97	45	464	97	47	396	83	30
85	478	43	464	97	43	470	98	46	406	85	30
89	484	37	463	96	38	472	97	45	409	85	28
93	482	35	463	96	36	461	96	45	398	83	24
97	469	33	460	98	34	463	99	39	390	83	22
101	471	24	463	98	32	467	99	34	372	79	19
Mean for weeks											
1-13	232		226	97		226	97		225	97	
14-52	416		405	97		399	96		359	86	
53-101	476		462	97		461	97		390	82	

[a] Number of animals weighed was less than the number of animals surviving.

TABLE 8
Mean Body Weights and Survival of Female Rats in the 2-Year Dermal Study of Diisopropylcarbodiimide

Weeks on Study	Vehicle Control		10 mg/kg			20 mg/kg			40 mg/kg		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	90	50	90	101	50	91	102	50	90	100	50
2	104	50	104	100	50	105	101	50	105	101	50
3	118	50	118	100	50	118	100	50	117	99	50
4	132	50	132	100	50[a]	131	99	50	131	99	50
5	142	50	141	100	50	141	99	50	140	99	50
6	149	50	148	99	50	147	99	50	146	98	50
7	156	50	155	99	50	154	99	50	153	98	50
8	163	50	160	98	50	160	98	50	159	98	50
9	169	50	165	97	50	165	97	50	164	97	50
10	172	50	169	98	50	169	98	50	168	98	50
11	175	50	172	99	50	171	98	50	170	97	50
12	181	50	178	98	50	177	98	50	175	97	50
13	185	50	181	98	50	180	98	50	178	96	50
17	196	50	192	98	50	192	98	50	186	95	50
21	205	50	200	98	50	200	98	50	193	94	49
25	213	50	206	97	50	207	97	50	199	93	49
29	224	50	216	97	50	215	96	50	207	92	49
33	232	50	223	96	50	223	96	50	213	92	49
37	235	49	228	97	49	227	97	50	219	93	49
41	242	49	234	97	49	233	96	50	221	91	49
45	252	49	243	97	49	240	95	50	227	90	49
49	261	49	253	97	48	248	95	50	237	91	49
53	271	48	261	96	47	257	95	50	248	91	49
57	274	48	267	97	47	264	96	49	253	92	49
61	283	47	274	97	47	272	96	49	260	92	49
65	289	46	282	98	47	279	97	49	267	93	48
69	292	46	285	97	47	281	96	48	273	93	46
73	296	46	286	96	47	284	96	48	278	94	46
77	298	46	293	98	44	286	96	48	283	95	46
81	306	43	298	97	43	294	96	45	288	94	45
85	313	43	306	98	42	305	98	44	294	94	44
89	313	42	308	98	40	309	99	43	305	97	39
93	314	38	311	99	39	309	99	41	302	96	37
97	318	35	311	98	38	312	98	40	293	92	32
101	320	33	313	98	36	309	97	35	281	88	30
Mean for weeks											
1-13	149		147	99		147	99		146	98	
14-52	229		222	97		221	97		211	92	
53-101	299		292	98		289	97		279	93	

[a] Number of animals weighed was less than the number of animals surviving.

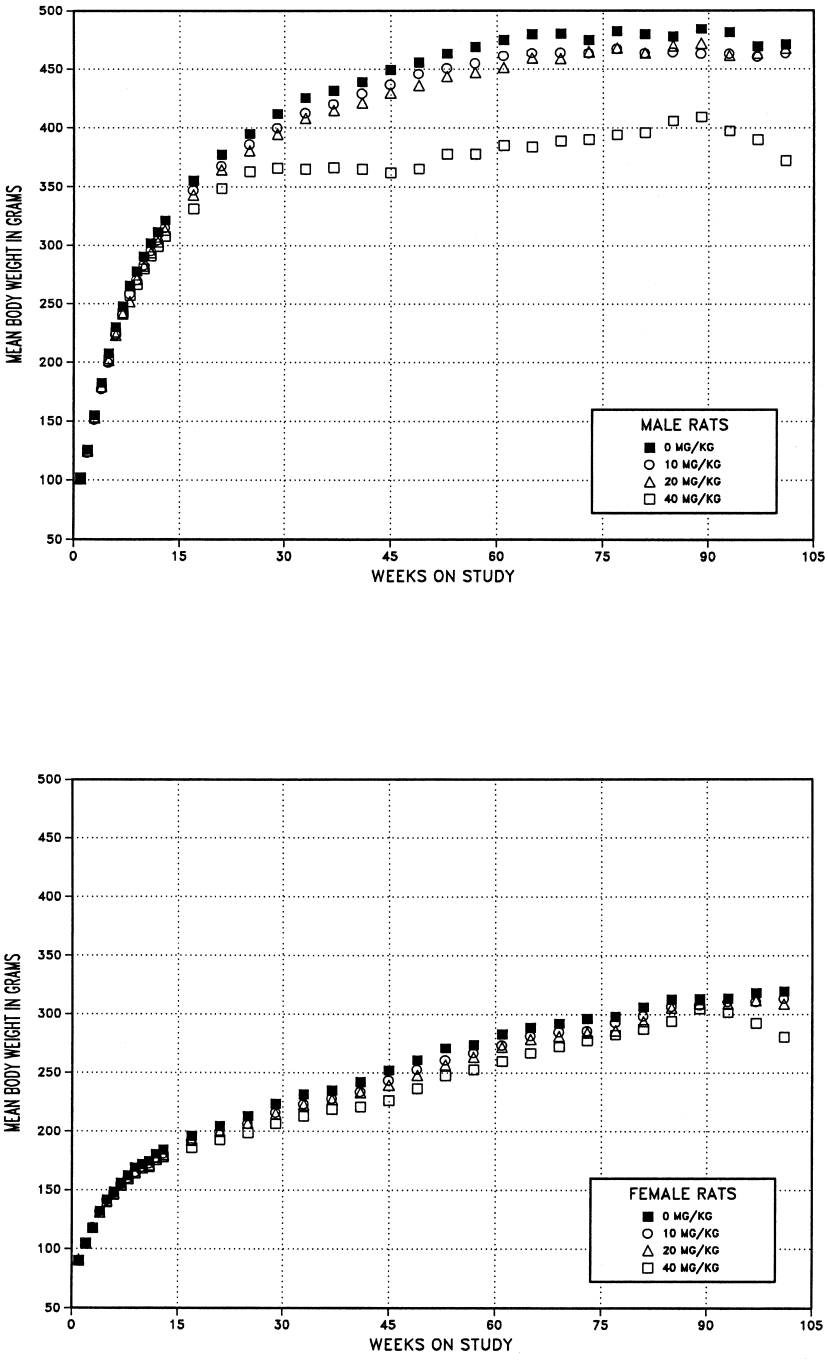


FIGURE 2
Growth Curves for Male and Female Rats Administered Diisopropylcarbodiimide Dermally for 2 Years

Pathology and Statistical Analysis

This section describes the statistically significant or biologically noteworthy changes in the incidences of neoplasms and nonneoplastic lesions of the brain, skin, lung, eye, adrenal gland, lymph node, spleen, and urinary bladder. 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.

Brain: Neurological signs were exhibited by the 40 mg/kg males (Table 9). The principal pathological findings included neuronal necrosis, hemorrhage, and/or fibrinoid arteriole necrosis (Tables 10 and A5). Areas of neuronal necrosis were evident in 40 mg/kg males. Regions most frequently affected included frontal, cingulate and parietal cortex, basal ganglia and thalamus. This lesion was characterized by focal, usually bilateral, symmetrical presence of necrosis in regions of the cerebral cortex. Necrotic neurons were eosinophilic and shrunken (Plate 1) or were represented by "ghost forms" that were barely visible. The regions of neuronal necrosis were well defined, unaccompanied by reactive cells or hemorrhage. They were limited to specific cortical laminae, usually lamina 2 and 3 and surrounded by neurons that were well preserved. The severity of neuronal necrosis in affected foci was minimal to moderate, (one to five neurons affected) to an excess of 20 neurons affected.

TABLE 9
Clinical Findings in Rats in the 2-Year Dermal Study of Diisopropylcarbodiimide[a]

Clinical Finding	Vehicle Control	10 mg/kg	20 mg/kg	40 mg/kg[b]
Male				
Abnormal breathing	0/50	1/50	1/50	7/50
Apprehensive appearance	0/50	0/50	0/50	2/50
Ataxia	0/50	0/50	0/50	38/50
Excitability	0/50	0/50	0/50	17/50
Hyperactivity	0/50	0/50	0/50	2/50
Impaired gait	0/50	0/50	0/50	15/50
Lethargic	1/50	4/50	2/50	7/50
Low muscle tone	0/50	0/50	0/50	13/50
Straub tail	0/50	0/50	0/50	2/50
Vocalization	0/50	0/50	0/50	7/50
Female				
Apprehensive appearance	0/50	0/50	0/50	1/50
Hyperactivity	0/50	0/50	0/50	1/50
Vocalization	0/50	0/50	0/50	1/50

[a] Data are presented as number of rats in a group with a clinical finding/the total number of rats in the group.
[b] Includes data for one female rat inadvertently removed from the study during week 21.

TABLE 10
Incidences of Nonneoplastic Lesions of the Brain in Male Rats in the 2-Year Dermal Study of Diisopropylcarbodiimide

	Vehicle Control	10 mg/kg	20 mg/kg	40 mg/kg
Number Examined Microscopically	50	50	50	50
Hemorrhage[a]	1 (1.0)[b]	0	3 (1.7)	11** (2.5)
Necrosis, Neuron	0	1 (1.0)	0	16** (1.9)
Arteriole, Necrosis, Fibrinoid	0	0	0	5* (1.8)

* Significantly different ($P \leq 0.05$) from the vehicle control group by the Poly-3 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

Also present in the brain was fibrinoid necrosis of arteriole walls and parenchymal hemorrhage. Fibrinoid arteriole necrosis was characterized by a homogeneous, hyaline, eosinophilic deposit in the media and adventitia of affected arterioles and loss of nuclear detail of the vessel wall (Plate 2). Regions primarily affected with vascular lesions included frontal, cingulate, and parietal cortex, basal ganglia and dorsal thalamus. Fibrinoid arteriole necrosis was often focal but also in excess of six foci. Vascular lesions were sometimes accompanied by prominent fibrinous perivascular deposits that were more readily visible using Periodic Acid Schiff (PAS) staining. Many of the dosed animals examined using PAS staining had one or both of two arteriole lesions, fibrinoid arteriole necrosis or perivascular protein droplets (edema). These were characterized by focal, usually bilateral, symmetrical presence of fibrinoid arteriole necrosis and perivascular PAS positive proteinaceous droplets. Fibrinoid arteriole necrosis was characterized by expansion of the vascular walls by PAS positive fibrillar clumps in the media and adventitia (occasional venules and capillaries had similar lesions). The deposits in some cases were extensive enough to efface the morphology of the blood vessels. Distinct brightly PAS positive droplets 0.5 to 4 microns in diameter were apparent in Virchow-Robins spaces of arterioles that appeared to have no other demonstrable mural injury. Uncommonly, "lakes" of perivascular edema fluid, staining lightly PAS positive, were apparent in brain regions with fibrinoid arteriole necrosis. Evaluation of the acute cerebral hemorrhages showed that they correlated with the presence of fibrinoid arteriole necrosis using PAS staining. Parenchymal hemorrhages (Plate 3) were recent with no evidence of neutrophils, hemosiderin deposits or pigment phagocytosis. Hemorrhage commonly suffused the adventitia of the vessels in affected areas.

Skin (site of application): At the site of application, statistically significant increases in the incidences of epidermal hyperplasia occurred in all treated male groups and in 20 and 40 mg/kg females when compared to the vehicle controls (Tables 11, A5, and B4). Microscopically, this lesion of minimal severity was focal and characterized by a slight increase in thickness (two to three cell layers) of the squamous epithelium (Plate 4) when compared to controls (Plate 5). Significant increases in the incidences of chronic inflammation of minimal severity occurred in all treated male groups and 40 mg/kg females. Histologically, this lesion consisted of small numbers of mononuclear cells in the superficial dermis underlying lesions of epidermal hyperplasia (Plate 4).

TABLE 11
Incidences of Nonneoplastic Lesions of the Skin in Rats in the 2-Year Dermal Study of Diisopropylcarbodiimide

	Vehicle Control	10 mg/kg	20 mg/kg	40 mg/kg
Male				
Number Examined Microscopically	49	50	50	50
Site of Application, Epidermis, Hyperplasia[a]	1 (1.0)[b]	10** (1.0)	29** (1.1)	19** (1.1)
Site of Application, Inflammation, Chronic	0	6* (1.0)	12** (1.0)	11** (1.0)
Female				
Number Examined Microscopically	50	50	50	49
Site of Application, Epidermis, Hyperplasia	1 (1.0)	5 (1.0)	16** (1.0)	21** (1.0)
Site of Application, Inflammation, Chronic	0	0 (1.0)	3 (1.0)	10** (1.0)

* Significantly different ($P \leq 0.05$) from the vehicle control group by the Poly-3 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

Lung: The incidence of hemorrhage in 40 mg/kg males was significantly increased when compared to the vehicle controls (Tables 12 and A5). The acute lesion was characterized by minimal to mild numbers of erythrocytes spread diffusely in alveolar spaces and in the perivascular adventitia of small blood vessels. Dark brown to black pigment consistent with hemosiderin in fixed macrophages around large and small bronchioles and pulmonary vessels indicated a chronic hemorrhagic lesion. Statistically significant increases occurred in the incidences of chronic inflammation in 10 and 20 mg/kg females and alveolar epithelium hyperplasia in 20 mg/kg females (Tables 12 and B4). Chronic inflammation consisted of minimal to mild perivascular infiltrates of lymphocytes, plasma cells, and macrophages. Alveolar epithelium hyperplasia was of minimal to mild severity and was characterized by increased numbers of cuboidal epithelial cells that lined alveoli.

Eye: A statistically significant increase in the incidence of corneal hyperplasia occurred in 40 mg/kg males (Tables 13 and A5). This lesion was of mild severity and was characterized by a slight increase in thickness of the corneal epithelium. Significantly increased incidences of chronic corneal inflammation of minimal severity occurred in 20 and 40 mg/kg males. Neovascularization of the corneal stroma with infiltration by variable numbers of inflammatory cells characterized this lesion.

Adrenal Gland (Medulla): The incidences of benign pheochromocytoma (vehicle control, 3/50; 10 mg/kg, 2/48, 20 mg/kg, 8/50; 40 mg/kg, 7/50) and benign, complex, or malignant pheochromocytoma (combined) (6/50, 6/48, 12/50, 9/50) occurred with positive trends in males. The incidences were not significantly different from the vehicle control group in any single dosed group and were within the historical control ranges [benign: 185/1,451 (13% ± 6%), range 3% to 24%; benign, complex, or malignant (combined): 217/1,451 (15% ± 6%), range 5% to 28%] from 2-year NTP studies (Tables A3 and A4). The incidence of hyperplasia in 20 mg/kg males was significantly greater than that of the vehicle controls (7/50, 9/49, 16/50, 3/50; Table A5).

Other Organs: The incidences of hemorrhage in the mediastinal lymph node (2/18, 1/14, 4/16, 6/13), pigmentation in the spleen (9/50, 5/50, 6/50, 25/50), and chronic inflammation in the urinary bladder (0/50, 0/50, 2/50, 4/49) of 40 mg/kg males were significantly increased (Table A5).

TABLE 12
Incidences of Nonneoplastic Lesions of the Lung in Rats in the 2-Year Dermal Study of Diisopropylcarbodiimide

	Vehicle Control	10 mg/kg	20 mg/kg	40 mg/kg
Male				
Number Examined Microscopically	50	50	50	50
Hemorrhage[a]	6 (1.7)[b]	6 (2.0)	7 (2.1)	17** (2.0)
Female				
Number Examined Microscopically	50	50	50	49
Inflammation Chronic	10 (1.9)	22** (1.5)	19* (1.5)	10 (1.1)
Alveolar Epithelium, Hyperplasia	3 (1.3)	4 (2.3)	10* (1.9)	1 (1.0)

* Significantly different ($P \leq 0.05$) from the vehicle control group by the Poly-3 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

TABLE 13
Incidences of Nonneoplastic Lesions of the Eye in Male Rats in the 2-Year Dermal Study of Diisopropylcarbodiimide

	Vehicle Control	10 mg/kg	20 mg/kg	40 mg/kg
Number Examined Microscopically	50	50	50	50
Cornea Hyperplasia[a]	0	0	1 (2.0)[b]	5* (2.4)
Cornea Inflammation Chronic	0	1 (1.0)	5* (1.8)	23** (1.7)

* Significantly different ($P \leq 0.05$) from the vehicle control group by the Poly-3 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

MICE

2-WEEK STUDY

No toxicity data related to diisopropylcarbodiimide were available in the literature. Therefore, the high dose group in this study received 0.1 mL of neat diisopropylcarbodiimide (81 mg/animal). For the lower dose groups, diisopropylcarbodiimide was diluted with ethanol and administered at concentrations of 1, 3, 9, or 27 mg/animal; each animal received a total volume of 0.1 mL. The vehicle controls were administered 0.1 mL of ethanol only. Doses of 1, 3, 9, 27, and 81 mg/animal were approximately equal to 40, 120, 380, 1,200, and 3,500 mg diisopropylcarbodiimide/kg body weight to male mice and 50, 140, 470, 1,500 and 4,200 mg/kg to female mice.

All 9, 27, and 81 mg males and females died before the end of the study (Table 14). Final body weights of the surviving groups were similar to those of the vehicle controls. Organ weights of 1 and 3 mg mice were generally similar to those of vehicle controls (Table G3). The dose levels selected for the 3-month studies were 0, 17.5, 35, 70, 140, or 280 mg/kg.

TABLE 14
Survival and Body Weights of Mice in the 2-Week Dermal Study of Diisopropylcarbodiimide

Dose (mg/animal)	Survival[a]	Mean Body Weight[b] (g)			Final Weight Relative to Controls (%)
		Initial	Final	Change	
Male					
0	5/5	23.4 ± 0.5	25.3 ± 0.8	1.9 ± 0.4	
1	5/5	23.7 ± 0.8	25.7 ± 1.0	2.0 ± 0.2	101
3	5/5	23.6 ± 0.8	25.3 ± 0.8	1.7 ± 0.2	100
9	0/5[c]	23.4 ± 0.5	—	—	
27	0/5[d]	23.4 ± 0.4	—	—	
81	0/5[e]	23.4 ± 0.4	—	—	
Female					
0	5/5	19.6 ± 0.7	22.8 ± 0.6	3.2 ± 0.4	
1	5/5	18.9 ± 0.6	22.3 ± 0.4	3.4 ± 0.4	98
3	5/5	19.1 ± 0.4	22.9 ± 0.3	3.8 ± 0.2	100
9	0/5[f]	19.3 ± 0.3	—	—	
27	0/5[g]	17.6 ± 1.2	—	—	
81	0/5[e]	19.1 ± 1.0	—	—	

[a] Number of animals surviving at 2 weeks/number initially in group
[b] Weights and weight changes are given as mean ± standard error. Subsequent calculations are based on animals surviving to the end of the study. Differences from the vehicle control groups are not significant by Dunnett's test.
[c] Day of death: 7, 7, 8, 8, 8
[d] Day of deaths: 2
[e] Day of deaths: 1
[f] Day of death: 7, 7, 7, 9, 9
[g] Day of death: 1, 2, 2, 2, 2

3-Month Study

All 280 mg/kg males and females and all but two 140 mg/kg males and females died before the end of the study (Table 15). The final mean body weight gain of 70 mg/kg males was significantly less than that of the vehicle control group; the surviving 140 mg/kg male lost weight, and the final body weight of the surviving 140 mg/kg female was 77% that of the vehicle control group. Clinical findings observed in 140 and 280 mg/kg males and females included abnormal breathing, ataxia, comatose conditions, convulsions/seizures, irritation at the site of application, lethargy, ruffled fur, and thinness. No differences in the hematology parameters were observed (Table F2). Significant increases in absolute and relative kidney weights occurred in 17.5 and 35 mg/kg males; organ weights of the remaining groups were generally similar to those of the vehicle control groups (Table G4). Significant decreases in total spermatid heads per testis and average spermatid count occurred in 17.5 mg/kg males. No other significant differences in reproductive tissue parameters or estrous cycle characterization occurred (Tables H3 and H4).

Table 15
Survival and Body Weights of Mice in the 3-Month Dermal Study of Diisopropylcarbodiimide

Dose (mg/kg)	Survival[a]	Mean Body Weight[b] (g)			Final Weight Relative to Controls (%)
		Initial	Final	Change	
Male					
0	10/10	25.5 ± 0.6	33.6 ± 1.0	8.1 ± 0.6	
17.5	10/10	25.7 ± 0.5	32.5 ± 0.6	6.8 ± 0.3	97
35	10/10	25.9 ± 0.5	32.7 ± 0.7	6.8 ± 0.4	97
70	10/10	25.8 ± 0.5	31.8 ± 0.6	6.1 ± 0.4**	95
140	1/10[c]	25.8 ± 0.4	22.9	–2.9	68
280	0/10[d]	25.5 ± 0.5	—	—	
Female					
0	10/10	20.7 ± 0.2	28.1 ± 0.6	7.4 ± 0.5	
17.5	10/10	20.6 ± 0.3	28.3 ± 0.7	7.7 ± 0.5	101
35	10/10	20.6 ± 0.3	27.9 ± 0.8	7.3 ± 0.8	99
70	10/10	21.0 ± 0.3	28.7 ± 0.8	7.7 ± 0.6	102
140	1/10[e]	20.9 ± 0.4	21.5	0.6	77
280	0/10[f]	20.6 ± 0.4	—	—	

** Significantly different ($P \leq 0.01$) from the vehicle control group by William's test
[a] Number of animals surviving at 3 months/number initially in group
[b] Weights and weight changes are given as mean ± standard error. Subsequent calculations are based on animals surviving to the end of the study.
[c] Week of death: 4, 4, 4, 4, 5, 6, 6, 7, 8
[d] Week of deaths: 1
[e] Week of death: 6, 6, 7, 7, 8, 9, 9, 10, 11
[f] Week of death: 1, 1, 1, 2, 2, 2, 2, 2, 2, 2

At the site of application, the incidences of epidermal hyperplasia in males and females administered 70 mg/kg or greater, chronic inflammation in 140 and 280 mg/kg males and 70 mg/kg or greater females, and sebaceous gland hyperplasia in 140 mg/kg males were significantly increased (Table 16). Thymic atrophy was significantly increased in 140 and 280 mg/kg males and females.

Dose Selection Rationale: Based on mortality, body weight changes, and an increase in chronic active inflammation in females at the site of application at 70 mg/kg, 40 mg/kg per day was selected as the high dose for both sexes of $B6C3F_1$ mice in the 2-year study of diisopropylcarbodiimide.

TABLE 16
Incidences of Selected Nonneoplastic Lesions in Mice in the 3-Month Dermal Study of Diisopropylcarbodiimide

	Vehicle Control		17.5 mg/kg		35 mg/kg		70 mg/kg		140 mg/kg		280 mg/kg	
Male												
Skin (Site of Application)[a]	10		10		10		10		10		10	
Epidermis, Hyperplasia[b]	2	(1.5)[c]	1	(2.0)	1	(2.0)	9**	(1.0)	10**	(1.8)	6	(1.8)
Epidermis, Necrosis	0		0		1	(1.0)	0		0		8**	(2.6)
Sebaceous Gland, Hyperplasia	0		0		0		2	(1.0)	5*	(1.6)	0	
Inflammation, Chronic, Active	2	(2.5)	1	(2.0)	1	(2.0)	0		9**	(1.3)	8*	(3.5)
Thymus	10		0		0		10		9		10	
Atrophy	0						0		7**	(3.1)	7**	(2.3)
Female												
Skin (Site of Application)	10		10		10		10		10		10	
Epidermis, Hyperplasia	0		0		2	(1.0)	10**	(1.6)	10**	(2.0)	10**	(1.8)
Inflammation, Chronic, Active	0		0		2	(1.0)	8**	(1.3)	9**	(1.6)	10**	(3.1)
Thymus	10		0		0		10		9		10	
Atrophy	0						0		7**	(3.9)	7**	(3.9)

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

2-YEAR STUDY

Survival

Estimates of 2-year survival probabilities for mice are shown in Table 17 and in the Kaplan-Meier survival curves (Figure 3). Survival of all dosed groups was similar to that of the vehicle control groups.

Body Weights and Clinical Findings

Mean body weights of dosed groups of mice were generally similar to those of the vehicle control groups throughout the study (Tables 18 and 19; Figure 4). There were no clinical findings related to the administration of diisopropylcarbodiimide.

TABLE 17
Survival of Mice in the 2-Year Dermal Study of Diisopropylcarbodiimide

	Vehicle Control	10 mg/kg	20 mg/kg	40 mg/kg
Male				
Animals initially in study	50	50	50	50
Accidental death[a]	0	0	0	1
Moribund	4	1	2	4
Natural deaths	7	9	10	9
Animals surviving to study termination	39[e]	40	38	36
Percent probability of survival at end of study[b]	78	80	76	74
Mean survival (days)[c]	710	697	683	673
Survival analysis[d]	P=0.499	P=1.000N	P=0.911	P=0.672
Female				
Animals initially in study	50	50	50	50
Accidental deaths[a]	0	1	1	1
Moribund	12	11	4	5
Natural deaths	5	5	6	4
Animals surviving to study termination	33	33[e]	39[e]	40
Percent probability of survival at end of study	66	67	80	82
Mean survival (days)	672	684	678	693
Survival analysis	P=0.065N	P=0.985N	P=0.211N	P=0.125N

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

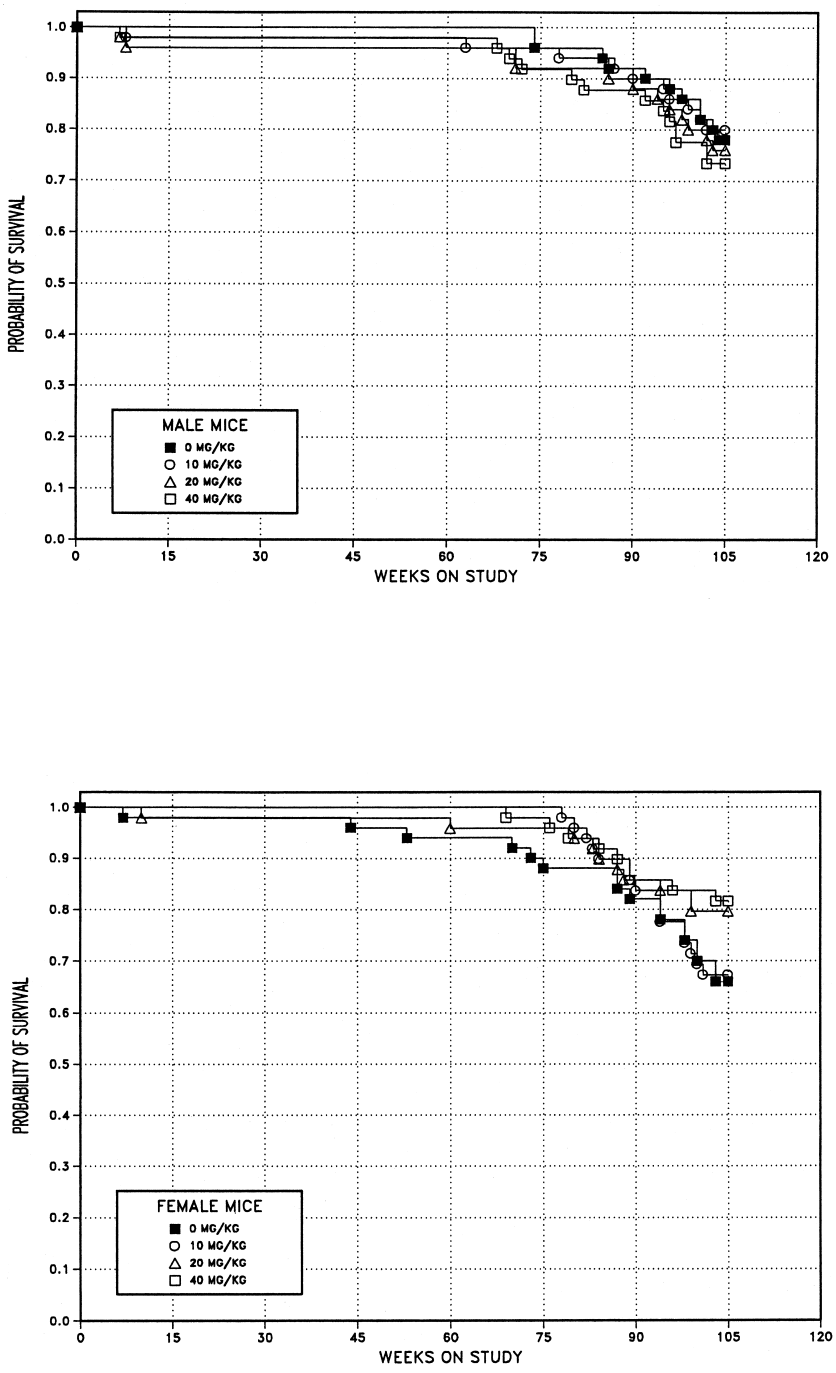


FIGURE 3
Kaplan-Meier Survival Curves for Male and Female Mice Administered Diisopropylcarbodiimide Dermally for 2 Years

TABLE 18
Mean Body Weights and Survival of Male Mice in the 2-Year Dermal Study of Diisopropylcarbodiimide

Weeks on Study	Vehicle Control		10 mg/kg			20 mg/kg			40 mg/kg		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	22.4	50	22.4	100	50	22.4	100	50	22.4	100	50
2	23.6	50	23.4	99	50	23.6	100	50	23.7	100	50
3	25.3	50	25.1	99	50	25.4	100	50	25.3	100	50
4	26.0	50	25.9	100	50	26.1	100	50	26.2	101	50
5	27.0	50	27.1	100	50	27.3	101	50	27.4	102	50
6	28.4	50	28.2	99	50	28.5	100	50[a]	28.3	100	49[a]
7	29.6	50	29.4	99	50	29.4	99	49	29.2	99	48
8	30.3	50	29.8	98	50	30.0	99	49	29.9	99	48
9	30.6	50	31.0	101	49	31.2	102	48	30.9	101	48
10	32.0	50	31.5	98	49	31.5	98	48	31.4	98	48
11	33.3	50	32.5	98	49	32.4	97	48	32.4	97	48
12	33.8	50	33.3	99	49	33.6	99	48	33.5	99	48
13	34.4	50	34.2	99	49	34.3	100	48	34.3	100	48
17	37.2	50	37.0	100	49	37.5	101	48	37.1	100	48
21	40.8	50	40.0	98	49	40.2	99	48	39.2	96	48
25	42.7	50	41.8	98	49	42.0	98	48	41.2	97	48
29	46.0	50	44.9	98	49	45.1	98	48	44.7	97	48
33	47.8	50	46.8	98	49	46.4	97	48	45.8	96	48
37	48.5	50	47.8	99	49	47.2	97	48	46.9	97	48
41	49.2	50	47.4	96	49	48.4	98	48	47.5	97	48
45	49.7	50	49.3	99	49	48.2	97	48	48.1	97	48
49	50.2	50	49.9	99	49	49.3	98	48	49.5	99	48
53	51.2	50	51.0	100	49	50.4	98	48	50.2	98	48
57	51.2	50	51.2	100	49	50.8	99	48	50.7	99	48
61	52.2	50	51.7	99	49	51.5	99	48	51.4	99	48
65	51.7	50	52.1	101	48	51.6	100	48	51.4	99	48
69	51.6	50	52.2	101	48	51.5	100	48	51.3	99	47
73	51.1	50	51.8	101	48	51.4	101	46	51.2	100	45
77	51.8	48	52.3	101	48	51.9	100	46	51.3	99	45
81	52.6	48	53.4	102	47	53.0	101	46	53.2	101	44
85	51.6	48	52.4	102	47	52.2	101	46	52.3	101	43
89	51.3	46	52.0	101	46	53.0	103	45	52.1	102	43
93	51.8	45	51.6	100	45	52.8	102	44	51.6	100	42
97	50.3	44	51.2	102	43	52.5	104	42	51.8	103	39
101	49.8	43	50.9	102	41	52.1	105	40	51.3	103	38
Mean for weeks											
1-13	29.0		28.8	99		28.9	100		28.8	99	
14-52	45.8		45.0	98		44.9	98		44.4	97	
53-101	51.4		51.8	101		51.9	101		51.5	100	

[a] Number of animals weighed was less than number of animals surviving.

TABLE 19
Mean Body Weights and Survival of Female Mice in the 2-Year Dermal Study of Diisopropylcarbodiimide

Weeks on Study	Vehicle Control		10 mg/kg			20 mg/kg			40 mg/kg		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	18.6	50	18.6	100	50	18.5	100	50	18.7	101	50
2	19.3	50	19.4	101	50	19.5	101	50	19.7	102	50
3	21.2	50	21.1	100	49	21.0	99	49	21.2	100	50
4	22.5	50	22.6	100	49	22.5	100	49	22.6	100	50
5	23.3	50	23.0	99	49	23.2	100	49	23.5	101	50
6	24.4	50[a]	24.5	100	49	24.2	99	49	24.8	102	50
7	25.9	49	25.9	100	49	25.6	99	49	25.9	100	50
8	26.3	49	26.4	100	49	26.4	100	49	26.5	101	50
9	27.5	49	27.2	99	49	27.4	100	49	27.2	99	50
10	27.8	49	27.3	98	49	27.5	99	49	27.5	99	50
11	28.3	49	28.4	100	49	28.6	101	48	28.4	100	50
12	29.3	49	29.4	100	49	29.4	100	48	29.1	99	50
13	30.3	49	30.7	101	49	30.7	101	48	30.3	100	50
17	33.3	49	34.6	104	49	35.0	105	48	33.9	102	49
21	37.1	49	37.6	101	49	37.9	102	48	36.7	99	49
25	40.4	49	40.4	100	49	40.9	101	48	40.1	99	49
29	44.8	49	44.5	99	49	44.9	100	48	43.3	97	49
33	46.4	49	46.6	100	49	46.6	100	48	44.9	97	49
37	47.7	49	47.6	100	49	48.0	101	48	46.6	98	49
41	49.9	49	49.4	99	49	49.7	100	48	48.3	97	49
45	52.2	48	51.5	99	49	51.3	98	48	50.1	96	49
49	54.9	48	53.9	98	49	53.7	98	48	52.3	95	49
53	56.9	47	55.8	98	49	55.5	98	48	54.1	95	49
57	59.6	47	58.2	98	49	57.8	97	48	57.1	96	49
61	61.5	47	59.6	97	49	60.2	98	47	59.4	97	49
65	62.9	47	60.1	96	49	60.2	96	47	59.9	95	49
69	62.2	47	59.9	96	49	59.5	96	47	59.7	96	49
73	62.0	45	60.2	97	49	59.6	96	47	59.5	96	48
77	63.3	44	59.3	94	49	59.0	93	47	59.4	94	47
81	65.7	44	63.0	96	47	61.4	94	46	62.1	95	46
85	63.8	44	63.5	100	44	61.2	96	44	61.4	96	45
89	63.2	41	63.3	100	42	61.8	98	42	62.4	99	42
93	62.2	41	61.5	99	41	60.2	97	42	61.2	98	42
97	61.0	39	60.9	100	38	58.9	97	41	60.3	99	41
101	59.2	35	61.8	104	34	57.9	98	39	58.6	99	41
Mean for weeks											
1-13	25.0		25.0	100		25.0	100		25.0	100	
14-52	45.2		45.1	100		45.3	100		44.0	97	
53-101	61.8		60.5	98		59.5	96		59.6	96	

[a] Number of animals weighed was less than number of animals surviving.

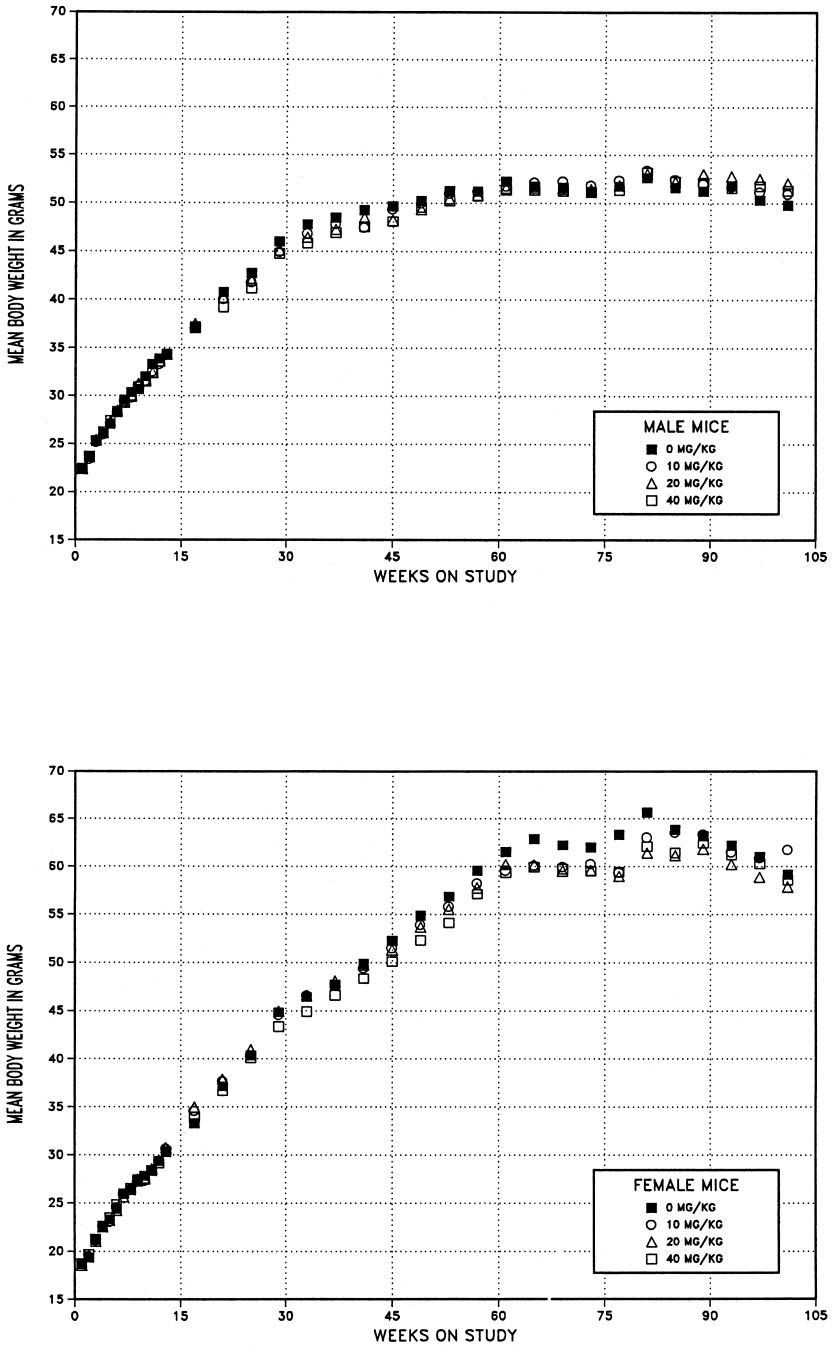


FIGURE 4
Growth Curves for Male and Female Mice Administered Diisopropylcarbodiimide Dermally for 2 Years

Pathology and Statistical Findings

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

Lung: The incidence of alveolar/bronchiolar carcinoma in 40 mg/kg females was significantly greater than that of the vehicle controls (vehicle control, 0/50; 10 mg/kg, 2/50; 20 mg/kg, 2/50; 40 mg/kg, 5/50); however, there was no treatment effect when alveolar/bronchiolar adenomas and carcinomas were combined (4/50, 4/50, 5/50, 6/50; Table D3).

Skin (site of application): Statistically significant increases in the incidences of minimal epidermal hyperplasia and focal inflammation of the dermis occurred in 20 mg/kg males when compared to the vehicle controls (Tables 20 and C4). Microscopically, epidermal hyperplasia was focal and characterized by a slight increase in the thickness of the squamous epithelium. Focal dermal inflammation consisted of small numbers of mononuclear cells in the superficial dermis underlying lesions of epidermal hyperplasia.

Harderian Gland: There was a significant negative trend in the incidences of harderian gland adenoma in females, and the incidence in the 40 mg/kg group was significantly decreased when compared to vehicle controls (vehicle control, 9/50; 10 mg/kg, 5/50; 20 mg/kg, 5/50; 40 mg/kg, 3/50; Table D3). The incidence of this neoplasm in the vehicle controls was at the high end of the historical control range for all routes [122/1,558 (8% ± 6%), range 0% to 22%], and the decreased incidences in the dosed groups were not considered related to the administration of diisopropylcarbodiimide.

GENETIC TOXICOLOGY

Diisopropylcarbodiimide was not mutagenic in *Salmonella typhimurium* strains TA97, TA98, TA100, or TA1535, with or without induced rat or hamster liver S9 activation enzymes (Table E1). Results of *in vivo* tests for chromosomal effects in mice and rats were discussed in detail by Witt *et al.* (1999) and data are presented in Tables E2 through E6. Diisopropylcarbodiimide, administered dermally for 3 months, induced significant increases in the frequency of micronucleated normochromatic erythrocytes (NCEs) in peripheral blood of male and female mice (Table E5). The percentage of polychromatic erythrocytes (PCEs) in these mice was unaffected by chemical treatment. Negative results were obtained in a subsequent acute exposure bone marrow micronucleus test in male F344/N rats using an intraperitoneal injection route of chemical administration at doses that produced clear evidence of bone marrow toxicity based on decreases in percentage of PCEs (Table E2). Diisopropylcarbodiimide was then tested for induction of micronucleated PCEs in male B6C3F$_1$ mice, the same strain employed in the 3-month dermal study, and the results of this test, assaying the frequency of micronucleated PCEs in bone marrow, were negative (Table E3). The values of PCE percentages in this

TABLE 20
Incidences of Nonneoplastic Lesions of the Skin in Male Mice in the 2-Year Dermal Study of Diisopropylcarbodiimide

	Vehicle Control		10 mg/kg		20 mg/kg		40 mg/kg	
Number Examined Microscopically	50		50		50		50	
Site of Application, Epidermis, Hyperplasia[a]	2	(2.0)[b]	3	(2.3)	10*	(1.8)	1	(1.0)
Site of Application, Dermis, Inflammation, Focal	2	(2.0)	2	(2.0)	9*	(1.4)	1	(1.0)

* Significantly different (P≤0.05) from the vehicle 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

mouse study were unchanged with increasing dose, even though chemical-related toxicity was noted at the two highest doses tested. To permit the administration of a higher dose of diisopropylcarbodiimide in mice and to allow scoring of both blood and bone marrow erythrocytes in the same animals, single injection micronucleus studies were conducted with sampling at 24 and 48 hours posttreatment. Micronucleated erythrocytes were significantly increased in peripheral blood PCEs at 48 hours in both trials, but bone marrow smears showed increases in micronucleated PCEs that were not statistically significant at 24 or 48 hours (Table E4). As seen in the acute rat bone marrow study, the percent of PCEs in the bone marrow of mice in Trial 1 was significantly depressed. To clarify the mixed responses in the acute and subchronic tests, a second dermal study of diisopropylcarbodiimide in male mice was performed. Analysis of the mean frequencies of micronucleated PCEs and NCEs in peripheral blood, derived from the pooling of data from interim samplings over the 4-month course of treatment, showed highly significant increases (Table E6). The frequency of micronucleated PCEs in the bone marrow of treated mice on day 124 (final day of treatment) was not significantly increased over the solvent control level. The percentage of PCEs were not significantly altered at any of the sample times in either bone marrow or peripheral blood in the 4-month dermal study (data not shown; Witt *et al*., 1999).

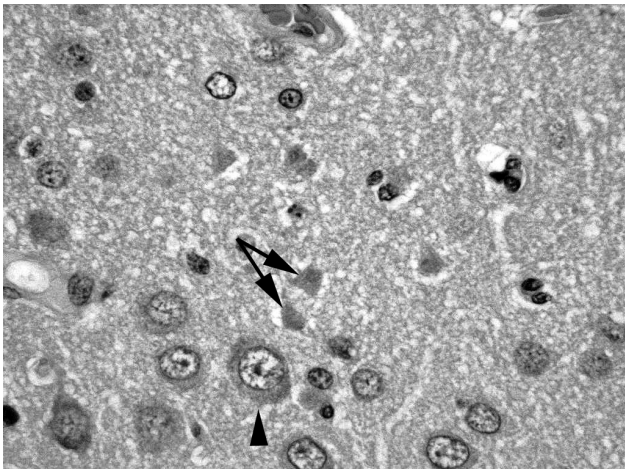


PLATE 1
Area of neuronal necrosis in the brain of a male rat dermally administered 40 mg/kg diisopropylcarbodiimide for 2 years. Note normal neuron (arrowhead) surrounded by shrunken, eosinophilic necrotic neurons (arrows). H&E; 40×

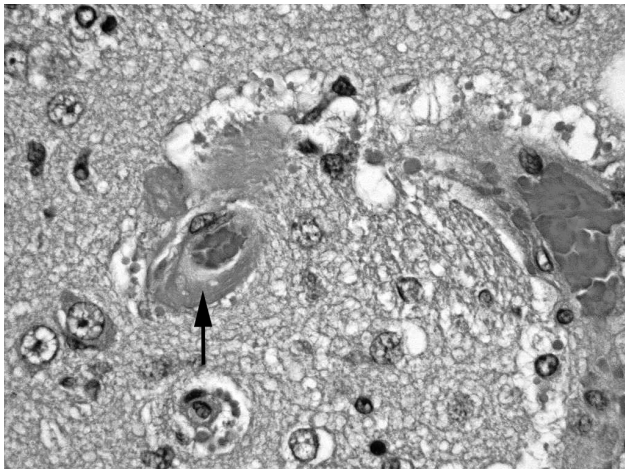


PLATE 2
Fibrinoid arteriole necrosis in the brain of a male rat dermally administered 40 mg/kg diisopropylcarbodiimide for 2 years. Note the thickening of the arteriole wall by homogeneous, hyaline, eosinophilic deposits with loss of nuclear detail (arrow). H&E; 40×

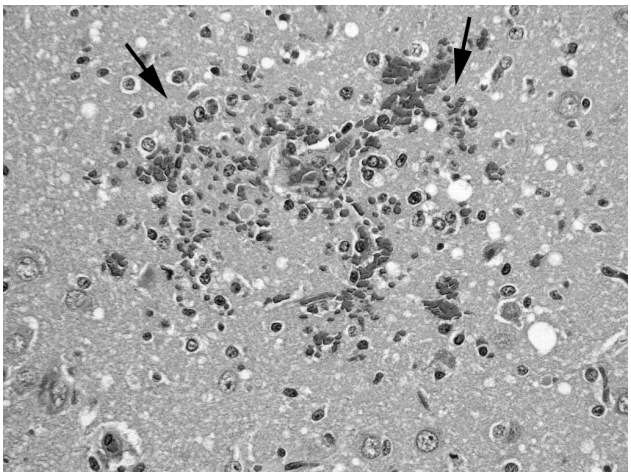


PLATE 3
Hemorrhage (arrows) in the brain of a male rat dermally administered 40 mg/kg diisopropylcarbodiimide for 2 years. H&E; 20×

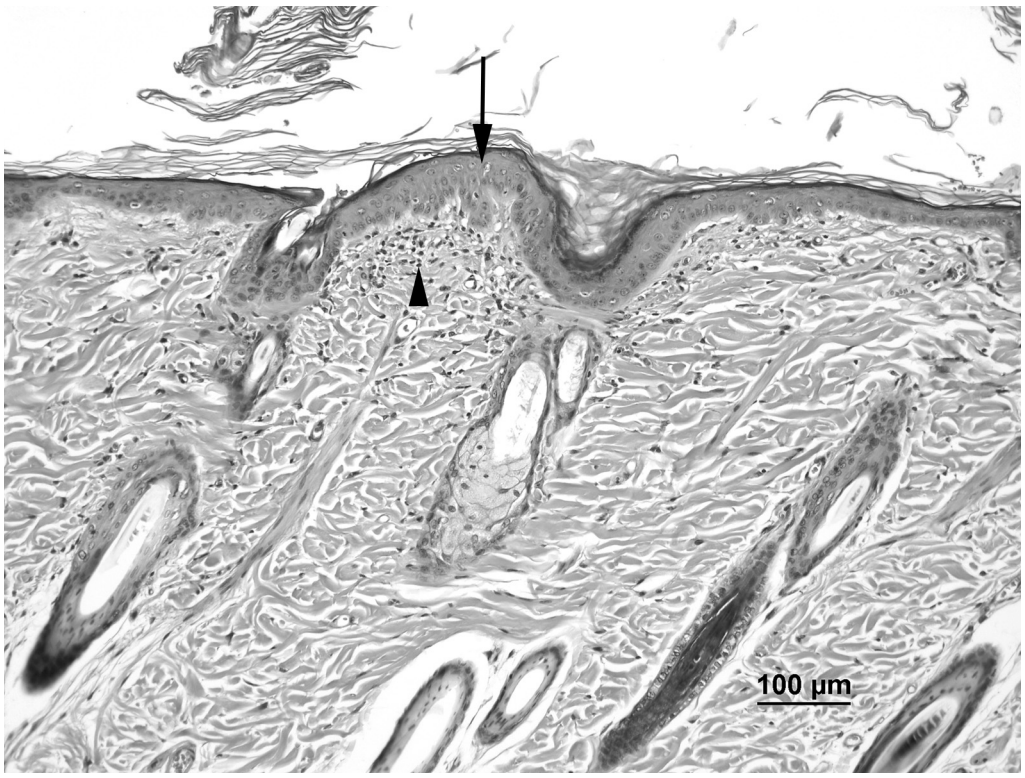


PLATE 4
Epidermal hyperplasia and chronic inflammation of minimal severity in the skin of a male rat dermally administered 40 mg/kg diisopropylcarbodiimide for 2 years. Note the increased thickness of the squamous epithelium (arrow) and the focal infiltration of mononuclear cells in the superficial dermis (arrowhead) when compared to skin of a vehicle control rat (Plate 5). H&E; 16×

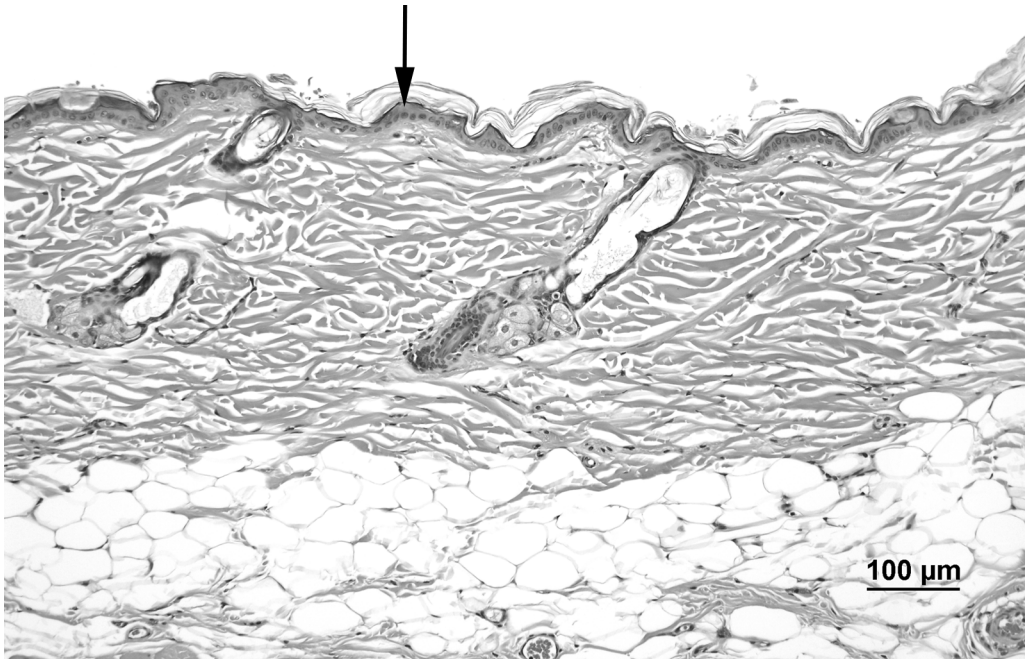


PLATE 5
Skin of a vehicle control male rat from the 2-year dermal study of diisopropylcarbodiimide. Note the normal thickness (one to two cell layers) of the squamous epithelium (arrow). H&E; 16×

DISCUSSION AND CONCLUSIONS

Diisopropylcarbodiimide and dicyclohexylcarbodiimide were studied by the NTP as representatives of the carbodiimide class of chemicals. The results of the dicyclohexylcarbodiimide studies in genetically modified mice were presented for peer review August 28, 2006, and will be reported separately in NTP (2007b).

Only one diisopropylcarbodiimide oral acute toxicity study in mice was found in the literature. The studies reported here show that rats are more sensitive to the toxic effects of diisopropylcarbodiimide than mice. The major organs of toxicity were identified as skin at the site of application and the central nervous system in both rats and mice, and lung toxicity was observed in rats. Mice could have tolerated higher dose concentrations.

Dose-related increases in inflammation and hyperplasia of the skin at the site of application were observed in the 2-week, 3-month, and 2-year studies in rats and mice, with the severity of lesions generally more pronounced in rats. The eyes were not examined in the 2-week or 3-month studies for diisopropylcarbodiimide-related effects. Inflammation of the eye and corneal hyperplasia were observed in rats but not in mice in the 2-year studies. These results are consistent with previously published results demonstrating the irritant capacity of the chemical. Diisopropylcarbodiimide has been shown to be both a skin and eye irritant in humans after occupational exposure (Moyer, 1990; Hayes *et al.*, 1998).

The disposition studies conducted by the NTP in rats and mice using the dermal route of exposure showed that diisopropylcarbodiimide is not readily absorbed (Appendix L). Only small percentages of the radiolabeled diisopropylcarbodiimide, ranging from 1.1% to 6.6% in rats and about 2.3% in mice, were absorbed. The majority of the dosing material applied at the site of application appeared to have been volatilized and was not available for absorption. The tissues analyzed for distribution had minimal levels of diisopropylcarbodiimide, and in some experiments, the tissue:blood ratio could not be determined because the measured radioactivity in blood was not significantly different from the background level. These studies suggest that animals in the current dermal studies were also exposed by inhalation to diisopropylcarbodiimide vapors emitted from the site of application that was not occluded. The central nervous system toxicity and lung effects observed were considered due to systemic absorption of the chemical by inhalation as well as by oral ingestion (grooming) rather than dermal exposure alone.

The central nervous system was adversely affected by diisopropylcarbodiimide exposure in both rats and mice. There were species and sex differences in expression of the clinical signs of central nervous system toxicity. The clinical signs of neurotoxicity such as ataxia, seizures, excitability, hyperactivity, impaired gait, and low muscle tone occurred in rats and mice in the 2-week and 3-month studies but only in rats during the 2-year studies. Male rats displayed more severe and more frequent signs of central nervous system toxicity than females. Some of the 40 mg/kg male rats in the 2-year studies reacted to skin touch by displaying violent spasms and vocalization expressive of pain. These clinical signs of toxicity were accompanied with pathological findings in the brain. Lesions in the brain included neuronal necrosis, cerebral hemorrhage, and/or fibroid arteriole necrosis. The phenomenon of generalized pain as a result of brain injury has been well described in the literature and includes a steady painful sensation that is increased significantly by light touch (Xu *et al.*, 1992; Beric, 1998; Vespa *et al.*, 2003; Nicholson, 2004). It is possible that the reaction to stimuli observed in 40 mg/kg males in the current study is due to a similar phenomenon resulting from brain and spinal cord injury.

Lung congestion in the 3-month studies and dose-related increases in the incidences of hemorrhage in the 2-year studies were observed in rats only. The hemorrhage in the male rat lung was characterized by minimal to mild numbers of erythrocytes spread diffusely in alveolar spaces and in the perivascular adventitia of small blood vessels. The presence of acute hemorrhage and dark brown to black pigment in fixed macrophages around large and small bronchioles and pulmonary vessels

suggests ongoing and prior events. These findings, combined with the incidences of fibroid arteriole necrosis in 40 mg/kg male rat brains, suggest the blood vessel is a target of diisopropylcarbodiimide.

It is well established that inhibition of cell membrane ATPase interferes with the normal function of cell membrane by impairment of the Na^+-K^+ pump. Also, it is proposed that inhibition of sodium-potassium-ATPase is a potentially ubiquitous mechanism contributing to central nervous system neuropathy (Lees, 1991). Diisopropylcarbodiimide is shown to inactivate ATPase in *Escherichia coli* (Satre *et al*., 1979). It is possible the neurotoxicity observed in these studies is due to inhibition of ATPase by diisopropylcarbodiimide.

No carcinogenic activity that was related to diisopropylcarbodiimide exposure was identified in the current studies in rats or mice. Data from the NTP diisopropylcarbodiimide study with the p53 haploinsufficient mouse model also show no carcinogenic effects related to diisopropylcarbodiimide treatment (NTP, 2007a).

Diisopropylcarbodiimide is not mutagenic in the *Salmonella* assay, but results of a series of *in vivo* mutagenicity tests showed clear evidence of increased micronucleus frequencies in the blood of male and female mice following three or more months of exposure via skin painting (Witt *et al.*, 1999). In contrast, bone marrow micronucleus tests in rats and mice, using intraperitoneal injection as the route of exposure, were negative, and no increase in micronucleus frequency was seen in male mouse bone marrow following the 4-month skin painting exposure. Results of a single intraperitoneal injection mouse micronucleus test with diisopropylcarbodiimide showed significant increases in micronucleated polychromatic erythrocytes in peripheral blood 48 hours after dosing; results were again negative in bone marrow 24 hours after dosing, although frequencies of micronucleated cells were elevated in all treated groups. Together, these data suggest that diisopropylcarbodiimide may induce damage in bone marrow soon after treatment, and at the 24-hour posttreatment sample time much of the damaged cell population has already moved from the bone marrow into the peripheral blood. It is also possible that diisopropylcarbodiimide targets the spleen, thereby producing elevated frequencies of micronucleated erythrocytes in blood, but not bone marrow. The results of the peripheral blood micronucleus tests are somewhat surprising because a strong correlation has been reported between positive results in subchronic peripheral blood micronucleus tests and rodent carcinogenicity (Witt *et al.*, 2000). The number of positive studies from which this correlation derives is small, although additional support for the relationship between positive rodent micronucleus test data and carcinogenicity was provided by Morita *et al.* (1997), who reported a 90.5% correlation between carcinogenic activity in humans and positive results in the rodent micronucleus test when data were corrected for known structure-activity considerations with regard to micronucleus assay sensitivity. In addition, Zeiger (1998) reported a 70% correlation between rodent carcinogencity and positive results in the mouse bone marrow micronucleus test in an unadjusted dataset of 83 chemicals tested by the NTP. Thus, the pattern of activity shown by diisopropylcarbodiimide is unusual.

CONCLUSIONS

Under the conditions of these 2-year dermal studies, there was *no evidence of carcinogenic activity** of diisopropylcarbodiimide in male or female F344/N rats or $B6C3F_1$ mice administered 10, 20, or 40 mg/kg.

Clinical and histological signs of neurotoxicity in male rats were associated with diisopropylcarbodiimide administration.

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

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APPENDIX A
SUMMARY OF LESIONS IN MALE RATS IN THE 2-YEAR DERMAL STUDY OF DIISOPROPYLCARBODIIMIDE

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

	Vehicle Control	10 mg/kg	20 mg/kg	40 mg/kg
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Moribund	18	12	10	23
Natural deaths	12	8	8	10
Survivors				
Terminal sacrifice	20	30	32	17
Animals examined microscopically	50	50	50	50
Alimentary System				
Intestine large, colon	(50)	(50)	(50)	(50)
Adenoma	1 (2%)			
Carcinoma		1 (2%)		
Schwannoma malignant, metastatic, mesentery		1 (2%)		
Intestine large, cecum	(50)	(50)	(50)	(49)
Intestine small, duodenum	(49)	(49)	(49)	(49)
Schwannoma malignant, metastatic, mesentery		1 (2%)		
Intestine small, jejunum	(49)	(49)	(48)	(49)
Intestine small, ileum	(49)	(49)	(50)	(48)
Liver	(50)	(50)	(50)	(50)
Hepatocellular adenoma		2 (4%)	1 (2%)	
Mesentery	(9)	(9)	(12)	(6)
Schwannoma malignant		1 (11%)		1 (17%)
Oral mucosa			(2)	
Squamous cell carcinoma			2 (100%)	
Pancreas	(50)	(50)	(50)	(50)
Mixed tumor malignant		1 (2%)		
Squamous cell carcinoma, metastatic, stomach, forestomach			1 (2%)	
Acinus, adenoma	3 (6%)	1 (2%)	2 (4%)	
Salivary glands	(49)	(50)	(50)	(50)
Sarcoma	1 (2%)			
Stomach, forestomach	(50)	(50)	(50)	(49)
Squamous cell carcinoma			1 (2%)	
Squamous cell papilloma	1 (2%)	1 (2%)		1 (2%)
Stomach, glandular	(50)	(50)	(50)	(49)
Tongue	(1)	(1)	(1)	(1)
Squamous cell papilloma			1 (100%)	
Cardiovascular System				
Heart	(50)	(50)	(50)	(50)
Schwannoma malignant	1 (2%)			1 (2%)

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Dermal Study of Diisopropylcarbodiimide

	Vehicle Control	10 mg/kg	20 mg/kg	40 mg/kg
Endocrine System				
Adrenal cortex	(50)	(49)	(50)	(50)
Adrenal medulla	(50)	(48)	(50)	(50)
Ganglioneuroma		1 (2%)		
Pheochromocytoma malignant	3 (6%)	4 (8%)	4 (8%)	2 (4%)
Pheochromocytoma malignant, multiple	1 (2%)			
Pheochromocytoma complex				1 (2%)
Pheochromocytoma benign	3 (6%)	2 (4%)	8 (16%)	7 (14%)
Islets, pancreatic	(50)	(50)	(50)	(50)
Adenoma	4 (8%)	12 (24%)	9 (18%)	5 (10%)
Adenoma, multiple	1 (2%)		1 (2%)	
Carcinoma	2 (4%)	1 (2%)	1 (2%)	
Parathyroid gland	(49)	(48)	(49)	(48)
Adenoma				1 (2%)
Pituitary gland	(50)	(50)	(50)	(50)
Pars distalis, adenoma	28 (56%)	33 (66%)	38 (76%)	17 (34%)
Pars distalis, adenoma, multiple	1 (2%)		4 (8%)	3 (6%)
Pars distalis, carcinoma	5 (10%)	1 (2%)		2 (4%)
Pars intermedia, adenoma	2 (4%)			
Pars intermedia, carcinoma	1 (2%)			
Thyroid gland	(50)	(50)	(50)	(50)
Sarcoma, metastatic, salivary glands	1 (2%)			
Bilateral, C-cell, adenoma	1 (2%)			
C-cell, adenoma	3 (6%)	8 (16%)	8 (16%)	4 (8%)
C-cell, adenoma, multiple	1 (2%)	1 (2%)		
C-cell, carcinoma	5 (10%)	1 (2%)	2 (4%)	
Follicular cell, adenoma	1 (2%)			
General Body System				
Tissue NOS		(1)	(1)	
Hemangioma		1 (100%)		
Lipoma			1 (100%)	
Genital System				
Preputial gland	(50)	(50)	(50)	(50)
Adenoma	1 (2%)	1 (2%)	1 (2%)	4 (8%)
Carcinoma	1 (2%)	2 (4%)		
Prostate	(50)	(50)	(50)	(50)
Adenoma	1 (2%)	2 (4%)	1 (2%)	
Seminal vesicle	(50)	(50)	(50)	(50)
Testes	(50)	(50)	(50)	(50)
Bilateral, interstitial cell, adenoma	21 (42%)	27 (54%)	15 (30%)	14 (28%)
Interstitial cell, adenoma	15 (30%)	10 (20%)	16 (32%)	8 (16%)
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(50)
Lymph node	(18)	(14)	(16)	(13)
Mediastinal, hemangiosarcoma			1 (6%)	
Lymph node, mesenteric	(50)	(50)	(50)	(50)
Schwannoma malignant, metastatic, mesentery		1 (2%)		
Spleen	(50)	(50)	(50)	(50)
Thymus	(49)	(46)	(46)	(49)
Thymoma benign			1 (2%)	

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Dermal Study of Diisopropylcarbodiimide

	Vehicle Control	10 mg/kg	20 mg/kg	40 mg/kg
Integumentary System				
Mammary gland	(49)	(48)	(47)	(48)
Carcinoma			1 (2%)	
Fibroadenoma		4 (8%)	1 (2%)	1 (2%)
Skin	(49)	(50)	(50)	(50)
Keratoacanthoma	3 (6%)	1 (2%)	3 (6%)	1 (2%)
Squamous cell papilloma	1 (2%)	1 (2%)	1 (2%)	
Sebaceous gland, carcinoma	1 (2%)	1 (2%)	1 (2%)	
Subcutaneous tissue, fibroma	5 (10%)	4 (8%)	2 (4%)	3 (6%)
Subcutaneous tissue, fibrosarcoma			1 (2%)	
Subcutaneous tissue, lipoma		3 (6%)	1 (2%)	
Subcutaneous tissue, schwannoma malignant	2 (4%)		2 (4%)	2 (4%)
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Osteoma				1 (2%)
Osteosarcoma				1 (2%)
Skeletal muscle	(3)	(1)	(1)	(5)
Lipoma	1 (33%)			
Sarcoma	1 (33%)			
Nervous System				
Brain	(50)	(50)	(50)	(50)
Astrocytoma malignant	1 (2%)			
Carcinoma, metastatic, pituitary gland	5 (10%)	1 (2%)		1 (2%)
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Alveolar/bronchiolar adenoma	1 (2%)	2 (4%)		
Pheochromocytoma malignant, metastatic, adrenal medulla	1 (2%)		2 (4%)	
Schwannoma malignant, metastatic, mesentery		1 (2%)		
Squamous cell carcinoma, metastatic, stomach, forestomach			1 (2%)	
Nose	(50)	(50)	(50)	(50)
Squamous cell carcinoma	1 (2%)			
Special Senses System				
Eye	(50)	(50)	(50)	(50)
Harderian gland	(50)	(50)	(50)	(50)
Zymbal's gland				(1)
Carcinoma				1 (100%)
Urinary System				
Kidney	(50)	(50)	(50)	(50)

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Dermal Study of Diisopropylcarbodiimide

	Vehicle Control	10 mg/kg	20 mg/kg	40 mg/kg
Systemic Lesions				
Multiple organs[b]	(50)	(50)	(50)	(50)
Leukemia mononuclear	13 (26%)	22 (44%)	13 (26%)	6 (12%)
Lymphoma malignant	2 (4%)			1 (2%)
Mesothelioma malignant	1 (2%)	2 (4%)	4 (8%)	1 (2%)
Neoplasm Summary				
Total animals with primary neoplasms[c]	50	50	50	33
Total primary neoplasms	141	154	148	89
Total animals with benign neoplasms	47	48	50	32
Total benign neoplasms	99	117	115	70
Total animals with malignant neoplasms	34	31	27	15
Total malignant neoplasms	42	37	33	19
Total animals with metastatic neoplasms	7	2	3	1
Total metastatic neoplasms	7	5	4	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 Dermal Study of Diisopropylcarbodiimide: Vehicle Control

Number of Days on Study	463	522	533	533	533	535	582	593	593	599	606	608	612	637	637	657	662	676	677	677	688	688	690	692	697
Carcass ID Number	00343	00441	00401	00244	00443	00447	00332	00366	00446	00146	00337	00177	00338	00228	00333	00306	00444	00422	00445	00458	00222	00188	00407	00144	00355
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																	X								
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery	+												+			+			+				+	+	
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Acinus, adenoma																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma						X																			
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma															X										
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue																+									
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Schwannoma malignant																									
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant																						X			
Pheochromocytoma malignant, multiple																									
Pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma												X				X							X		
Adenoma, multiple																									
Carcinoma																									
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma		X	X	X	X			X		X	X	X					X			X			X		X
Pars distalis, adenoma, multiple																			X						
Pars distalis, carcinoma	X						X														X				
Pars intermedia, adenoma			X													X									
Pars intermedia, carcinoma																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, metastatic, salivary glands						X																			
Bilateral, C-cell, adenoma																									
C-cell, adenoma																									
C-cell, adenoma, multiple																									
C-cell, carcinoma									X																
Follicular cell, adenoma																									

+: 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 Dermal Study of Diisopropylcarbodiimide: Vehicle Control

Number of Days on Study	701	705	714	716	716	729	729	729	729	729	730	730	730	730	730	730	730	730	730	730	730	730	731	731	731	
Carcass ID Number	01 19	00 02	05 00	00 05	03 39	00 99	01 13	11 35	33 54	04 49	00 08	11 01	11 12	22 00	22 01	22 23	22 25	22 57	22 79	23 90	40 00	40 04	01 40	12 06	03 61	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	I	47
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery		+			+			+																		9
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Acinus, adenoma																X			X					X		3
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Sarcoma																										1
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma																										1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tongue																										1
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Schwannoma malignant																X										1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant				X	X																					3
Pheochromocytoma malignant, multiple			X																							1
Pheochromocytoma benign					X										X							X				3
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma										X																4
Adenoma, multiple																								X		1
Carcinoma																		X					X			2
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		28
Pars distalis, adenoma, multiple																										1
Pars distalis, carcinoma					X												X									5
Pars intermedia, adenoma																										2
Pars intermedia, carcinoma							X																			1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma, metastatic, salivary glands																										1
Bilateral, C-cell, adenoma	X																									1
C-cell, adenoma							X					X					X									3
C-cell, adenoma, multiple										X																1
C-cell, carcinoma					X								X											X	X	5
Follicular cell, adenoma												X														1

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

Number of Days on Study	463	522	533	533	533	535	538	592	593	599	606	608	612	637	637	657	662	676	677	677	688	688	690	692	697
Carcass ID Number	00343	00411	00011	00244	00443	00447	00332	00336	00446	00166	00367	00177	00318	00228	00333	00306	00444	00442	00445	00448	00222	00188	00107	00145	00335
General Body System																									
None																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Carcinoma																									
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma						X			X		X				X	X	X	X							
Interstitial cell, adenoma					X							X		X						X		X	X	X	X
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node		+			+		+		+		+	+	+	+						+		+		+	+
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma																	X								
Squamous cell papilloma																				X					
Sebaceous gland, carcinoma																									
Subcutaneous tissue, fibroma												X							X						
Subcutaneous tissue, schwannoma malignant											X														
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle		+																							
Lipoma																									
Sarcoma																									
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma malignant																									
Carcinoma, metastatic, pituitary gland	X						X													X					
Peripheral nerve		+												+									+		
Spinal cord		+												+									+		

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

Number of Days on Study	701	705	714	716	716	729	729	729	729	729	730	730	730	730	730	730	730	730	730	730	730	730	731	731	731	731	
Carcass ID Number	01019	01022	01050	01055	01039	01009	01013	01115	01034	01049	01008	01011	01012	01020	01021	01023	01025	01027	01029	01030	01034	01040	01041	01046	01062	01063	Total Tissues/ Tumors
General Body System																											
None																											
Genital System																											
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma							X																				1
Carcinoma			X																								1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										X	1
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, interstitial cell, adenoma		X	X			X	X	X	X		X	X	X		X					X	X			X		X	21
Interstitial cell, adenoma	X									X				X			X	X			X			X			15
Hematopoietic System																											
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+				+	+				+							+						+				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	M	
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Integumentary System																											
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Skin	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Keratoacanthoma				X				X																			3
Squamous cell papilloma																											1
Sebaceous gland, carcinoma							X																				1
Subcutaneous tissue, fibroma		X										X		X													5
Subcutaneous tissue, schwannoma malignant																		X									2
Musculoskeletal System																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle											+						+										3
Lipoma											X																1
Sarcoma																	X										1
Nervous System																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Astrocytoma malignant																						X					1
Carcinoma, metastatic, pituitary gland					X												X										5
Peripheral nerve																											3
Spinal cord																											3

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

Number of Days on Study	463	522	533	533	533	535	582	593	593	599	606	608	612	637	637	657	662	676	677	677	688	688	690	692	697
Carcass ID Number	00343	00411	00401	00244	00443	00447	00332	00336	00446	00116	00337	00177	00318	00228	00333	00306	00444	00422	00445	00448	00222	00188	00107	00144	00335
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Pheochromocytoma malignant, metastatic, adrenal medulla																						X			
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma															X										
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear		X			X								X	X				X	X					X	X
Lymphoma malignant												X													
Mesothelioma malignant																X									

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

Number of Days on Study	701	705	714	716	716	729	729	729	729	729	730	730	730	730	730	730	730	730	730	730	730	730	731	731	731	731	
Carcass ID Number	00119	00202	00500	00505	00339	00009	00113	00115	00334	00409	00408	00111	00112	00120	00221	00223	00225	00227	00229	00230	00400	00404	00110	00126	00231	Total Tissues/ Tumors
Respiratory System																											
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma			X																								1
Pheochromocytoma malignant, metastatic, adrenal medulla																											1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma																											1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																											
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X				X							X							X	X							13
Lymphoma malignant									X																		2
Mesothelioma malignant																											1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Dermal Study of Diisopropylcarbodiimide: 10 mg/kg

Number of Days on Study	4 4 4	4 8 5	5 2 2	5 4 2	5 4 6	5 7 1	5 7 5	5 9 3	5 9 3	6 0 0	6 0 1	6 0 3	6 1 7	6 2 1	6 5 4	6 7 3	6 7 6	6 8 2	7 0 3	7 1 6	7 2 9	7 2 9	7 2 9	7 2 9
Carcass ID Number	0 9 4	1 0 0	0 8 1	0 7 6	0 5 3	0 6 6	0 8 2	0 6 2	0 6 4	0 5 2	0 5 1	0 8 5	0 7 8	0 7 1	0 7 9	0 9 8	0 6 0	0 9 9	0 6 8	0 7 4	0 5 8	0 5 9	0 6 1	0 6 3	0 6 7
Alimentary System																								
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma									X															
Schwannoma malignant, metastatic, mesentery																			X					
Intestine large, rectum	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Schwannoma malignant, metastatic, mesentery																			X					
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																		X						
Mesentery											+						+		+		+	+		
Schwannoma malignant																			X					
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mixed tumor malignant															X									
Acinus, adenoma																							X	
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																								
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue													+											
Cardiovascular System																								
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																								
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Ganglioneuroma																							X	
Pheochromocytoma malignant																						X	X	
Pheochromocytoma benign																								X
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma													X									X		X
Carcinoma																								
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma	X		X		X		X	X	X	X			X	X	X	X	X	X		X		X	X	
Pars distalis, carcinoma				X																				X
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma								X				X						X	X					
C-cell, adenoma, multiple																	X							
C-cell, carcinoma																						X		
General Body System																								
Tissue NOS												+												
Hemangioma												X												

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Dermal Study of Diisopropylcarbodiimide: 10 mg/kg

Number of Days on Study	729	729	729	729	729	729	729	729	729	729	730	730	730	730	730	730	730	730	730	730	730	730	731	731	731	
Carcass ID Number	07575	08343	08847	08877	08889	08899	09090	09901	09913	09955	09954	10555	10556	10567	10575	10665	10690	10770	10792	10886	10902	10926	10963	11073	11077	11090	11097	Total Tissues/ Tumors
Alimentary System																												
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																												1
Schwannoma malignant, metastatic, mesentery																												1
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Schwannoma malignant, metastatic, mesentery																												1
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma				X																								2
Mesentery												+										+				+		9
Schwannoma malignant																												1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mixed tumor malignant																												1
Acinus, adenoma																												1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma					X																							1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tongue																												1
Cardiovascular System																												
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																												
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	48
Ganglioneuroma																												1
Pheochromocytoma malignant																									X			4
Pheochromocytoma benign										X										X								2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma	X	X			X								X		X		X		X		X			X				12
Carcinoma																									X			1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma	X	X	X	X	X		X		X		X		X	X	X		X	X	X			X		X				33
Pars distalis, carcinoma																												1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma		X								X	X									X								8
C-cell, adenoma, multiple																												1
C-cell, carcinoma																												1
General Body System																												
Tissue NOS																												1
Hemangioma																												1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Dermal Study of Diisopropylcarbodiimide: 10 mg/kg

Number of Days on Study	4 4 4	4 8 5	5 2 2	5 4 2	5 4 6	5 7 1	5 7 5	5 9 3	5 9 3	6 0 0	6 0 1	6 0 3	6 1 7	6 2 1	6 5 4	6 7 3	6 7 6	6 8 2	7 0 3	7 1 6	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9
Carcass ID Number	0 9 4	1 0 0	0 8 1	0 7 6	0 5 3	0 6 6	0 8 2	0 6 2	0 6 4	0 5 2	0 5 1	0 8 5	0 7 8	0 7 1	0 7 9	0 9 8	0 6 0	0 9 9	0 6 8	0 7 4	0 5 8	0 5 9	0 6 1	0 6 3	0 6 7
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Carcinoma														X						X					
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
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
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node			+	+		+	+						+		+	+		+					+	+	+
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Schwannoma malignant, metastatic, mesentery																			X						
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M
Integumentary System																									
Mammary gland	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma																		X							
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma																									
Squamous cell papilloma																							X		
Sebaceous gland, carcinoma		X																							
Subcutaneous tissue, fibroma																		X					X		
Subcutaneous tissue, lipoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																		+							
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, pituitary gland				X																					
Peripheral nerve															M										
Spinal cord															+										
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Schwannoma malignant, metastatic, mesentery																			X						
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Dermal Study of Diisopropylcarbodiimide: 10 mg/kg

Number of Days on Study	729	729	729	729	729	729	729	729	729	729	730	730	730	730	730	730	730	730	730	730	731	731	731	731	
Carcass ID Number	07575	08033	08044	08787	08808	08899	09090	09901	09913	09925	09954	09955	09956	09957	09965	09969	09970	09972	09986	09992	09996	09973	09977	09980	09997	Total Tissues/ Tumors
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma					X																					1
Carcinoma																										2
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma						X																X				2
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	27
Interstitial cell, adenoma	X	X											X				X		X							10
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node							+							+	+											14
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	1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Schwannoma malignant, metastatic, mesentery																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	48
Fibroadenoma																		X			X	X				4
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Keratoacanthoma																					X					1
Squamous cell papilloma																										1
Sebaceous gland, carcinoma																										1
Subcutaneous tissue, fibroma		X																X								4
Subcutaneous tissue, lipoma	X											X		X												3
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, pituitary gland																										1
Peripheral nerve																										
Spinal cord																										1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma							X																	X		2
Schwannoma malignant, metastatic, mesentery																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Dermal Study of Diisopropylcarbodiimide: 10 mg/kg

Number of Days on Study	4	4	5	5	5	5	5	5	5	6	6	6	6	6	6	6	6	6	7	7	7	7	7	7	7
	4	8	2	4	4	7	7	9	9	0	0	0	1	2	5	7	7	8	0	1	2	2	2	2	2
	4	5	2	2	6	1	5	3	3	0	1	3	7	1	4	3	6	2	3	6	9	9	9	9	9
Carcass ID Number	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	9	0	8	7	5	6	8	6	6	5	5	8	7	7	7	9	6	9	6	7	5	5	6	6	6
	4	0	1	6	3	6	2	2	4	2	1	5	8	1	9	8	0	9	8	4	8	9	1	3	7
Special Senses System																									
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear			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 Dermal Study of Diisopropylcarbodiimide: 10 mg/kg

Number of Days on Study	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	0 7 5	0 8 3	0 8 4	0 8 7	0 8 8	0 8 9	0 9 0	0 9 1	0 9 3	0 9 5	0 5 4	0 5 5	0 5 6	0 5 7	0 6 5	0 6 9	0 7 0	0 7 2	0 8 6	0 8 9	0 9 2	0 9 6	0 7 3	0 7 7	0 8 0	0 9 7	Total Tissues/ Tumors
Special Senses System																										
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear			X	X			X	X			X	X		X			X								X	22
Mesothelioma malignant																										2

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Dermal Study of Diisopropylcarbodiimide: 20 mg/kg

Number of Days on Study	4 4 4	4 9 1	5 5 6	5 6 3	6 1 5	6 4 5	6 4 7	6 4 9	6 5 2	6 6 0	6 6 3	6 7 6	6 8 6	6 8 8	6 9 4	6 9 6	7 0 3	7 2 0	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9
Carcass ID Number	1 0 4	1 1 5	1 2 7	1 2 9	1 0 6	1 2 3	1 3 0	1 4 3	1 1 3	1 3 2	1 0 9	1 4 5	1 1 9	1 5 0	1 1 6	1 2 2	1 0 3	1 3 7	1 1 5	1 1 2	1 1 4	1 2 1	1 2 5	1 2 6	1 3 3
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																									
Mesentery								+							+			+			+				
Oral mucosa						+										+									
Squamous cell carcinoma						X										X									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, metastatic, stomach, forestomach																									
Acinus, adenoma				X																					
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma																									
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue																									
Squamous cell papilloma																									
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant				X					X											X					
Pheochromocytoma benign																							X		
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma				X		X								X				X			X				X
Adenoma, multiple																									
Carcinoma																								X	
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma	X	X	X	X	X		X	X	X	X	X	X	X	X	X			X	X	X	X	X		X	X
Pars distalis, adenoma, multiple																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma						X										X	X						X		
C-cell, carcinoma																						X	X		
General Body System																									
Tissue NOS																									
Lipoma																									

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Dermal Study of Diisopropylcarbodiimide: 20 mg/kg

Number of Days on Study	729	729	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	731	731	731	731	731	731	
Carcass ID Number	13436	14402	10707	11010	11101	11117	11188	12020	12024	12028	13101	13404	13505	13909	14040	14401	14404	14407	14408	11012	10002	10808	13838	14406	14409	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma									X																	1
Mesentery			+		+			+	+	+					+		+			+					12
Oral mucosa																										2
Squamous cell carcinoma																										2
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma, metastatic, stomach, forestomach																								X		1
Acinus, adenoma									X																	2
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma																								X		1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tongue																	+									1
Squamous cell papilloma																	X									1
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant											X															4
Pheochromocytoma benign						X	X		X						X	X	X			X						8
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma					X			X														X				9
Adenoma, multiple																			X							1
Carcinoma																										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	38
Pars distalis, adenoma, multiple			X					X		X				X												4
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma			X									X					X		X							8
C-cell, carcinoma																										2
General Body System																										
Tissue NOS																+										1
Lipoma																X										1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Dermal Study of Diisopropylcarbodiimide: 20 mg/kg

Number of Days on Study	4 4 4	4 9 1	5 5 6	5 6 3	6 1 5	6 4 5	6 4 7	6 4 9	6 5 2	6 6 0	6 6 3	6 7 6	6 8 6	6 8 8	6 9 4	6 9 6	7 0 3	7 2 0	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9
Carcass ID Number	1 0 4	1 1 5	1 2 7	1 2 9	1 0 6	1 2 3	1 3 0	1 4 3	1 1 3	1 3 2	1 0 9	1 4 5	1 1 9	1 5 0	1 1 6	1 2 2	1 0 3	1 3 7	1 0 5	1 1 2	1 1 4	1 2 1	1 2 5	1 2 6	1 3 3
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Penis														+											
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									X
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma																X	X					X			
Interstitial cell, adenoma	X					X		X			X			X	X			X	X				X		
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node		+	+	+	+	+		+	+	+	+			+		+	+				+				
Mediastinal, hemangiosarcoma																X									
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymoma benign																						X			
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma						X																			
Fibroadenoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma																									
Squamous cell papilloma																									
Sebaceous gland, carcinoma																									
Subcutaneous tissue, fibroma																						X			
Subcutaneous tissue, fibrosarcoma								X																	
Subcutaneous tissue, lipoma																									
Subcutaneous tissue, schwannoma malignant																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																									
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve															+										
Spinal cord															+										

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Dermal Study of Diisopropylcarbodiimide: 20 mg/kg

Number of Days on Study	729	729	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	731	731	731	731	731	731	
Carcass ID Number	13 36	14 02	10 07	11 10	11 01	11 17	11 18	12 00	12 04	12 28	13 01	13 34	13 05	13 09	14 00	14 01	14 04	14 07	14 08	10 01	10 12	10 28	13 38	14 06	14 09	Total Tissues/ Tumors
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Penis																										1
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma													X													1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, interstitial cell, adenoma		X	X	X		X	X	X			X			X			X	X		X				X		15
Interstitial cell, adenoma	X								X				X						X		X	X	X			16
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node								+	+											+						16
Mediastinal, hemangiosarcoma																										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	4
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	I	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Thymoma benign																										1
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	47
Carcinoma																										1
Fibroadenoma										X																1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Keratoacanthoma					X										X									X		3
Squamous cell papilloma						X																				1
Sebaceous gland, carcinoma							X																			1
Subcutaneous tissue, fibroma		X																								2
Subcutaneous tissue, fibrosarcoma																										1
Subcutaneous tissue, lipoma												X														1
Subcutaneous tissue, schwannoma malignant																X						X				2
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle									+																	1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Peripheral nerve														+												2
Spinal cord														+												2

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Dermal Study of Diisopropylcarbodiimide: 20 mg/kg

Number of Days on Study	4 4 4	4 9 1	5 5 6	5 6 3	6 1 5	6 4 5	6 4 7	6 4 9	6 5 2	6 6 0	6 6 3	6 7 6	6 8 6	6 8 8	6 9 4	6 9 6	7 0 3	7 2 0	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9
Carcass ID Number	1 0 4	1 1 5	1 2 7	1 2 9	1 0 6	1 2 3	1 3 0	1 4 3	1 1 3	1 3 2	1 0 9	1 4 5	1 1 9	1 5 0	1 1 6	1 2 2	1 0 3	1 3 7	1 0 5	1 1 2	1 1 4	1 2 1	1 2 5	1 2 6	1 3 3
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant, metastatic, adrenal medulla				X																					
Squamous cell carcinoma, metastatic, stomach, forestomach																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urethra														+											
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear			X						X	X	X			X	X		X				X			X	
Mesothelioma malignant															X			X							

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Dermal Study of Diisopropylcarbodiimide: 20 mg/kg

Number of Days on Study	729	729	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	731	731	731	731	731	731	
Carcass ID Number	13436	14402	14707	15010	15111	15117	15118	15220	15224	15228	15231	15234	15235	15239	15240	15241	15244	15247	15248	15301	15302	15308	15338	15346	15349	Total Tissues/ Tumors
Respiratory System																											
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant, metastatic, adrenal medulla											X																2
Squamous cell carcinoma, metastatic, stomach, forestomach																									X		1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																											
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urethra																											1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear									X												X		X		X		13
Mesothelioma malignant									X								X										4

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Dermal Study of Diisopropylcarbodiimide: 40 mg/kg

Number of Days on Study	204	237	237	266	273	277	277	278	278	278	281	285	290	290	298	298	319	325	513	553	606	607	617	623	630
Carcass ID Number	15505	16505	18800	17702	19707	19908	19909	15606	18806	18807	17303	20000	18303	19101	18909	19404	17401	18915	18854	15407	16622	19202	17003	19303
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery																									
Schwannoma malignant																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Stomach, glandular	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue																						+			
Cardiovascular System																									
Blood vessel																			+						
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Schwannoma malignant																									
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant																									
Pheochromocytoma complex																									X
Pheochromocytoma benign																									X
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																			X					X	
Parathyroid gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma														X					X					X	X
Pars distalis, adenoma, multiple																									
Pars distalis, carcinoma																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																						X			
General Body System																									
None																									

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Dermal Study of Diisopropylcarbodiimide: 40 mg/kg

Number of Days on Study	6 3 4	6 6 7	6 6 9	6 7 6	6 8 3	6 9 1	7 0 4	7 0 6	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	1 8 4	1 5 8	1 7 1	1 7 7	1 8 8	1 7 6	1 7 9	1 5 7	1 6 1	1 6 3	1 6 8	1 6 9	1 9 0	1 9 5	1 5 9	1 6 0	1 6 6	1 7 5	1 7 8	1 9 6	1 5 2	1 5 3	1 6 4	1 8 1	1 8 2	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	I	+	48
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery	+			+	+									+	+			+								6
Schwannoma malignant					X																					1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Squamous cell papilloma								X																		1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Tongue																										1
Cardiovascular System																										
Blood vessel																										1
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Schwannoma malignant					X																					1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant																				X		X				2
Pheochromocytoma complex																										1
Pheochromocytoma benign						X		X	X	X						X			X							7
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma									X										X				X			5
Parathyroid gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma								X																		1
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma	X	X		X		X			X		X	X							X		X	X	X	X	X	17
Pars distalis, adenoma, multiple										X				X				X								3
Pars distalis, carcinoma																X				X						2
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma															X		X	X								4
General Body System																										
None																										

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Dermal Study of Diisopropylcarbodiimide: 40 mg/kg

Number of Days on Study	204	237	237	266	273	277	277	278	278	278	281	285	290	290	298	298	319	325	513	553	606	607	617	623	630
Carcass ID Number	15955	16550	18802	17702	19737	19988	19989	15966	18866	18867	17733	20004	18303	19911	18994	19404	17544	18955	15854	16667	16622	19922	17304	19933
Genital System																									
Coagulating gland																			+						
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																						X			
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma																						X			
Interstitial cell, adenoma																					X		X		
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node							+						+			+	+						+		
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+
Fibroadenoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma																									
Subcutaneous tissue, fibroma																					X		X		
Subcutaneous tissue, schwannoma malignant																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteoma																									
Osteosarcoma																									
Skeletal muscle	+	+	+	+																					
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, pituitary gland																									
Peripheral nerve	+	+	+	+				+					+		+	+			+						
Spinal cord	+	+	+	+				+					+		+	+			+						
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Dermal Study of Diisopropylcarbodiimide: 40 mg/kg

Number of Days on Study	6 3 4	6 6 7	6 6 9	6 7 6	6 8 3	6 9 1	7 0 4	7 0 6	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	1 8 4	1 5 8	1 7 1	1 7 7	1 8 8	1 7 6	1 7 9	1 5 7	1 6 1	1 6 3	1 6 8	1 6 9	1 9 0	1 9 5	1 5 9	1 6 0	1 6 6	1 7 5	1 7 8	1 9 6	1 5 2	1 5 3	1 6 4	1 8 1	1 8 2	Total Tissues/ Tumors
Genital System																										
Coagulating gland																										1
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma	X													X											X	4
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, interstitial cell, adenoma			X				X	X		X				X	X		X	X	X	X	X	X		X		14
Interstitial cell, adenoma					X				X		X		X			X							X			8
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node					+	+		+		+							+	+					+		+	13
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	1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	48
Fibroadenoma																								X		1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Keratoacanthoma													X													1
Subcutaneous tissue, fibroma							X																			3
Subcutaneous tissue, schwannoma malignant																			X					X		2
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteoma				X																						1
Osteosarcoma																	X									1
Skeletal muscle																								+		5
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, pituitary gland																				X						1
Peripheral nerve		+					+																	+		12
Spinal cord		+					+																	+		12
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Dermal Study of Diisopropylcarbodiimide: 40 mg/kg

Number of Days on Study	204	237	237	266	273	277	277	278	288	287	288	285	290	290	298	298	319	325	351	355	606	600	617	712	763
Carcass ID Number	15595	16655	18800	17972	19977	19988	19999	15566	18686	18877	17733	20200	18833	19911	18999	19494	17441	15111	18855	15544	16677	16622	19922	17700	19993
Special Senses System																									
Ear																			+						
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lacrimal gland																			+						
Zymbal's gland																	+								
Carcinoma																	X								
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																					X				
Lymphoma malignant																									
Mesothelioma malignant																									

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Dermal Study of Diisopropylcarbodiimide: 40 mg/kg

Number of Days on Study	6 3 4	6 6 7	6 6 9	6 7 6	6 8 3	6 9 1	7 0 4	7 0 6	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	1 8 4	1 5 8	1 7 1	1 7 7	1 8 8	1 7 6	1 7 9	1 5 7	1 6 1	1 6 3	1 6 8	1 6 9	1 9 0	1 9 5	1 5 9	1 6 0	1 6 6	1 7 5	1 7 8	1 9 6	1 5 2	1 5 3	1 6 4	1 8 1	1 8 2	Total Tissues/ Tumors
Special Senses System																										
Ear																										1
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lacrimal gland																										1
Zymbal's gland																										1
Carcinoma																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	49
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear					X			X	X											X			X			6
Lymphoma malignant																		X								1
Mesothelioma malignant	X																									1

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Dermal Study of Diisopropylcarbodiimide

	Vehicle Control	10 mg/kg	20 mg/kg	40 mg/kg
Adrenal Medulla: Benign Pheochromocytoma				
Overall rate[a]	3/50 (6%)	2/48 (4%)	8/50 (16%)	7/50 (14%)
Adjusted rate[b]	7.5%	5.0%	18.0%	24.2%
Terminal rate[c]	2/20 (10%)	2/29 (7%)	8/32 (25%)	4/17 (24%)
First incidence (days)	716	729 (T)	729 (T)	630
Poly-3 test[d]	P=0.012	P=0.506N	P=0.130	P=0.055
Adrenal Medulla: Malignant Pheochromocytoma				
Overall rate	4/50 (8%)	4/48 (8%)	4/50 (8%)	2/50 (4%)
Adjusted rate	9.9%	10.1%	8.8%	7.1%
Terminal rate	0/20 (0%)	4/29 (14%)	2/32 (6%)	2/17 (12%)
First incidence (days)	688	729 (T)	563	729 (T)
Poly-3 test	P=0.396N	P=0.634	P=0.582N	P=0.511N
Adrenal Medulla: Benign, Complex, or Malignant Pheochromocytoma				
Overall rate	6/50 (12%)	6/48 (13%)	12/50 (24%)	9/50 (18%)
Adjusted rate	14.8%	15.1%	26.5%	31.1%
Terminal rate	2/20 (10%)	6/29 (21%)	10/32 (31%)	6/17 (35%)
First incidence (days)	688	729 (T)	563	630
Poly-3 test	P=0.038	P=0.609	P=0.142	P=0.093
Mammary Gland: Fibroadenoma				
Overall rate	0/50 (0%)	4/50 (8%)	1/50 (2%)	1/50 (2%)
Adjusted rate	0.0%	9.6%	2.3%	3.5%
Terminal rate	0/20 (0%)	3/30 (10%)	1/32 (3%)	1/17 (6%)
First incidence (days)	—[e]	682	729 (T)	729 (T)
Poly-3 test	P=0.509	P=0.065	P=0.520	P=0.432
Mammary Gland: Fibroadenoma or Carcinoma				
Overall rate	0/50 (0%)	4/50 (8%)	2/50 (4%)	1/50 (2%)
Adjusted rate	0.0%	9.6%	4.5%	3.5%
Terminal rate	0/20 (0%)	3/30 (10%)	1/32 (3%)	1/17 (6%)
First incidence (days)	—	682	645	729 (T)
Poly-3 test	P=0.432	P=0.065	P=0.262	P=0.432
Pancreas: Adenoma				
Overall rate	3/50 (6%)	1/50 (2%)	2/50 (4%)	0/50 (0%)
Adjusted rate	7.5%	2.4%	4.5%	0.0%
Terminal rate	3/20 (15%)	1/30 (3%)	1/32 (3%)	0/17 (0%)
First incidence (days)	729 (T)	729 (T)	563	—
Poly-3 test	P=0.150N	P=0.292N	P=0.449N	P=0.194N
Pancreatic Islets: Adenoma				
Overall rate	5/50 (10%)	12/50 (24%)	10/50 (20%)	5/50 (10%)
Adjusted rate	12.2%	28.6%	22.0%	17.0%
Terminal rate	2/20 (10%)	11/30 (37%)	6/32 (19%)	3/17 (18%)
First incidence (days)	608	617	563	513
Poly-3 test	P=0.414	P=0.054	P=0.178	P=0.412
Pancreatic Islets: Adenoma or Carcinoma				
Overall rate	7/50 (14%)	13/50 (26%)	11/50 (22%)	5/50 (10%)
Adjusted rate	17.1%	30.9%	24.2%	17.0%
Terminal rate	4/20 (20%)	12/30 (40%)	7/32 (22%)	3/17 (18%)
First incidence (days)	608	617	563	513
Poly-3 test	P=0.484N	P=0.107	P=0.291	P=0.622N

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Dermal Study of Diisopropylcarbodiimide

	Vehicle Control	10 mg/kg	20 mg/kg	40 mg/kg
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	29/50 (58%)	33/50 (66%)	42/50 (84%)	20/50 (40%)
Adjusted rate	63.8%	69.9%	84.9%	63.4%
Terminal rate	14/20 (70%)	19/30 (63%)	27/32 (84%)	12/17 (71%)
First incidence (days)	522	444	444	290
Poly-3 test	P=0.262	P=0.338	P=0.011	P=0.582N
Pituitary Gland (Pars Distalis): Carcinoma				
Overall rate	5/50 (10%)	1/50 (2%)	0/50 (0%)	2/50 (4%)
Adjusted rate	12.0%	2.4%	0.0%	7.1%
Terminal rate	1/20 (5%)	0/30 (0%)	0/32 (0%)	2/17 (12%)
First incidence (days)	463	542	—	729 (T)
Poly-3 test	P=0.143N	P=0.097N	P=0.025N	P=0.397N
Pituitary Gland (Pars Distalis): Adenoma or Carcinoma				
Overall rate	34/50 (68%)	34/50 (68%)	42/50 (84%)	22/50 (44%)
Adjusted rate	72.5%	71.1%	84.9%	69.7%
Terminal rate	15/20 (75%)	19/30 (63%)	27/32 (84%)	14/17 (82%)
First incidence (days)	463	444	444	290
Poly-3 test	P=0.376	P=0.534N	P=0.095	P=0.496N
Pituitary Gland (Pars Intermedia): Adenoma or Carcinoma				
Overall rate	3/50 (6%)	0/50 (0%)	0/50 (0%)	0/50 (0%)
Adjusted rate	7.3%	0.0%	0.0%	0.0%
Terminal rate	1/20 (5%)	0/30 (0%)	0/32 (0%)	0/17 (0%)
First incidence (days)	533	—	—	—
Poly-3 test	P=0.033N	P=0.115N	P=0.105N	P=0.199N
Preputial Gland: Adenoma				
Overall rate	1/50 (2%)	1/50 (2%)	1/50 (2%)	4/50 (8%)
Adjusted rate	2.5%	2.4%	2.3%	13.8%
Terminal rate	1/20 (5%)	1/30 (3%)	1/32 (3%)	2/17 (12%)
First incidence (days)	729 (T)	729 (T)	729 (T)	607
Poly-3 test	P=0.046	P=0.753N	P=0.738N	P=0.097
Preputial Gland: Adenoma or Carcinoma				
Overall rate	2/50 (4%)	3/50 (6%)	1/50 (2%)	4/50 (8%)
Adjusted rate	5.0%	7.1%	2.3%	13.8%
Terminal rate	1/20 (5%)	1/30 (3%)	1/32 (3%)	2/17 (12%)
First incidence (days)	714	621	729 (T)	607
Poly-3 test	P=0.220	P=0.520	P=0.466N	P=0.203
Skin: Keratoacanthoma				
Overall rate	3/50 (6%)	1/50 (2%)	3/50 (6%)	1/50 (2%)
Adjusted rate	7.4%	2.4%	6.8%	3.5%
Terminal rate	1/20 (5%)	1/30 (3%)	3/32 (9%)	1/17 (6%)
First incidence (days)	662	729 (T)	729 (T)	729 (T)
Poly-3 test	P=0.430N	P=0.294N	P=0.619N	P=0.441N
Skin: Squamous Cell Papilloma or Keratoacanthoma				
Overall rate	4/50 (8%)	2/50 (4%)	4/50 (8%)	1/50 (2%)
Adjusted rate	9.8%	4.8%	9.0%	3.5%
Terminal rate	1/20 (5%)	2/30 (7%)	4/32 (13%)	1/17 (6%)
First incidence (days)	662	729 (T)	729 (T)	729 (T)
Poly-3 test	P=0.314N	P=0.325N	P=0.594N	P=0.307N

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Dermal Study of Diisopropylcarbodiimide

	Vehicle Control	10 mg/kg	20 mg/kg	40 mg/kg
Skin (Subcutaneous Tissue): Lipoma				
Overall rate	0/50 (0%)	3/50 (6%)	1/50 (2%)	0/50 (0%)
Adjusted rate	0.0%	7.2%	2.3%	0.0%
Terminal rate	0/20 (0%)	3/30 (10%)	1/32 (3%)	0/17 (0%)
First incidence (days)	—	729 (T)	729 (T)	—
Poly-3 test	P=0.466N	P=0.124	P=0.520	—[f]
Skin (Subcutaneous Tissue): Fibroma				
Overall rate	5/50 (10%)	4/50 (8%)	2/50 (4%)	3/50 (6%)
Adjusted rate	12.2%	9.6%	4.5%	10.3%
Terminal rate	2/20 (10%)	3/30 (10%)	2/32 (6%)	0/17 (0%)
First incidence (days)	608	682	729 (T)	606
Poly-3 test	P=0.330N	P=0.486N	P=0.183N	P=0.549N
Skin (Subcutaneous Tissue): Fibroma or Fibrosarcoma				
Overall rate	5/50 (10%)	4/50 (8%)	3/50 (6%)	3/50 (6%)
Adjusted rate	12.2%	9.6%	6.7%	10.3%
Terminal rate	2/20 (10%)	3/30 (10%)	2/32 (6%)	0/17 (0%)
First incidence (days)	608	682	649	606
Poly-3 test	P=0.382N	P=0.486N	P=0.308N	P=0.549N
Testes: Adenoma				
Overall rate	36/50 (72%)	37/50 (74%)	31/50 (62%)	22/50 (44%)
Adjusted rate	79.8%	82.4%	66.5%	73.0%
Terminal rate	18/20 (90%)	26/30 (87%)	22/32 (69%)	15/17 (88%)
First incidence (days)	533	571	444	606
Poly-3 test	P=0.111N	P=0.479	P=0.101N	P=0.330N
Thyroid Gland (C-cell): Adenoma				
Overall rate	5/50 (10%)	9/50 (18%)	8/50 (16%)	4/50 (8%)
Adjusted rate	12.4%	20.9%	17.8%	13.9%
Terminal rate	4/20 (20%)	4/30 (13%)	5/32 (16%)	3/17 (18%)
First incidence (days)	701	593	645	607
Poly-3 test	P=0.508	P=0.227	P=0.349	P=0.569
Thyroid Gland (C-cell): Carcinoma				
Overall rate	5/50 (10%)	1/50 (2%)	2/50 (4%)	0/50 (0%)
Adjusted rate	12.3%	2.4%	4.5%	0.0%
Terminal rate	3/20 (15%)	1/30 (3%)	2/32 (6%)	0/17 (0%)
First incidence (days)	593	729 (T)	729 (T)	—
Poly-3 test	P=0.038N	P=0.094N	P=0.181N	P=0.075N
Thyroid Gland (C-cell): Adenoma or Carcinoma				
Overall rate	10/50 (20%)	10/50 (20%)	9/50 (18%)	4/50 (8%)
Adjusted rate	24.5%	23.2%	20.0%	13.9%
Terminal rate	7/20 (35%)	5/30 (17%)	6/32 (19%)	3/17 (18%)
First incidence (days)	593	593	645	607
Poly-3 test	P=0.172N	P=0.548N	P=0.405N	P=0.222N
All Organs: Mononuclear Cell Leukemia				
Overall rate	13/50 (26%)	22/50 (44%)	13/50 (26%)	6/50 (12%)
Adjusted rate	30.2%	48.3%	28.2%	20.7%
Terminal rate	3/20 (15%)	12/30 (40%)	6/32 (19%)	3/17 (18%)
First incidence (days)	522	522	556	606
Poly-3 test	P=0.112N	P=0.059	P=0.507N	P=0.270N

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Dermal Study of Diisopropylcarbodiimide

	Vehicle Control	10 mg/kg	20 mg/kg	40 mg/kg
All Organs: Malignant Mesothelioma				
Overall rate	1/50 (2%)	2/50 (4%)	4/50 (8%)	1/50 (2%)
Adjusted rate	2.5%	4.7%	9.0%	3.5%
Terminal rate	0/20 (0%)	0/30 (0%)	2/32 (6%)	0/17 (0%)
First incidence (days)	657	601	694	634
Poly-3 test	P=0.358	P=0.516	P=0.209	P=0.678
All Organs: Benign Neoplasms				
Overall rate	47/50 (94%)	48/50 (96%)	50/50 (100%)	32/50 (64%)
Adjusted rate	97.2%	98.6%	100.0%	95.8%
Terminal rate	20/20 (100%)	30/30 (100%)	32/32 (100%)	17/17 (100%)
First incidence (days)	522	444	444	290
Poly-3 test	P=0.602N	P=0.637	P=0.321	P=0.677N
All Organs: Malignant Neoplasms				
Overall rate	34/50 (68%)	31/50 (62%)	27/50 (54%)	15/50 (30%)
Adjusted rate	72.1%	64.3%	56.9%	49.0%
Terminal rate	12/20 (60%)	14/30 (47%)	15/32 (47%)	9/17 (53%)
First incidence (days)	463	485	556	319
Poly-3 test	P=0.020N	P=0.274N	P=0.086N	P=0.032N
All Organs: Benign or Malignant Neoplasms				
Overall rate	50/50 (100%)	50/50 (100%)	50/50 (100%)	33/50 (66%)
Adjusted rate	100.0%	100.0%	100.0%	96.2%
Terminal rate	20/20 (100%)	30/30 (100%)	32/32 (100%)	17/17 (100%)
First incidence (days)	463	444	444	290
Poly-3 test	P<0.001N	—	—	P=0.131N

(T) Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, pancreas, 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 is the P value 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 A4
Historical Incidence of Adrenal Gland Pheochromocytoma in Control Male F344/N Rats[a]

Study	Incidence in Controls			
	Benign	Complex	Malignant	Benign, Complex Malignant, or NOS
Historical Incidence: All Routes				
Benzophenone (feed)	8/50	0/50	0/50	8/50
Bromodichloromethane (drinking water)	8/50	2/50	1/50	11/50
trans-Cinnamaldehyde (feed)	5/100	0/100	0/100	5/100
Citral (feed)	10/100	1/100	0/100	11/100
Decalin (inhalation)	7/49	0/49	2/49	8/49
Dibromoacetic acid (drinking water)	7/49	0/49	0/49	7/49
p,p′-Dichlorodiphenyl sulfone (feed)	4/50	0/50	2/50	6/50
Diisopropylcarbodiimide (dermal)	3/50	0/50	4/50	6/50
Dipropylene glycol (drinking water)	4/47	0/47	5/47	9/47
Divinylbenzene (inhalation)	12/50	0/50	1/50	13/50
Elmiron® (gavage)	7/50	0/50	1/50	7/50
2,4-Hexadienal (gavage)	7/50	0/50	0/50	7/50
Indium phosphide (inhalation)	10/50	0/50	0/50	10/50
60-Hz Magnetic fields (whole body exposure)	24/98	0/98	2/98	26/98
Methacrylonitrile (gavage)	3/50	0/50	1/50	4/50
2-Methylimidazole (feed)	8/50	0/50	0/50	8/50
4-Methylimidazole (feed)	8/50	2/50	0/50	10/50
Methyl isobutyl ketone (inhalation)	8/50	0/50	0/50	8/50
Naphthalene (inhalation)	4/49	0/49	1/49	5/49
o-Nitrotoluene (feed)	2/60	0/60	2/60	4/60
p-Nitrotoluene (feed)	3/50	0/50	0/50	3/50
Propylene glycol mono-*t*-butyl ether (inhalation)	12/50	0/50	2/50	14/50
Sodium chlorate (drinking water)	6/49	0/49	3/49	9/49
Sodium nitrite (drinking water)	6/50	0/50	1/50	7/50
Stoddard Solvent IIC (inhalation)	5/50	0/50	1/50	6/50
Vanadium pentoxide (inhalation)	4/50	0/50	1/50	5/50
Overall Historical Incidence: All Routes				
Total (%)	185/1,451 (12.8%)	5/1,451 (0.3%)	30/1,451 (2.1%)	217/1,451 (15.0%)
Mean ± standard deviation	12.8% ± 6.0%	0.4% ± 1.1%	2.2% ± 2.7%	15.1% ± 6.2%
Range	3%-24%	0%-4%	0%-11%	5%-28%

[a] Data as of January 28, 2005; the current study of diisopropylcarbodiimide is the only dermal study in the historical database

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

	Vehicle Control	10 mg/kg	20 mg/kg	40 mg/kg
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Moribund	18	12	10	23
Natural deaths	12	8	8	10
Survivors				
Terminal sacrifice	20	30	32	17
Animals examined microscopically	50	50	50	50
Alimentary System				
Intestine large, colon	(50)	(50)	(50)	(50)
Inflammation, chronic active		1 (2%)		
Intestine large, cecum	(50)	(50)	(50)	(49)
Edema	1 (2%)	2 (4%)	4 (8%)	2 (4%)
Hemorrhage			1 (2%)	
Ulcer	1 (2%)			
Intestine small, duodenum	(49)	(49)	(49)	(49)
Epithelium, hyperplasia		1 (2%)	2 (4%)	1 (2%)
Liver	(50)	(50)	(50)	(50)
Angiectasis	2 (4%)	2 (4%)	1 (2%)	1 (2%)
Basophilic focus	14 (28%)	14 (28%)	22 (44%)	9 (18%)
Clear cell focus	16 (32%)	11 (22%)	14 (28%)	8 (16%)
Cyst				1 (2%)
Degeneration, cystic	3 (6%)	5 (10%)	4 (8%)	
Eosinophilic focus	6 (12%)	2 (4%)	7 (14%)	4 (8%)
Hemorrhage			2 (4%)	1 (2%)
Hepatodiaphragmatic nodule	5 (10%)	5 (10%)	7 (14%)	8 (16%)
Infiltration cellular, mixed cell		2 (4%)	4 (8%)	
Metaplasia, atypical				1 (2%)
Mixed cell focus	4 (8%)	6 (12%)	6 (12%)	4 (8%)
Necrosis, focal		1 (2%)	1 (2%)	
Regeneration		1 (2%)	1 (2%)	
Bile duct, hyperplasia	33 (66%)	36 (72%)	31 (62%)	17 (34%)
Centrilobular, necrosis	4 (8%)	3 (6%)	2 (4%)	
Hepatocyte, vacuolization cytoplasmic	6 (12%)	6 (12%)	7 (14%)	1 (2%)
Kupffer cell, pigmentation		2 (4%)		
Mesentery	(9)	(9)	(12)	(6)
Accessory spleen	1 (11%)			
Fat, necrosis	7 (78%)	6 (67%)	8 (67%)	3 (50%)
Pancreas	(50)	(50)	(50)	(50)
Atrophy	18 (36%)	28 (56%)	32 (64%)	21 (42%)
Cyst	2 (4%)	3 (6%)	5 (10%)	3 (6%)
Hemorrhage			1 (2%)	
Acinus, cytoplasmic alteration		1 (2%)	1 (2%)	1 (2%)
Acinus, hyperplasia, focal	2 (4%)	5 (10%)	4 (8%)	
Salivary glands	(49)	(50)	(50)	(50)
Atrophy	1 (2%)		1 (2%)	2 (4%)
Necrosis		1 (2%)	1 (2%)	

[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 Dermal Study of Diisopropylcarbodiimide

	Vehicle Control	10 mg/kg	20 mg/kg	40 mg/kg
Alimentary System (continued)				
Stomach, forestomach	(50)	(50)	(50)	(49)
Diverticulum		1 (2%)		
Edema	3 (6%)	3 (6%)	5 (10%)	2 (4%)
Erosion	1 (2%)	1 (2%)	1 (2%)	
Inflammation, chronic	2 (4%)	1 (2%)		2 (4%)
Perforation	1 (2%)		1 (2%)	
Ulcer	7 (14%)	6 (12%)	6 (12%)	2 (4%)
Epithelium, hyperplasia	7 (14%)	6 (12%)	8 (16%)	5 (10%)
Stomach, glandular	(50)	(50)	(50)	(49)
Cyst		1 (2%)	1 (2%)	
Edema		2 (4%)		
Erosion	7 (14%)	6 (12%)	3 (6%)	3 (6%)
Inflammation, chronic	1 (2%)	1 (2%)		
Ulcer	4 (8%)	2 (4%)	3 (6%)	1 (2%)
Glands, hyperplasia	2 (4%)		1 (2%)	1 (2%)
Cardiovascular System				
Heart	(50)	(50)	(50)	(50)
Cardiomyopathy	41 (82%)	44 (88%)	44 (88%)	36 (72%)
Inflammation, chronic		1 (2%)	1 (2%)	
Thrombosis	5 (10%)	1 (2%)	5 (10%)	
Endocrine System				
Adrenal cortex	(50)	(49)	(50)	(50)
Accessory adrenal cortical nodule	17 (34%)	16 (33%)	16 (32%)	9 (18%)
Degeneration, fatty	12 (24%)	11 (22%)	15 (30%)	8 (16%)
Hyperplasia, diffuse	1 (2%)			
Hyperplasia, focal	8 (16%)	8 (16%)	5 (10%)	5 (10%)
Hypertrophy, focal	3 (6%)	2 (4%)	7 (14%)	3 (6%)
Adrenal medulla	(50)	(48)	(50)	(50)
Hyperplasia	7 (14%)	9 (19%)	16 (32%)	3 (6%)
Islets, pancreatic	(50)	(50)	(50)	(50)
Hyperplasia	2 (4%)			
Parathyroid gland	(49)	(48)	(49)	(48)
Hyperplasia		1 (2%)		
Hyperplasia, focal				1 (2%)
Pituitary gland	(50)	(50)	(50)	(50)
Pars distalis, angiectasis		4 (8%)	1 (2%)	2 (4%)
Pars distalis, cyst	2 (4%)	3 (6%)	1 (2%)	1 (2%)
Pars distalis, hyperplasia, focal	3 (6%)	7 (14%)	7 (14%)	5 (10%)
Pars intermedia, cyst		1 (2%)	1 (2%)	1 (2%)
Thyroid gland	(50)	(50)	(50)	(50)
Ultimobranchial cyst	1 (2%)			2 (4%)
C-cell, hyperplasia	8 (16%)	12 (24%)	3 (6%)	3 (6%)
Follicle, cyst	4 (8%)	5 (10%)	2 (4%)	3 (6%)
Follicular cell, hyperplasia	3 (6%)		1 (2%)	
General Body System				
None				

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Dermal Study of Diisopropylcarbodiimide

	Vehicle Control	10 mg/kg	20 mg/kg	40 mg/kg
Genital System				
Epididymis	(50)	(50)	(50)	(50)
Granuloma sperm				1 (2%)
Preputial gland	(50)	(50)	(50)	(50)
Cyst		2 (4%)	2 (4%)	1 (2%)
Hyperplasia	2 (4%)			1 (2%)
Inflammation, chronic	18 (36%)	26 (52%)	17 (34%)	9 (18%)
Prostate	(50)	(50)	(50)	(50)
Inflammation, chronic	40 (80%)	32 (64%)	35 (70%)	25 (50%)
Epithelium, hyperplasia	4 (8%)	10 (20%)	2 (4%)	3 (6%)
Testes	(50)	(50)	(50)	(50)
Germinal epithelium, atrophy	12 (24%)	11 (22%)	24 (48%)	14 (28%)
Interstitial cell, hyperplasia	6 (12%)	6 (12%)	8 (16%)	8 (16%)
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(50)
Hyperplasia	3 (6%)	7 (14%)	3 (6%)	1 (2%)
Infiltration cellular, histiocyte			1 (2%)	1 (2%)
Myelofibrosis	2 (4%)	1 (2%)		
Lymph node	(18)	(14)	(16)	(13)
Mediastinal, ectasia	3 (17%)	1 (7%)	1 (6%)	
Mediastinal, hemorrhage	2 (11%)	1 (7%)	4 (25%)	6 (46%)
Mediastinal, hyperplasia, lymphoid	7 (39%)	5 (36%)	5 (31%)	7 (54%)
Mediastinal, pigmentation	2 (11%)	3 (21%)	5 (31%)	3 (23%)
Pancreatic, ectasia			1 (6%)	
Pancreatic, hemorrhage	2 (11%)		2 (13%)	2 (15%)
Pancreatic, hyperplasia, lymphoid		1 (7%)	2 (13%)	
Pancreatic, pigmentation	1 (6%)	1 (7%)		3 (23%)
Lymph node, mandibular		(1)	(4)	(1)
Ectasia			2 (50%)	
Hemorrhage				1 (100%)
Lymph node, mesenteric	(50)	(50)	(50)	(50)
Ectasia	3 (6%)	5 (10%)	3 (6%)	1 (2%)
Hemorrhage	10 (20%)	3 (6%)	11 (22%)	6 (12%)
Hyperplasia, lymphoid	18 (36%)	15 (30%)	20 (40%)	15 (30%)
Pigmentation	15 (30%)	8 (16%)	16 (32%)	12 (24%)
Spleen	(50)	(50)	(50)	(50)
Fibrosis	2 (4%)	3 (6%)	2 (4%)	2 (4%)
Hematopoietic cell proliferation	10 (20%)	9 (18%)	11 (22%)	4 (8%)
Hemorrhage		1 (2%)		
Necrosis	2 (4%)	1 (2%)	1 (2%)	1 (2%)
Pigmentation	9 (18%)	5 (10%)	6 (12%)	25 (50%)
Lymphoid follicle, atrophy	1 (2%)		1 (2%)	2 (4%)
Lymphoid follicle, hyperplasia		1 (2%)		1 (2%)
Thymus	(49)	(46)	(46)	(49)
Hemorrhage	1 (2%)			5 (10%)

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Dermal Study of Diisopropylcarbodiimide

	Vehicle Control	10 mg/kg	20 mg/kg	40 mg/kg
Integumentary System				
Mammary gland	(49)	(48)	(47)	(48)
Hyperplasia	31 (63%)	25 (52%)	29 (62%)	10 (21%)
Skin	(49)	(50)	(50)	(50)
Cyst epithelial inclusion		4 (8%)	2 (4%)	
Inflammation, chronic	5 (10%)	1 (2%)	2 (4%)	2 (4%)
Ulcer	4 (8%)	5 (10%)	5 (10%)	4 (8%)
Epidermis, hyperplasia	9 (18%)	7 (14%)	8 (16%)	6 (12%)
Epidermis, skin, site of application, hyperplasia	1 (2%)	10 (20%)	29 (58%)	19 (38%)
Skin, site of application, erosion			1 (2%)	
Skin, site of application, inflammation, chronic		6 (12%)	12 (24%)	11 (22%)
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Cranium, osteopetrosis				1 (2%)
Femur, osteopetrosis	1 (2%)			
Nervous System				
Brain	(50)	(50)	(50)	(50)
Compression	16 (32%)	10 (20%)	15 (30%)	4 (8%)
Hydrocephalus	7 (14%)	1 (2%)	5 (10%)	2 (4%)
Hemorrhage	1 (2%)		3 (6%)	11 (22%)
Gliosis			1 (2%)	2 (4%)
Arteriole, necrosis, fibrinoid				5 (10%)
Neuron, necrosis		1 (2%)		16 (32%)
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Edema	2 (4%)	2 (4%)		2 (4%)
Hemorrhage	6 (12%)	6 (12%)	7 (14%)	17 (34%)
Infiltration cellular, histiocyte	21 (42%)	19 (38%)	21 (42%)	12 (24%)
Inflammation, chronic	9 (18%)	13 (26%)	16 (32%)	12 (24%)
Metaplasia, osseous		2 (4%)	2 (4%)	1 (2%)
Alveolar epithelium, hyperplasia	10 (20%)	4 (8%)	6 (12%)	6 (12%)
Nose	(50)	(50)	(50)	(50)
Foreign body	13 (26%)	22 (44%)	12 (24%)	12 (24%)
Inflammation, chronic	15 (30%)	22 (44%)	13 (26%)	11 (22%)
Respiratory epithelium, hyperplasia	11 (22%)	11 (22%)	8 (16%)	9 (18%)
Respiratory epithelium, metaplasia, squamous	2 (4%)			1 (2%)
Special Senses System				
Eye	(50)	(50)	(50)	(50)
Cataract		1 (2%)	2 (4%)	1 (2%)
Cornea, hyperplasia			1 (2%)	5 (10%)
Cornea, inflammation, chronic		1 (2%)	5 (10%)	23 (46%)
Cornea, ulcer				1 (2%)
Retina, degeneration	4 (8%)	1 (2%)	6 (12%)	3 (6%)
Harderian gland	(50)	(50)	(50)	(50)
Hyperplasia, focal		1 (2%)		1 (2%)
Inflammation, chronic		1 (2%)	1 (2%)	

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Dermal Study of Diisopropylcarbodiimide

	Vehicle Control	10 mg/kg	20 mg/kg	40 mg/kg
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Cyst				1 (2%)
Inflammation, chronic	3 (6%)	5 (10%)	9 (18%)	1 (2%)
Nephropathy	43 (86%)	46 (92%)	42 (84%)	30 (60%)
Renal tubule, accumulation, hyaline droplet		1 (2%)		
Renal tubule, dilatation		1 (2%)		1 (2%)
Renal tubule, hyperplasia	1 (2%)			
Renal tubule, necrosis	2 (4%)		2 (4%)	
Renal tubule, pigmentation	2 (4%)	4 (8%)		
Transitional epithelium, hyperplasia			1 (2%)	
Urethra			(1)	
Angiectasis			1 (100%)	
Urinary bladder	(50)	(50)	(50)	(49)
Hemorrhage			1 (2%)	3 (6%)
Inflammation, chronic			2 (4%)	4 (8%)
Transitional epithelium, hyperplasia			1 (2%)	

APPENDIX B
SUMMARY OF LESIONS IN FEMALE RATS IN THE 2-YEAR DERMAL STUDY OF DIISOPROPYLCARBODIIMIDE

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

	Vehicle Control	10 mg/kg	20 mg/kg	40 mg/kg
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Moribund	13	9	10	14
Natural deaths	7	9	8	10
Survivors				
Terminal sacrifice	30	32	32	25
Other				1
Animals examined microscopically	50	50	50	49
Alimentary System				
Intestine large, colon	(50)	(50)	(49)	(49)
Intestine large, cecum	(50)	(50)	(50)	(49)
Intestine small, duodenum	(49)	(50)	(50)	(49)
Leiomyoma				1 (2%)
Intestine small, jejunum	(47)	(50)	(50)	(46)
Intestine small, ileum	(48)	(49)	(50)	(49)
Liver	(50)	(50)	(50)	(49)
Carcinoma, metastatic, thyroid gland				1 (2%)
Hepatocellular adenoma	6 (12%)	1 (2%)	2 (4%)	1 (2%)
Mesentery	(11)	(12)	(9)	(9)
Fibrosarcoma			1 (11%)	
Oral mucosa	(1)		(2)	
Squamous cell carcinoma	1 (100%)		1 (50%)	
Pancreas	(50)	(50)	(50)	(49)
Salivary glands	(50)	(50)	(50)	(48)
Stomach, forestomach	(50)	(50)	(50)	(49)
Squamous cell papilloma			1 (2%)	
Stomach, glandular	(50)	(50)	(50)	(49)
Tongue	(2)		(1)	
Squamous cell papilloma	2 (100%)		1 (100%)	
Cardiovascular System				
Heart	(50)	(50)	(50)	(49)
Carcinoma, metastatic, thyroid gland				1 (2%)
Schwannoma malignant	1 (2%)			
Endocrine System				
Adrenal cortex	(50)	(50)	(50)	(49)
Adenoma	3 (6%)			1 (2%)
Adrenal medulla	(49)	(50)	(50)	(49)
Pheochromocytoma malignant				1 (2%)
Pheochromocytoma benign		1 (2%)	1 (2%)	1 (2%)
Islets, pancreatic	(50)	(50)	(50)	(49)
Adenoma				2 (4%)
Pituitary gland	(50)	(50)	(50)	(49)
Pars distalis, adenoma	28 (56%)	32 (64%)	30 (60%)	24 (49%)
Pars distalis, adenoma, multiple	5 (10%)	2 (4%)	3 (6%)	3 (6%)
Pars distalis, carcinoma	3 (6%)	1 (2%)	1 (2%)	4 (8%)
Pars intermedia, adenoma		1 (2%)		

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Dermal Study of Diisopropylcarbodiimide

	Vehicle Control	10 mg/kg	20 mg/kg	40 mg/kg
Endocrine System (continued)				
Thyroid gland	(50)	(50)	(50)	(49)
C-cell, adenoma	3 (6%)	2 (4%)	6 (12%)	6 (12%)
C-cell, carcinoma	2 (4%)		2 (4%)	3 (6%)
Follicular cell, adenoma		2 (4%)		
Follicular cell, carcinoma	1 (2%)			
General Body System				
None				
Genital System				
Clitoral gland	(50)	(49)	(50)	(49)
Adenoma	2 (4%)	3 (6%)	5 (10%)	2 (4%)
Carcinoma	2 (4%)	6 (12%)		2 (4%)
Carcinoma, multiple			1 (2%)	
Ovary	(50)	(50)	(50)	(49)
Uterus	(50)	(50)	(50)	(49)
Carcinoma				2 (4%)
Leiomyoma	1 (2%)			1 (2%)
Polyp stromal	10 (20%)	10 (20%)	9 (18%)	9 (18%)
Polyp stromal, multiple			1 (2%)	1 (2%)
Sarcoma				1 (2%)
Vagina	(6)	(6)	(5)	(11)
Granular cell tumor benign		1 (17%)		
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(49)
Lymph node	(13)	(10)	(14)	(8)
Deep cervical, carcinoma, metastatic, thyroid gland	1 (8%)			1 (13%)
Mediastinal, carcinoma, metastatic, thyroid gland	1 (8%)			1 (13%)
Renal, carcinoma, metastatic, thyroid gland				1 (13%)
Lymph node, mandibular	(3)	(7)	(1)	(2)
Lymph node, mesenteric	(50)	(50)	(50)	(48)
Spleen	(50)	(50)	(50)	(49)
Thymus	(50)	(48)	(49)	(46)
Carcinoma, metastatic, thyroid gland				1 (2%)
Integumentary System				
Mammary gland	(50)	(50)	(50)	(48)
Adenoma		1 (2%)	1 (2%)	1 (2%)
Carcinoma	4 (8%)		2 (4%)	
Fibroadenoma	10 (20%)	9 (18%)	20 (40%)	13 (27%)
Fibroadenoma, multiple	2 (4%)	2 (4%)	1 (2%)	3 (6%)
Skin	(50)	(50)	(50)	(49)
Keratoacanthoma	1 (2%)			
Sebaceous gland, adenoma		1 (2%)		
Subcutaneous tissue, fibroma			1 (2%)	3 (6%)
Subcutaneous tissue, fibrosarcoma		2 (4%)		
Subcutaneous tissue, schwannoma malignant	2 (4%)			
Musculoskeletal System				
None				

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Dermal Study of Diisopropylcarbodiimide

	Vehicle Control	10 mg/kg	20 mg/kg	40 mg/kg
Nervous System				
Brain	(50)	(50)	(50)	(49)
Carcinoma, metastatic, pituitary gland	3 (6%)			2 (4%)
Glioma malignant, mixed cell			2 (4%)	1 (2%)
Granular cell tumor benign		1 (2%)		
Respiratory System				
Lung	(50)	(50)	(50)	(49)
Alveolar/bronchiolar adenoma		1 (2%)		
Carcinoma, metastatic, thyroid gland	1 (2%)			1 (2%)
Special Senses System				
Eye	(50)	(50)	(50)	(49)
Iris, amelanotic melanoma, benign	1 (2%)			
Harderian gland	(50)	(50)	(50)	(49)
Adenoma				1 (2%)
Zymbal's gland		(1)		
Carcinoma		1 (100%)		
Urinary System				
Kidney	(50)	(50)	(50)	(49)
Renal tubule, adenoma				1 (2%)
Urinary bladder	(50)	(50)	(50)	(49)
Papilloma			1 (2%)	
Systemic Lesions				
Multiple organs[b]	(50)	(50)	(50)	(49)
Leukemia mononuclear	9 (18%)	9 (18%)	7 (14%)	15 (31%)
Neoplasm Summary				
Total animals with primary neoplasms[c]	48	45	44	45
Total primary neoplasms	99	89	100	103
Total animals with benign neoplasms	44	41	41	39
Total benign neoplasms	74	70	83	74
Total animals with malignant neoplasms	22	14	16	23
Total malignant neoplasms	25	19	17	29
Total animals with metastatic neoplasms	4			3
Total metastatic neoplasms	6			9

[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 Dermal Study of Diisopropylcarbodiimide: Vehicle Control

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

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

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

Number of Days on Study	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	
Carcass ID Number	2 4 3	2 4 8	2 0 6	2 0 7	2 1 3	2 1 5	2 2 5	2 2 8	2 3 0	2 3 7	2 3 8	2 4 1	2 4 2	2 4 4	2 4 5	2 0 3	2 1 1	2 1 2	2 1 9	2 2 0	2 2 2	2 2 6	2 2 7	2 3 5	2 4 7	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma																		X		X						6
Mesentery							+		+					+				+	+		+	+				11
Oral mucosa																										1
Squamous cell carcinoma																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tongue											+														+	2
Squamous cell papilloma											X														X	2
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Schwannoma malignant																										1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma									X																	3
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	M	+	+	+	M	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	45
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma		X	X	X	X		X			X	X	X		X		X	X	X	X	X		X		X	X	28
Pars distalis, adenoma, multiple	X							X	X																	5
Pars distalis, carcinoma																					X					3
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma			X										X										X			3
C-cell, carcinoma																				X						2
Follicular cell, carcinoma																								X		1
General Body System																										
None																										

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

Number of Days on Study	2 4 1	3 5 9	3 9 4	4 3 7	5 3 5	5 5 0	5 5 6	6 0 6	6 2 1	6 2 6	6 3 2	6 3 2	6 5 4	6 6 7	6 7 3	6 7 6	6 8 2	7 0 3	7 1 0	7 2 3	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1
Carcass ID Number	2 2 1	2 4 6	2 0 5	2 5 0	2 1 6	2 3 4	2 4 9	2 1 8	2 0 4	2 3 2	2 2 4	2 3 3	2 3 6	2 0 2	2 0 8	2 1 7	2 0 1	2 2 3	2 2 9	2 0 9	2 1 0	2 1 4	2 3 1	2 3 9	2 4 0
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																								X	
Carcinoma							X																		
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyoma																									
Polyp stromal			X				X				X					X									X
Vagina					+											+		+	+						
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+				+		+							+	+		+	+		+					
Deep cervical, carcinoma, metastatic, thyroid gland																	X								
Mediastinal, carcinoma, metastatic, thyroid gland																	X								
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																			X						
Fibroadenoma									X						X			X							
Fibroadenoma, multiple								X																	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma																									
Subcutaneous tissue, schwannoma, malignant													X												
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, pituitary gland										X				X											
Peripheral nerve					+											+									
Spinal cord					+											+									
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, thyroid gland																	X								
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

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

Number of Days on Study	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	
Carcass ID Number	2 4 3	2 4 8	2 0 6	2 0 7	2 1 3	2 1 5	2 2 5	2 2 8	2 3 0	2 3 7	2 3 8	2 4 1	2 4 2	2 4 4	2 4 5	2 0 3	2 1 1	2 1 2	2 1 9	2 2 0	2 2 2	2 2 6	2 2 7	2 3 5	2 4 7	Total Tissues/ Tumors
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma								X																		2
Carcinoma																				X						2
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyoma		X																								1
Polyp stromal			X			X													X	X					X	10
Vagina		+														+										6
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node					+										+			+		+				+		13
Deep cervical, carcinoma, metastatic, thyroid gland																										1
Mediastinal, carcinoma, metastatic, thyroid gland																										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	M	3
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma				X			X														X					4
Fibroadenoma	X		X				X		X				X								X				X	10
Fibroadenoma, multiple																		X								2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Keratoacanthoma																					X					1
Subcutaneous tissue, schwannoma, malignant																						X				2
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, pituitary gland																					X					3
Peripheral nerve																										2
Spinal cord																										2
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, thyroid gland																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

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

Number of Days on Study	241	359	394	437	535	550	556	606	621	626	632	632	654	667	673	676	682	703	710	723	731	731	731	731	731
Carcass ID Number	22165	24166	20505	25070	21316	23464	24949	21018	20404	23032	22424	23033	23636	20062	20088	21017	21013	22239	22099	20911	21104	21131	23319	23399	24040
Special Senses System																									
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Iris, amelanotic melanoma, benign									X																
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lacrimal gland									+																
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear					X										X	X		X		X	X		X		

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

Number of Days on Study	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	
Carcass ID Number	2 4 3	2 4 8	2 0 6	2 0 7	2 1 3	2 1 5	2 2 5	2 2 8	2 3 0	2 3 7	2 3 8	2 4 1	2 4 2	2 4 4	2 4 5	2 0 3	2 1 1	2 1 2	2 1 9	2 2 0	2 2 2	2 2 6	2 2 7	2 3 5	2 4 7	Total Tissues/ Tumors
Special Senses System																										
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Iris, amelanotic melanoma, benign																										1
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lacrimal gland																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear							X								X											9

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Dermal Study of Diisopropylcarbodiimide: 10 mg/kg

Number of Days on Study	24 8	32 7	34 7	51 3	52 2	52 2	55 4	57 0	59 3	59 5	62 1	65 2	66 9	67 7	70 3	71 2	72 3	72 8	73 1	73 1	73 1	73 1	73 1	73 1	73 1
Carcass ID Number	29 97	26 77	27 00	26 69	25 66	29 55	28 88	25 89	28 66	29 91	28 13	26 65	26 33	29 33	29 90	29 96	29 94	27 77	25 52	25 77	25 58	26 66	26 68	27 72	27 78
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																									
Mesentery											+				+										
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																						X			
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma					X	X	X	X	X	X	X	X	X	X			X	X			X	X		X	
Pars distalis, adenoma, multiple																									
Pars distalis, carcinoma																X									
Pars intermedia, adenoma																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma															X										
Follicular cell, adenoma																									
General Body System																									
None																									
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Carcinoma				X														X							X
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal											X										X	X	X		
Vagina								+			+				+	+									
Granular cell tumor benign																									

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Dermal Study of Diisopropylcarbodiimide: 10 mg/kg

Number of Days on Study	731	731	732	732	732	732	732	732	732	732	732	732	732	732	732	733	733	733	733	733	733	733	733	733	733	
Carcass ID Number	28505	30001	25201	25513	25514	26060	26061	26062	27074	28080	28081	28082	28084	29098	29099	25555	26064	27071	27073	27075	27076	27079	28087	28089	29092	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	48
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma	X																									1
Mesentery				+				+		+	+			+							+	+	+	+		12
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Blood vessel			+																							1
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign																										1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	45
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma	X	X	X		X	X		X			X	X	X	X	X			X	X	X		X		X	X	32
Pars distalis, adenoma, multiple																					X		X			2
Pars distalis, carcinoma																										1
Pars intermedia, adenoma																				X						1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma											X															2
Follicular cell, adenoma																	X								X	2
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma									X									X				X				3
Carcinoma										X		X								X						6
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp stromal		X	X		X				X							X									X	10
Vagina			+																				+			6
Granular cell tumor benign			X																							1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Dermal Study of Diisopropylcarbodiimide: 10 mg/kg

Number of Days on Study	24 8	32 7	34 7	51 3	52 2	52 2	55 4	57 0	59 3	59 5	62 1	65 2	66 9	67 7	70 3	71 2	72 3	72 8	73 1	73 1	73 1	73 1	73 1	73 1	73 1
Carcass ID Number	29 7	26 7	27 0	26 9	25 6	29 5	28 8	25 9	28 6	29 1	28 3	26 5	26 3	29 3	29 0	29 6	29 4	27 7	25 2	25 7	25 8	26 6	26 8	27 2	27 8
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node		+			+										+										
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma														X											
Fibroadenoma																		X	X						
Fibroadenoma, multiple																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sebaceous gland, adenoma																							X		
Subcutaneous tissue, fibrosarcoma															X										
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granular cell tumor benign																									
Peripheral nerve				+	+						+					+									
Spinal cord				+	+						+					+									
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Zymbal's gland																+									
Carcinoma																X									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear											X					X			X		X				

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Dermal Study of Diisopropylcarbodiimide: 10 mg/kg

Number of Days on Study	731	731	732	732	732	732	732	732	732	732	732	732	732	732	732	733	733	733	733	733	733	733	733	733	733	
Carcass ID Number	28585	30010	25051	25533	25544	26060	26061	26062	26074	26080	26081	26082	26084	26098	26099	26555	26644	26711	26713	26755	26763	26799	26877	26899	26902	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+							+	+				+		+	+		+								10
Lymph node, mandibular	M	+	M	M	+	M	M	M	M	M	M	+	M	M	M	M	M	M	M	+	M	M	M	+	M	7
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Fibroadenoma	X					X	X	X								X				X			X			9
Fibroadenoma, multiple					X													X								2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sebaceous gland, adenoma																										1
Subcutaneous tissue, fibrosarcoma																							X			2
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Granular cell tumor benign		X																								1
Peripheral nerve																	+									5
Spinal cord																	+									5
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma															X											1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Zymbal's gland																										1
Carcinoma																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear						X				X	X	X											X			9

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Dermal Study of Diisopropylcarbodiimide: 20 mg/kg

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

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Dermal Study of Diisopropylcarbodiimide: 20 mg/kg

Number of Days on Study	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	
Carcass ID Number	3 0 2	3 1 0	3 1 9	3 2 1	3 2 3	3 3 1	3 3 6	3 3 7	3 4 1	3 4 5	3 4 8	3 0 1	3 0 3	3 0 4	3 0 5	3 1 1	3 1 5	3 1 8	3 2 2	3 2 5	3 3 3	3 3 8	3 4 3	3 4 4	3 5 0	Total Tissues/ Tumors
Alimentary System																												
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	I	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	43
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma									X														X					2
Mesentery							+			+	+								+	+		+						9
Fibrosarcoma										X																		1
Oral mucosa																												2
Squamous cell carcinoma																												1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma																			X									1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tongue													+															1
Squamous cell papilloma													X															1
Cardiovascular System																												
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																												
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign																											X	1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma		X				X	X	X		X	X	X	X	X				X	X		X	X	X	X				30
Pars distalis, adenoma, multiple	X		X																	X								3
Pars distalis, carcinoma									X																			1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma							X													X			X					6
C-cell, carcinoma													X															2
General Body System																												
None																												
Genital System																												
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma										X						X			X				X					5
Carcinoma, multiple																												1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp stromal		X	X			X					X					X												9
Polyp stromal, multiple																												1
Vagina														+														5

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Dermal Study of Diisopropylcarbodiimide: 20 mg/kg

Number of Days on Study	3 8 4	4 6 5	5 3 5	5 3 5	5 3 6	5 7 0	6 0 6	6 4 1	6 4 6	6 4 9	6 8 2	6 8 4	6 8 6	6 9 0	7 0 1	7 0 3	7 1 2	7 2 3	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1
Carcass ID Number	3 2 4	3 1 4	3 2 0	3 4 2	3 4 9	3 0 7	3 3 0	3 4 0	3 2 9	3 4 6	3 0 8	3 3 4	3 3 2	3 3 9	3 4 7	3 2 7	3 1 6	3 2 6	3 0 6	3 0 9	3 1 2	3 1 3	3 1 7	3 2 8	3 3 5
Hematopoietic System																								
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node			+	+		+	+						+				+							+
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																								
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																								
Carcinoma													X											
Fibroadenoma		X													X	X					X	X		X
Fibroadenoma, multiple							X																	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibroma																								
Musculoskeletal System																								
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																					+			
Nervous System																								
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Glioma malignant, mixed cell		X																						
Peripheral nerve												+		+				+			+			
Spinal cord												+		+				+			+			
Respiratory System																								
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																								
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary System																								
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma																								
Systemic Lesions																								
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear				X						X						X	X							

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Dermal Study of Diisopropylcarbodiimide: 20 mg/kg

Number of Days on Study	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	
Carcass ID Number	3 0 2	3 1 0	3 1 9	3 2 1	3 2 3	3 3 1	3 3 6	3 3 7	3 4 1	3 4 5	3 4 8	3 0 1	3 0 3	3 0 4	3 0 5	3 1 1	3 1 5	3 1 8	3 2 2	3 2 5	3 3 3	3 3 8	3 4 3	3 4 4	3 5 0	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+			+	+				+					+						+		+				14
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
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																								X		1
Carcinoma																								X		2
Fibroadenoma		X	X		X	X		X			X	X		X					X	X	X	X	X	X		20
Fibroadenoma, multiple																										1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, fibroma										X																1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																									+	2
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Glioma malignant, mixed cell												X														2
Peripheral nerve								+								+									+	7
Spinal cord								+								+									+	7
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Papilloma													X													1
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear									X					X											X	7

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Dermal Study of Diisopropylcarbodiimide: 40 mg/kg

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

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Dermal Study of Diisopropylcarbodiimide: 40 mg/kg

Number of Days on Study	729	729	729	729	729	731	731	731	732	732	732	732	732	732	732	733	733	733	733	733	733	733	733	733	733	
Carcass ID Number	35 1	35 3	37 7	38 0	39 1	35 4	35 8	38 2	35 2	37 8	38 5	38 6	38 7	39 4	39 5	35 6	36 1	36 4	36 8	37 2	38 9	39 6	39 7	39 8	39 9	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	I	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	44
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leiomyoma										X																1
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma, metastatic, thyroid gland																										1
Hepatocellular adenoma																		X								1
Mesentery	+											+	+				+		+					+	+	9
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	48
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma, metastatic, thyroid gland																										1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma							X																			1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma malignant																										1
Pheochromocytoma benign																										1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma										X																2
Parathyroid gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma	X	X					X	X	X		X	X	X	X	X			X				X	X		X	24
Pars distalis, adenoma, multiple										X							X									3
Pars distalis, carcinoma			X																							4
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
C-cell, adenoma									X							X	X									6
C-cell, carcinoma																										3
General Body System																										
None																										

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Dermal Study of Diisopropylcarbodiimide: 40 mg/kg

Number of Days on Study	4 4 6	4 5 6	4 6 9	5 5 9	5 8 7	5 9 3	5 9 3	6 0 1	6 1 7	6 1 7	6 2 7	6 4 6	6 6 2	6 6 3	6 6 7	6 7 0	6 7 3	6 9 1	6 9 7	7 0 3	7 0 3	7 0 5	7 1 3	7 2 5
Carcass ID Number	3 8 3	3 7 1	3 6 5	3 7 5	3 9 3	3 6 6	3 7 6	3 9 2	3 6 0	3 7 4	3 8 1	3 7 3	3 5 5	3 5 9	3 6 7	3 8 4	3 6 3	3 9 0	3 5 7	3 6 2	3 6 9	3 8 8	3 7 9	3 7 0
Genital System																								
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																	X							
Carcinoma																								
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																								
Leiomyoma																								
Polyp stromal		X							X				X				X		X		X			
Polyp stromal, multiple																								
Sarcoma																							X	
Vagina				+	+	+		+		+			+	+				+	+					
Hematopoietic System																								
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node					+				+	+				+										
Deep cervical, carcinoma, metastatic, thyroid gland									X															
Mediastinal, carcinoma, metastatic, thyroid gland									X															
Renal, carcinoma, metastatic, thyroid gland									X															
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	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	M	+	+	+	+	+	+
Carcinoma, metastatic, thyroid gland									X															
Integumentary System																								
Mammary gland	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																								
Fibroadenoma				X						X		X					X		X		X	X		
Fibroadenoma, multiple																								
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibroma													X		X									
Musculoskeletal System																								
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																								
Nervous System																								
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, pituitary gland							X	X																
Glioma malignant, mixed cell		X																						
Peripheral nerve		+										+						+		+				
Spinal cord		+										+						+		+				

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Dermal Study of Diisopropylcarbodiimide: 40 mg/kg

Number of Days on Study	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	
Carcass ID Number	3 5 1	3 5 3	3 5 7	3 8 0	3 9 1	3 5 4	3 5 8	3 8 2	3 5 2	3 7 8	3 8 5	3 8 6	3 8 7	3 9 4	3 9 5	3 5 6	3 6 1	3 6 4	3 6 8	3 7 2	3 8 9	3 9 6	3 9 7	3 9 8	3 9 9	Total Tissues/ Tumors
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma																				X						2
Carcinoma	X																	X								2
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma			X															X								2
Leiomyoma													X													1
Polyp stromal					X												X								X	9
Polyp stromal, multiple													X													1
Sarcoma																										1
Vagina			+										+													11
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node		+	+										+													8
Deep cervical, carcinoma, metastatic, thyroid gland																										1
Mediastinal, carcinoma, metastatic, thyroid gland																										1
Renal, carcinoma, metastatic, thyroid gland																										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	2
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Carcinoma, metastatic, thyroid gland																										1
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma											X															1
Fibroadenoma	X	X		X							X	X			X											13
Fibroadenoma, multiple					X				X					X												3
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Subcutaneous tissue, fibroma																		X								3
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Skeletal muscle										+																1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma, metastatic, pituitary gland																										2
Glioma malignant, mixed cell																										1
Peripheral nerve										+																5
Spinal cord										+																5

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Dermal Study of Diisopropylcarbodiimide: 40 mg/kg

Number of Days on Study	446	456	469	559	587	593	593	601	617	617	627	646	662	663	667	707	733	791	917	903	903	905	913	972
Carcass ID Number	383	371	655	755	939	636	676	692	600	674	681	673	555	599	667	844	663	907	572	662	668	848	779	770
Respiratory System																								
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, thyroid gland									X															
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																								
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																			X					
Urinary System																								
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Renal tubule, adenoma																		X						
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																								
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear						X	X			X	X			X		X				X				

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Dermal Study of Diisopropylcarbodiimide: 40 mg/kg

Number of Days on Study	729	729	729	729	729	731	731	731	732	732	732	732	732	732	732	733	733	733	733	733	733	733	733	733	733	
Carcass ID Number	35 1	35 3	37 7	38 0	39 1	35 4	35 8	38 2	35 2	37 8	38 5	38 6	38 7	39 4	39 5	35 6	36 1	36 4	36 8	37 2	38 9	39 6	39 7	39 8	39 9	Total Tissues/ Tumors
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma, metastatic, thyroid gland																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Special Senses System																										
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Renal tubule, adenoma																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia mononuclear	X		X												X					X	X	X	X		X	15

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Dermal Study of Diisopropylcarbodiimide

	Vehicle Control	10 mg/kg	20 mg/kg	40 mg/kg
Adrenal Cortex: Adenoma				
Overall rate[a]	3/50 (6%)	0/50 (0%)	0/50 (0%)	1/49 (2%)
Adjusted rate[b]	7.2%	0.0%	0.0%	2.4%
Terminal rate[c]	2/30 (7%)	0/32 (0%)	0/32 (0%)	1/25 (4%)
First incidence (days)	710	—[e]	—	729 (T)
Poly-3 test[d]	P=0.248N	P=0.117N	P=0.110N	P=0.310N
Clitoral Gland: Adenoma				
Overall rate	2/50 (4%)	3/49 (6%)	5/50 (10%)	2/49 (4%)
Adjusted rate	4.8%	7.3%	11.3%	4.8%
Terminal rate	2/30 (7%)	3/31 (10%)	4/32 (13%)	1/25 (4%)
First incidence (days)	729 (T)	729 (T)	606	673
Poly-3 test	P=0.578N	P=0.494	P=0.240	P=0.692
Clitoral Gland: Carcinoma				
Overall rate	2/50 (4%)	6/49 (12%)	1/50 (2%)	2/49 (4%)
Adjusted rate	4.7%	14.4%	2.3%	4.9%
Terminal rate	1/30 (3%)	4/31 (13%)	1/32 (3%)	2/25 (8%)
First incidence (days)	556	513	729 (T)	729 (T)
Poly-3 test	P=0.321N	P=0.127	P=0.487N	P=0.685
Clitoral Gland: Adenoma or Carcinoma				
Overall rate	4/50 (8%)	9/49 (18%)	6/50 (12%)	4/49 (8%)
Adjusted rate	9.5%	21.6%	13.6%	9.7%
Terminal rate	3/30 (10%)	7/31 (23%)	5/32 (16%)	3/25 (12%)
First incidence (days)	556	513	606	673
Poly-3 test	P=0.373N	P=0.107	P=0.398	P=0.632
Liver: Hepatocellular Adenoma				
Overall rate	6/50 (12%)	1/50 (2%)	2/50 (4%)	1/49 (2%)
Adjusted rate	14.3%	2.4%	4.6%	2.4%
Terminal rate	4/30 (13%)	1/32 (3%)	2/32 (6%)	1/25 (4%)
First incidence (days)	632	729 (T)	729 (T)	729 (T)
Poly-3 test	P=0.049N	P=0.055N	P=0.119N	P=0.058N
Mammary Gland: Fibroadenoma				
Overall rate	12/50 (24%)	11/50 (22%)	21/50 (42%)	16/49 (33%)
Adjusted rate	28.1%	26.2%	46.5%	37.3%
Terminal rate	8/30 (27%)	10/32 (31%)	17/32 (53%)	9/25 (36%)
First incidence (days)	606	728	465	559
Poly-3 test	P=0.124	P=0.519N	P=0.055	P=0.245
Mammary Gland: Fibroadenoma or Adenoma				
Overall rate	12/50 (24%)	12/50 (24%)	21/50 (42%)	16/49 (33%)
Adjusted rate	28.1%	28.4%	46.5%	37.3%
Terminal rate	8/30 (27%)	10/32 (31%)	17/32 (53%)	9/25 (36%)
First incidence (days)	606	677	465	559
Poly-3 test	P=0.142	P=0.582	P=0.055	P=0.245
Mammary Gland: Carcinoma				
Overall rate	4/50 (8%)	0/50 (0%)	2/50 (4%)	0/49 (0%)
Adjusted rate	9.6%	0.0%	4.6%	0.0%
Terminal rate	3/30 (10%)	0/32 (0%)	1/32 (3%)	0/25 (0%)
First incidence (days)	710	—	686	—
Poly-3 test	P=0.060N	P=0.059N	P=0.313N	P=0.061N

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Dermal Study of Diisopropylcarbodiimide

	Vehicle Control	10 mg/kg	20 mg/kg	40 mg/kg
Mammary Gland: Adenoma or Carcinoma				
Overall rate	4/50 (8%)	1/50 (2%)	2/50 (4%)	1/49 (2%)
Adjusted rate	9.6%	2.4%	4.6%	2.4%
Terminal rate	3/30 (10%)	0/32 (0%)	1/32 (3%)	1/25 (4%)
First incidence (days)	710	677	686	729 (T)
Poly-3 test	P=0.167N	P=0.174N	P=0.313N	P=0.182N
Mammary Gland: Fibroadenoma, Adenoma, or Carcinoma				
Overall rate	14/50 (28%)	12/50 (24%)	22/50 (44%)	16/49 (33%)
Adjusted rate	32.7%	28.4%	48.6%	37.3%
Terminal rate	9/30 (30%)	10/32 (31%)	17/32 (53%)	9/25 (36%)
First incidence (days)	606	677	465	559
Poly-3 test	P=0.239	P=0.423N	P=0.093	P=0.411
Oral Cavity (Oral Mucosa and Tongue): Squamous Cell Papilloma or Squamous Cell Carcinoma				
Overall rate	3/50 (6%)	0/50 (0%)	2/50 (4%)	0/49 (0%)
Adjusted rate	7.1%	0.0%	4.6%	0.0%
Terminal rate	2/30 (7%)	0/32 (0%)	1/32 (3%)	0/25 (0%)
First incidence (days)	394	—	690	—
Poly-3 test	P=0.127N	P=0.120N	P=0.485N	P=0.124N
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	33/50 (66%)	34/50 (68%)	33/50 (66%)	27/49 (55%)
Adjusted rate	74.2%	73.3%	69.2%	61.6%
Terminal rate	24/30 (80%)	22/32 (69%)	22/32 (69%)	17/25 (68%)
First incidence (days)	437	522	465	469
Poly-3 test	P=0.090N	P=0.555N	P=0.379N	P=0.135N
Pituitary Gland (Pars Distalis): Carcinoma				
Overall rate	3/50 (6%)	1/50 (2%)	1/50 (2%)	4/49 (8%)
Adjusted rate	7.1%	2.4%	2.3%	9.5%
Terminal rate	1/30 (3%)	0/32 (0%)	1/32 (3%)	1/25 (4%)
First incidence (days)	626	712	729 (T)	593
Poly-3 test	P=0.300	P=0.306N	P=0.292N	P=0.498
Pituitary Gland (Pars Distalis): Adenoma or Carcinoma				
Overall rate	36/50 (72%)	35/50 (70%)	34/50 (68%)	30/49 (61%)
Adjusted rate	79.9%	75.3%	71.3%	67.0%
Terminal rate	25/30 (83%)	22/32 (69%)	23/32 (72%)	18/25 (72%)
First incidence (days)	437	522	465	469
Poly-3 test	P=0.090N	P=0.389N	P=0.229N	P=0.113N
Skin (Subcutaneous Tissue): Fibroma				
Overall rate	0/50 (0%)	0/50 (0%)	1/50 (2%)	3/49 (6%)
Adjusted rate	0.0%	0.0%	2.3%	7.2%
Terminal rate	0/30 (0%)	0/32 (0%)	1/32 (3%)	1/25 (4%)
First incidence (days)	—	—	729 (T)	662
Poly-3 test	P=0.019	—[f]	P=0.510	P=0.118
Skin (Subcutaneous Tissue): Fibroma or Fibrosarcoma				
Overall rate	0/50 (0%)	2/50 (4%)	1/50 (2%)	3/49 (6%)
Adjusted rate	0.0%	4.8%	2.3%	7.2%
Terminal rate	0/30 (0%)	1/32 (3%)	1/32 (3%)	1/25 (4%)
First incidence (days)	—	703	729 (T)	662
Poly-3 test	P=0.103	P=0.240	P=0.510	P=0.118

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Dermal Study of Diisopropylcarbodiimide

	Vehicle Control	10 mg/kg	20 mg/kg	40 mg/kg
Thyroid Gland (C-cell): Adenoma				
Overall rate	3/50 (6%)	2/50 (4%)	6/50 (12%)	6/49 (12%)
Adjusted rate	7.2%	4.8%	13.7%	14.3%
Terminal rate	3/30 (10%)	1/32 (3%)	4/32 (13%)	3/25 (12%)
First incidence (days)	729 (T)	703	703	593
Poly-3 test	P=0.107	P=0.494N	P=0.268	P=0.245
Thyroid Gland (C-cell): Carcinoma				
Overall rate	2/50 (4%)	0/50 (0%)	2/50 (4%)	3/49 (6%)
Adjusted rate	4.8%	0.0%	4.6%	7.2%
Terminal rate	1/30 (3%)	0/32 (0%)	2/32 (6%)	0/25 (0%)
First incidence (days)	682	—	729 (T)	617
Poly-3 test	P=0.236	P=0.236N	P=0.678N	P=0.501
Thyroid Gland (C-cell): Adenoma or Carcinoma				
Overall rate	5/50 (10%)	2/50 (4%)	8/50 (16%)	9/49 (18%)
Adjusted rate	12.0%	4.8%	18.2%	21.0%
Terminal rate	4/30 (13%)	1/32 (3%)	6/32 (19%)	3/25 (12%)
First incidence (days)	682	703	703	593
Poly-3 test	P=0.054	P=0.212N	P=0.307	P=0.203
Uterus: Stromal Polyp				
Overall rate	10/50 (20%)	10/50 (20%)	10/50 (20%)	10/49 (20%)
Adjusted rate	23.0%	23.6%	22.3%	23.3%
Terminal rate	6/30 (20%)	9/32 (28%)	6/32 (19%)	4/25 (16%)
First incidence (days)	394	621	465	456
Poly-3 test	P=0.545	P=0.574	P=0.570N	P=0.586
All Organs: Mononuclear Leukemia				
Overall rate	9/50 (18%)	9/50 (18%)	7/50 (14%)	15/49 (31%)
Adjusted rate	21.1%	21.2%	15.6%	34.6%
Terminal rate	4/30 (13%)	7/32 (22%)	3/32 (9%)	8/25 (32%)
First incidence (days)	535	621	535	593
Poly-3 test	P=0.075	P=0.598	P=0.352N	P=0.119
All Organs: Benign Neoplasms				
Overall rate	44/50 (88%)	41/50 (82%)	41/50 (82%)	39/49 (80%)
Adjusted rate	93.7%	88.1%	85.6%	83.7%
Terminal rate	29/30 (97%)	28/32 (88%)	28/32 (88%)	21/25 (84%)
First incidence (days)	394	522	465	456
Poly-3 test	P=0.084N	P=0.267N	P=0.148N	P=0.092N
All Organs: Malignant Neoplasms				
Overall rate	22/50 (44%)	14/50 (28%)	16/50 (32%)	23/49 (47%)
Adjusted rate	48.2%	32.4%	34.9%	50.6%
Terminal rate	9/30 (30%)	9/32 (28%)	9/32 (28%)	9/25 (36%)
First incidence (days)	394	513	465	456
Poly-3 test	P=0.297	P=0.093N	P=0.137N	P=0.491

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Dermal Study of Diisopropylcarbodiimide

	Vehicle Control	10 mg/kg	20 mg/kg	40 mg/kg
All Organs: Benign or Malignant Neoplasms				
Overall rate	48/50 (96%)	45/50 (90%)	44/50 (88%)	45/49 (92%)
Adjusted rate	99.7%	95.3%	89.9%	94.2%
Terminal rate	30/30 (100%)	30/32 (94%)	28/32 (88%)	23/25 (92%)
First incidence (days)	394	513	465	456
Poly-3 test	P=0.151N	P=0.217N	P=0.035N	P=0.143N

(T) Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, clitoral gland, liver, 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 is the P value 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
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Dermal Study of Diisopropylcarbodiimide[a]

	Vehicle Control	10 mg/kg	20 mg/kg	40 mg/kg
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Moribund	13	9	10	14
Natural deaths	7	9	8	10
Survivors				
Terminal sacrifice	30	32	32	25
Other				1
Animals examined microscopically	50	50	50	49
Alimentary System				
Intestine large, rectum	(50)	(48)	(43)	(44)
Hemorrhage				1 (2%)
Intestine large, cecum	(50)	(50)	(50)	(49)
Edema	1 (2%)	3 (6%)	1 (2%)	2 (4%)
Inflammation, chronic		1 (2%)		
Intestine small, duodenum	(49)	(50)	(50)	(49)
Epithelium, hyperplasia	1 (2%)			
Intestine small, jejunum	(47)	(50)	(50)	(46)
Epithelium, hyperplasia			1 (2%)	
Liver	(50)	(50)	(50)	(49)
Angiectasis			1 (2%)	1 (2%)
Basophilic focus	42 (84%)	43 (86%)	45 (90%)	40 (82%)
Clear cell focus	10 (20%)	6 (12%)	4 (8%)	4 (8%)
Cyst			1 (2%)	
Eosinophilic focus	4 (8%)	3 (6%)	8 (16%)	5 (10%)
Hematopoietic cell proliferation	1 (2%)		1 (2%)	
Hemorrhage		1 (2%)	2 (4%)	1 (2%)
Hepatodiaphragmatic nodule	11 (22%)	6 (12%)	12 (24%)	8 (16%)
Infiltration cellular, mixed cell	8 (16%)	11 (22%)	13 (26%)	8 (16%)
Mixed cell focus	3 (6%)	5 (10%)	7 (14%)	1 (2%)
Necrosis, focal	5 (10%)	1 (2%)	3 (6%)	4 (8%)
Regeneration	1 (2%)			2 (4%)
Bile duct, hyperplasia	5 (10%)	3 (6%)	2 (4%)	5 (10%)
Centrilobular, necrosis	1 (2%)			2 (4%)
Hepatocyte, vacuolization cytoplasmic	5 (10%)	5 (10%)	3 (6%)	4 (8%)
Kupffer cell, pigmentation	1 (2%)	1 (2%)		1 (2%)
Mesentery	(11)	(12)	(9)	(9)
Fat, necrosis	11 (100%)	11 (92%)	8 (89%)	9 (100%)
Oral mucosa	(1)		(2)	
Cyst			1 (50%)	
Pancreas	(50)	(50)	(50)	(49)
Atrophy	15 (30%)	16 (32%)	18 (36%)	19 (39%)
Cyst	4 (8%)	6 (12%)	5 (10%)	
Necrosis				1 (2%)
Acinus, cytoplasmic alteration		1 (2%)	1 (2%)	
Acinus, hyperplasia, focal		1 (2%)	1 (2%)	
Salivary glands	(50)	(50)	(50)	(48)
Atrophy	3 (6%)	1 (2%)	1 (2%)	1 (2%)
Stomach, forestomach	(50)	(50)	(50)	(49)
Edema	2 (4%)		1 (2%)	2 (4%)
Ulcer	3 (6%)		1 (2%)	4 (8%)
Epithelium, hyperplasia	4 (8%)		2 (4%)	2 (4%)

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

TABLE B4
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Dermal Study of Diisopropylcarbodiimide

	Vehicle Control	10 mg/kg	20 mg/kg	40 mg/kg
Alimentary System (continued)				
Stomach, glandular	(50)	(50)	(50)	(49)
Edema			1 (2%)	1 (2%)
Erosion	1 (2%)	1 (2%)	2 (4%)	4 (8%)
Ulcer		1 (2%)	1 (2%)	1 (2%)
Glands, hyperplasia	1 (2%)		1 (2%)	
Cardiovascular System				
Heart	(50)	(50)	(50)	(49)
Cardiomyopathy	30 (60%)	39 (78%)	35 (70%)	31 (63%)
Inflammation, chronic		1 (2%)		1 (2%)
Thrombosis	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Endocrine System				
Adrenal cortex	(50)	(50)	(50)	(49)
Accessory adrenal cortical nodule	9 (18%)	6 (12%)	9 (18%)	8 (16%)
Degeneration, fatty	20 (40%)	15 (30%)	16 (32%)	17 (35%)
Hyperplasia, focal	3 (6%)		4 (8%)	5 (10%)
Hypertrophy, focal	10 (20%)	10 (20%)	9 (18%)	8 (16%)
Adrenal medulla	(49)	(50)	(50)	(49)
Hyperplasia	5 (10%)	2 (4%)	4 (8%)	2 (4%)
Islets, pancreatic	(50)	(50)	(50)	(49)
Hyperplasia	1 (2%)		2 (4%)	
Metaplasia, hepatocyte		1 (2%)		
Pituitary gland	(50)	(50)	(50)	(49)
Pars distalis, angiectasis	1 (2%)	6 (12%)	4 (8%)	4 (8%)
Pars distalis, cyst	16 (32%)	6 (12%)	15 (30%)	14 (29%)
Pars distalis, hyperplasia, focal	7 (14%)	7 (14%)	10 (20%)	11 (22%)
Pars intermedia, angiectasis		1 (2%)	2 (4%)	2 (4%)
Pars intermedia, cyst	1 (2%)	1 (2%)	2 (4%)	
Thyroid gland	(50)	(50)	(50)	(49)
Ultimobranchial cyst				2 (4%)
C-cell, hyperplasia	17 (34%)	14 (28%)	10 (20%)	12 (24%)
Follicle, cyst	2 (4%)	2 (4%)	3 (6%)	1 (2%)
Follicular cell, hyperplasia	1 (2%)		1 (2%)	1 (2%)
General Body System				
None				
Genital System				
Clitoral gland	(50)	(49)	(50)	(49)
Cyst	1 (2%)	3 (6%)	1 (2%)	3 (6%)
Hyperplasia		2 (4%)	2 (4%)	
Inflammation, chronic	13 (26%)	2 (4%)	10 (20%)	3 (6%)
Ovary	(50)	(50)	(50)	(49)
Angiectasis	1 (2%)			
Cyst	11 (22%)	8 (16%)	9 (18%)	6 (12%)
Corpus luteum, hyperplasia	1 (2%)			
Uterus	(50)	(50)	(50)	(49)
Endometrium, hyperplasia, cystic	4 (8%)	10 (20%)	5 (10%)	9 (18%)
Vagina	(6)	(6)	(5)	(11)
Cyst	1 (17%)	1 (17%)		
Inflammation, chronic	1 (17%)			

TABLE B4
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Dermal Study of Diisopropylcarbodiimide

	Vehicle Control	10 mg/kg	20 mg/kg	40 mg/kg
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(49)
Hyperplasia	6 (12%)	8 (16%)	3 (6%)	6 (12%)
Infiltration cellular, histiocyte				2 (4%)
Myelofibrosis		1 (2%)	2 (4%)	2 (4%)
Lymph node	(13)	(10)	(14)	(8)
Deep cervical, hemorrhage		1 (10%)		
Deep cervical, hyperplasia, lymphoid		1 (10%)		
Deep cervical, pigmentation		1 (10%)		
Mediastinal, ectasia			1 (7%)	
Mediastinal, hemorrhage	4 (31%)	4 (40%)	4 (29%)	3 (38%)
Mediastinal, hyperplasia, lymphoid	3 (23%)	5 (50%)	7 (50%)	
Mediastinal, pigmentation	6 (46%)	6 (60%)	9 (64%)	2 (25%)
Pancreatic, hemorrhage	1 (8%)	3 (30%)	1 (7%)	1 (13%)
Pancreatic, hyperplasia, lymphoid		1 (10%)		
Pancreatic, pigmentation	1 (8%)	2 (20%)	1 (7%)	1 (13%)
Lymph node, mandibular	(3)	(7)	(1)	(2)
Ectasia	1 (33%)	4 (57%)		1 (50%)
Hyperplasia, lymphoid	1 (33%)			
Pigmentation	1 (33%)	1 (14%)		
Lymph node, mesenteric	(50)	(50)	(50)	(48)
Ectasia		1 (2%)		1 (2%)
Hemorrhage	11 (22%)	11 (22%)	6 (12%)	5 (10%)
Hyperplasia, lymphoid	16 (32%)	20 (40%)	12 (24%)	11 (23%)
Necrosis				1 (2%)
Pigmentation	25 (50%)	24 (48%)	27 (54%)	17 (35%)
Spleen	(50)	(50)	(50)	(49)
Fibrosis		1 (2%)		2 (4%)
Hematopoietic cell proliferation	21 (42%)	29 (58%)	29 (58%)	20 (41%)
Hemorrhage				2 (4%)
Hyperplasia, reticulum cell				1 (2%)
Necrosis	1 (2%)	1 (2%)	2 (4%)	
Pigmentation	10 (20%)	16 (32%)	13 (26%)	16 (33%)
Lymphoid follicle, atrophy		2 (4%)		1 (2%)
Lymphoid follicle, hyperplasia	1 (2%)		3 (6%)	1 (2%)
Thymus	(50)	(48)	(49)	(46)
Hemorrhage	2 (4%)	2 (4%)	1 (2%)	1 (2%)
Hyperplasia, lymphoid	1 (2%)	2 (4%)	1 (2%)	1 (2%)
Integumentary System				
Mammary gland	(50)	(50)	(50)	(48)
Hyperplasia	45 (90%)	46 (92%)	45 (90%)	41 (85%)
Skin	(50)	(50)	(50)	(49)
Cyst epithelial inclusion		1 (2%)		
Inflammation, chronic	2 (4%)	1 (2%)		
Ulcer			1 (2%)	
Epidermis, hyperplasia	2 (4%)	2 (4%)	2 (4%)	1 (2%)
Epidermis, skin, site of application, hyperplasia	1 (2%)	5 (10%)	16 (32%)	21 (43%)
Skin, site of application, inflammation, chronic			3 (6%)	10 (20%)
Musculoskeletal System				
None				

TABLE B4
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Dermal Study of Diisopropylcarbodiimide

	Vehicle Control	10 mg/kg	20 mg/kg	40 mg/kg
Nervous System				
Brain	(50)	(50)	(50)	(49)
Compression	14 (28%)	13 (26%)	14 (28%)	13 (27%)
Hydrocephalus	2 (4%)	8 (16%)	1 (2%)	2 (4%)
Necrosis	2 (4%)	1 (2%)	2 (4%)	
Gliosis	1 (2%)	1 (2%)	2 (4%)	
Hemorrhage	1 (2%)	8 (16%)		
Angiectasis	1 (2%)		1 (2%)	
Respiratory System				
Lung	(50)	(50)	(50)	(49)
Edema	4 (8%)	4 (8%)	3 (6%)	2 (4%)
Emphysema			1 (2%)	
Hemorrhage	8 (16%)	14 (28%)	9 (18%)	13 (27%)
Infiltration cellular, histiocyte	22 (44%)	26 (52%)	30 (60%)	27 (55%)
Inflammation, chronic	10 (20%)	22 (44%)	19 (38%)	10 (20%)
Metaplasia, osseous			2 (4%)	1 (2%)
Metaplasia, squamous	1 (2%)		1 (2%)	
Pigmentation				1 (2%)
Alveolar epithelium, hyperplasia	3 (6%)	4 (8%)	10 (20%)	1 (2%)
Nose	(50)	(50)	(50)	(49)
Foreign body	5 (10%)		2 (4%)	3 (6%)
Inflammation, chronic	6 (12%)	1 (2%)	2 (4%)	3 (6%)
Respiratory epithelium, hyperplasia	4 (8%)	1 (2%)	2 (4%)	1 (2%)
Special Senses System				
Eye	(50)	(50)	(50)	(49)
Cataract	2 (4%)	5 (10%)	3 (6%)	3 (6%)
Cornea, hyperplasia				3 (6%)
Cornea, inflammation, chronic	1 (2%)	1 (2%)		3 (6%)
Retina, degeneration	4 (8%)	7 (14%)	5 (10%)	4 (8%)
Retina, dysplasia			1 (2%)	
Harderian gland	(50)	(50)	(50)	(49)
Hyperplasia, focal	1 (2%)			
Inflammation, chronic		1 (2%)		
Urinary System				
Kidney	(50)	(50)	(50)	(49)
Cyst	1 (2%)			
Hemorrhage				1 (2%)
Infarct	1 (2%)		1 (2%)	
Inflammation, chronic	2 (4%)	2 (4%)	1 (2%)	
Inflammation, suppurative	1 (2%)			
Nephropathy	32 (64%)	32 (64%)	28 (56%)	21 (43%)
Papilla, necrosis				1 (2%)
Renal tubule, accumulation, hyaline droplet	2 (4%)	1 (2%)		2 (4%)
Renal tubule, dilatation	1 (2%)		1 (2%)	1 (2%)
Renal tubule, necrosis	1 (2%)	2 (4%)		2 (4%)
Transitional epithelium, hyperplasia			1 (2%)	
Urinary bladder	(50)	(50)	(50)	(49)
Hemorrhage			1 (2%)	

APPENDIX C
SUMMARY OF LESIONS
IN MALE MICE IN THE 2-YEAR DERMAL STUDY
OF DIISOPROPYLCARBODIIMIDE

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Dermal Study of Diisopropylcarbodiimide

	Vehicle Control	10 mg/kg	20 mg/kg	40 mg/kg
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Accidental death				1
Moribund	5	1	2	5
Natural deaths	6	9	10	8
Survivors				
Died last week of study	1			
Terminal sacrifice	38	40	38	36
Animals examined microscopically	50	50	50	50
Alimentary System				
Intestine large, cecum	(46)	(43)	(44)	(42)
Leiomyoma				1 (2%)
Intestine small, duodenum	(46)	(44)	(44)	(40)
Adenoma	1 (2%)	1 (2%)	1 (2%)	
Carcinoma			1 (2%)	
Intestine small, jejunum	(46)	(43)	(44)	(40)
Carcinoma			1 (2%)	1 (3%)
Intestine small, ileum	(46)	(44)	(44)	(40)
Carcinoma			1 (2%)	
Liver	(50)	(50)	(50)	(49)
Cholangiocarcinoma	1 (2%)			
Hemangiosarcoma		2 (4%)	1 (2%)	1 (2%)
Hepatoblastoma		1 (2%)		
Hepatocellular carcinoma	16 (32%)	8 (16%)	8 (16%)	8 (16%)
Hepatocellular carcinoma, multiple	4 (8%)	7 (14%)	3 (6%)	3 (6%)
Hepatocellular adenoma	9 (18%)	15 (30%)	11 (22%)	10 (20%)
Hepatocellular adenoma, multiple	9 (18%)	7 (14%)	8 (16%)	9 (18%)
Hepatocholangiocarcinoma			1 (2%)	
Histiocytic sarcoma	1 (2%)			
Squamous cell carcinoma, metastatic, stomach, forestomach				1 (2%)
Mesentery	(49)	(49)	(50)	(50)
Carcinoma, metastatic, pancreas				1 (2%)
Hepatocellular carcinoma, metastatic, liver		1 (2%)	1 (2%)	
Histiocytic sarcoma	1 (2%)			
Sarcoma				1 (2%)
Schwannoma malignant, metastatic, uncertain primary site				1 (2%)
Pancreas	(49)	(50)	(49)	(49)
Hepatocellular carcinoma, metastatic, liver		1 (2%)		
Sarcoma, metastatic, uncertain primary site				1 (2%)
Duct, carcinoma				1 (2%)
Salivary glands	(50)	(50)	(50)	(50)
Stomach, forestomach	(50)	(50)	(50)	(50)
Squamous cell carcinoma				1 (2%)
Squamous cell papilloma	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Serosa, carcinoma, metastatic, pancreas				1 (2%)
Stomach, glandular	(50)	(47)	(48)	(47)
Carcinoma, metastatic, pancreas				1 (2%)

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Dermal Study of Diisopropylcarbodiimide

	Vehicle Control	10 mg/kg	20 mg/kg	40 mg/kg
Cardiovascular System				
Heart	(50)	(50)	(50)	(50)
Hepatocellular carcinoma, metastatic, liver			1 (2%)	
Endocrine System				
Adrenal cortex	(50)	(50)	(50)	(49)
Adenoma	1 (2%)	1 (2%)		1 (2%)
Bilateral, subcapsular, adenoma	1 (2%)			
Subcapsular, adenoma	3 (6%)	2 (4%)	6 (12%)	4 (8%)
Adrenal medulla	(49)	(50)	(50)	(49)
Pheochromocytoma malignant				1 (2%)
Pheochromocytoma benign		1 (2%)		
Islets, pancreatic	(49)	(50)	(49)	(50)
Adenoma	1 (2%)	1 (2%)		1 (2%)
Carcinoma			1 (2%)	
Pituitary gland	(48)	(47)	(50)	(49)
Pars intermedia, adenoma			1 (2%)	
Thyroid gland	(49)	(50)	(50)	(50)
Follicular cell, adenoma		1 (2%)		1 (2%)
General Body System				
Peritoneum	(49)	(49)	(49)	(50)
Carcinoma, metastatic, pancreas				1 (2%)
Hepatocellular carcinoma, metastatic, liver		1 (2%)		
Sarcoma				1 (2%)
Tissue NOS			(3)	(2)
Abdominal, hepatocellular carcinoma, metastatic, liver			1 (33%)	
Mediastinum, hepatocellular carcinoma, metastatic, liver			1 (33%)	1 (50%)
Thoracic, hepatocellular carcinoma, metastatic, liver			1 (33%)	
Genital System				
Epididymis	(50)	(50)	(50)	(50)
Prostate	(50)	(50)	(50)	(50)
Carcinoma				1 (2%)
Seminal vesicle	(50)	(50)	(50)	(50)
Adenoma	1 (2%)			
Carcinoma, metastatic, pancreas				1 (2%)
Testes	(50)	(50)	(50)	(50)
Interstitial cell, adenoma			1 (2%)	1 (2%)
Hematopoietic System				
Bone marrow	(49)	(50)	(50)	(50)
Hemangiosarcoma			1 (2%)	2 (4%)
Lymph node	(6)	(5)	(5)	(4)
Mediastinal, carcinoma, metastatic, pancreas				1 (25%)
Mediastinal, hepatoblastoma, metastatic, liver	1 (17%)			
Mediastinal, sarcoma, metastatic, uncertain primary site				1 (25%)
Lymph node, mandibular	(47)	(48)	(47)	(47)
Lymph node, mesenteric	(50)	(48)	(49)	(48)
Histiocytic sarcoma	1 (2%)			
Sarcoma, metastatic, uncertain primary site				1 (2%)
Spleen	(49)	(50)	(50)	(47)
Hemangiosarcoma			1 (2%)	2 (4%)
Thymus	(47)	(44)	(47)	(46)
Hepatocellular carcinoma, metastatic, liver			1 (2%)	1 (2%)

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Dermal Study of Diisopropylcarbodiimide

	Vehicle Control	10 mg/kg	20 mg/kg	40 mg/kg
Integumentary System				
Mammary gland	(1)			(1)
Carcinoma	1 (100%)			
Skin	(50)	(50)	(50)	(50)
Subcutaneous tissue, fibroma	1 (2%)			
Subcutaneous tissue, fibrosarcoma		1 (2%)		
Subcutaneous tissue, hemangiosarcoma				1 (2%)
Subcutaneous tissue, hepatoblastoma, metastatic, liver	1 (2%)			
Subcutaneous tissue, site of application, lymphoma malignant			1 (2%)	
Musculoskeletal System				
Skeletal muscle	(2)	(2)	(2)	(5)
Alveolar/bronchiolar carcinoma, metastatic, lung				1 (20%)
Carcinoma, metastatic, pancreas				1 (20%)
Hemangiosarcoma			1 (50%)	
Hepatocellular carcinoma, metastatic, liver		1 (50%)		
Rhabdomyosarcoma	1 (50%)			
Nervous System				
Peripheral nerve	(1)		(1)	(3)
Schwannoma malignant				1 (33%)
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Alveolar/bronchiolar adenoma	6 (12%)	5 (10%)	7 (14%)	7 (14%)
Alveolar/bronchiolar adenoma, multiple		1 (2%)		1 (2%)
Alveolar/bronchiolar carcinoma	2 (4%)	3 (6%)	2 (4%)	2 (4%)
Alveolar/bronchiolar carcinoma, multiple			2 (4%)	
Carcinoma, metastatic, mammary gland	1 (2%)			
Carcinoma, metastatic, pancreas				1 (2%)
Cholangiocarcinoma, metastatic, liver	1 (2%)			
Hepatoblastoma, metastatic, liver	1 (2%)			
Hepatocellular carcinoma, metastatic, liver	7 (14%)	6 (12%)	4 (8%)	3 (6%)
Hepatocellular carcinoma, metastatic, lung	1 (2%)			
Sarcoma, metastatic, uncertain primary site				1 (2%)
Mediastinum, hepatocellular carcinoma, metastatic, liver		1 (2%)	1 (2%)	
Nose	(49)	(50)	(50)	(50)
Carcinoma, metastatic, harderian gland	1 (2%)			
Special Senses System				
Eye	(46)	(46)	(47)	(44)
Retrobulbar, carcinoma, metastatic, harderian gland	1 (2%)			
Retrobulbar, sarcoma	1 (2%)			
Harderian gland	(50)	(50)	(50)	(50)
Adenoma	6 (12%)	9 (18%)	10 (20%)	8 (16%)
Carcinoma	2 (4%)	1 (2%)		3 (6%)
Bilateral, adenoma	3 (6%)			

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Dermal Study of Diisopropylcarbodiimide

	Vehicle Control	10 mg/kg	20 mg/kg	40 mg/kg
Urinary System				
Kidney	(48)	(48)	(50)	(48)
Cholangiocarcinoma, metastatic, liver	1 (2%)			
Hepatocellular carcinoma, metastatic, liver			1 (2%)	
Histiocytic sarcoma	1 (2%)			
Schwannoma malignant, metastatic, uncertain primary site				1 (2%)
Capsule, carcinoma, metastatic, pancreas				1 (2%)
Renal tubule, adenoma		1 (2%)		
Urinary bladder	(50)	(50)	(49)	(50)
Hemangioma	1 (2%)		1 (2%)	
Serosa, hemangiosarcoma			1 (2%)	
Systemic Lesions				
Multiple organs[b]	(50)	(50)	(50)	(50)
Histiocytic sarcoma	1 (2%)			
Lymphoma malignant	2 (4%)	2 (4%)	2 (4%)	3 (6%)
Neoplasm Summary				
Total animals with primary neoplasms[c]	42	42	42	41
Total primary neoplasms	75	71	74	78
Total animals with benign neoplasms	29	31	33	31
Total benign neoplasms	44	46	47	45
Total animals with malignant neoplasms	27	21	22	23
Total malignant neoplasms	31	25	27	33
Total animals with metastatic neoplasms	8	6	4	8
Total metastatic neoplasms	16	11	12	22
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 Dermal Study of Diisopropylcarbodiimide: Vehicle Control

Number of Days on Study	5 1 5	5 1 7	5 9 2	5 9 8	6 4 0	6 7 2	6 8 2	7 0 2	7 0 6	7 2 1	7 2 5	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0
Carcass ID Number	0 2 2 9	0 4 4 6	0 2 6 7	0 5 7 0	0 3 3 6	0 3 6 1	0 2 1 3	0 2 2 2	0 2 2 5	0 3 3 7	0 1 1 8	0 0 4 4	0 0 6 6	0 0 8 8	0 0 9 9	0 1 2 2	0 1 1 6	0 1 3 8	0 0 2 2	0 0 3 3	0 0 0 7	0 2 2 4	0 2 2 8	0 3 3 0	0 3 3 9
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	A	A	A	A	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	A	A	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	A	A	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma													X												
Intestine small, jejunum	+	A	A	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	A	A	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cholangiocarcinoma										X															
Hepatocellular carcinoma	X	X	X	X	X						X		X				X	X				X			
Hepatocellular carcinoma, multiple								X		X															
Hepatocellular adenoma														X			X			X					
Hepatocellular adenoma, multiple																							X	X	X
Histiocytic sarcoma									X																
Mesentery	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma									X																
Pancreas	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma								X																	
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth					+		+					+			+						+	+	+		
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma															X										
Bilateral, subcapsular, adenoma																									
Subcapsular, adenoma							X							X											
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Islets, pancreatic	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid gland	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
General Body System																									
Peritoneum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

+: 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 Dermal Study of Diisopropylcarbodiimide: Vehicle Control

Number of Days on Study	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	
Carcass ID Number	0 4 0	0 4 1	0 4 2	0 4 3	0 4 8	0 4 9	0 0 1	0 0 5	0 1 0	0 1 1	0 1 3	0 1 5	0 1 9	0 2 1	0 2 6	0 3 2	0 3 3	0 4 4	0 4 5	0 4 4	0 1 4	0 1 7	0 2 0	0 3 4	0 3 5	0 4 7	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Adenoma																										1
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cholangiocarcinoma																										1
Hepatocellular carcinoma	X	X										X					X				X	X				16
Hepatocellular carcinoma, multiple				X														X								4
Hepatocellular adenoma	X		X				X						X											X	X		9
Hepatocellular adenoma, multiple		X				X		X							X				X							X	9
Histiocytic sarcoma																										1
Mesentery	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma																										1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tooth						+	+	+	+	+				+		+					+		+	+	+	18
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Bilateral, subcapsular, adenoma													X													1
Subcapsular, adenoma					X																					3
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma																					X					1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pituitary gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
General Body System																										
Peritoneum	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study of Diisopropylcarbodiimide: Vehicle Control

Number of Days on Study	5 1 5	5 1 7	5 9 2	5 9 8	6 4 0	6 7 2	6 8 2	7 0 2	7 0 6	7 2 1	7 2 5	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0
Carcass ID Number	0 2 9	0 4 6	0 2 7	0 5 0	0 3 6	0 3 1	0 2 3	0 2 2	0 2 5	0 3 7	0 1 8	0 0 4	0 0 6	0 0 8	0 0 9	0 1 2	0 1 6	0 1 8	0 0 2	0 0 3	0 0 7	0 2 4	0 2 8	0 3 0	0 3 9
Genital System																								
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																			X					
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hematopoietic System																								
Bone marrow	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node						+	+	+										+		+				
Mediastinal, hepatoblastoma, metastatic, liver																								
Lymph node, mandibular	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma									X															
Spleen	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	I	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
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
Carcinoma										X														
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibroma																								
Subcutaneous tissue, hepatoblastoma, metastatic, liver																								
Musculoskeletal System																								
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle						+	+																	
Rhabdomyosarcoma							X																	
Nervous System																								
Brain	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve								+																
Spinal cord								+																
Respiratory System																								
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma				X																X	X	X		
Alveolar/bronchiolar carcinoma														X										
Carcinoma, metastatic, mammary gland										X														
Cholangiocarcinoma, metastatic, liver										X														
Hepatoblastoma, metastatic, liver																								
Hepatocellular carcinoma, metastatic, liver			X					X		X	X							X						
Hepatocellular carcinoma, metastatic, lung					X																			
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, harderian gland											X													
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study of Diisopropylcarbodiimide: Vehicle Control

Number of Days on Study	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	
Carcass ID Number	0 4 0	0 4 1	0 4 2	0 4 3	0 4 8	0 4 9	0 0 1	0 0 5	0 1 0	0 1 1	0 1 3	0 1 5	0 1 9	0 2 1	0 2 6	0 3 2	0 3 3	0 4 4	0 4 5	0 1 4	0 1 7	0 2 0	0 3 4	0 3 5	0 4 7	Total Tissues/ Tumors
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node				+																						6
Mediastinal, hepatoblastoma, metastatic, liver				X																						1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	47
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
Carcinoma																										1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, fibroma			X																							1
Subcutaneous tissue, hepatoblastoma, metastatic, liver				X																						1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										2
Rhabdomyosarcoma																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Peripheral nerve																										1
Spinal cord																										1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma		X	X																							6
Alveolar/bronchiolar carcinoma																		X								2
Carcinoma, metastatic, mammary gland																										1
Cholangiocarcinoma, metastatic, liver																										1
Hepatoblastoma, metastatic, liver				X																						1
Hepatocellular carcinoma, metastatic, liver				X													X									7
Hepatocellular carcinoma, metastatic, lung																										1
Nose	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma, metastatic, harderian gland																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study of Diisopropylcarbodiimide: Vehicle Control

Number of Days on Study	5 1 5	5 1 7	5 9 2	5 9 8	6 4 0	6 7 2	6 8 2	7 0 2	7 0 6	7 2 1	7 2 5	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0
Carcass ID Number	0 2 9	0 4 6	0 2 7	0 5 0	0 3 6	0 3 1	0 2 3	0 2 2	0 2 5	0 3 7	0 1 8	0 0 4	0 0 6	0 0 8	0 0 9	0 1 2	0 1 6	0 3 8	0 3 0	0 0 3	0 0 7	0 2 4	0 2 8	0 3 0	0 3 9
Special Senses System																									
Eye	+	+	A	A	A	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Retrobulbar, carcinoma, metastatic, harderian gland											X														
Retrobulbar, sarcoma																									
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma									X			X					X				X				
Carcinoma											X	X													
Bilateral, adenoma																				X					
Urinary System																									
Kidney	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cholangiocarcinoma, metastatic, liver										X															
Histiocytic sarcoma									X																
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																				X					
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma									X																
Lymphoma malignant						X															X				

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study of Diisopropylcarbodiimide: Vehicle Control

Number of Days on Study	730	730	730	730	730	730	731	731	731	731	731	731	731	731	731	731	731	731	731	732	732	732	732	732	732	
Carcass ID Number	04040	04041	04042	04043	04048	04049	04091	04095	04100	04111	04113	04115	04119	04121	04126	04132	04133	04144	04145	04114	04117	04120	04134	04135	04137	Total Tissues/ Tumors
Special Senses System																										
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Retrobulbar, carcinoma, metastatic, harderian gland																										1
Retrobulbar, sarcoma																								X		1
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma	X																							X		6
Carcinoma																										2
Bilateral, adenoma								X																	X	3
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Cholangiocarcinoma, metastatic, liver																										1
Histiocytic sarcoma																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangioma																										1
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Lymphoma malignant																										2

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study of Diisopropylcarbodiimide: 10 mg/kg

Number of Days on Study	0 5 4	4 3 5	5 4 5	6 0 3	6 2 6	6 6 0	6 7 0	6 9 1	7 0 1	7 1 0	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0
Carcass ID Number	0 0 6 6	0 6 5	0 8 9	0 7 4	0 9 3	0 8 5	0 7 0	0 5 2	0 8 3	0 7 2	0 6 0	0 6 3	0 6 8	0 6 9	0 7 1	0 7 9	0 8 7	1 0 0	0 5 1	0 5 3	0 5 9	0 6 2	0 7 7	0 7 8	0 8 8
Alimentary System																								
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	I	A	+	A	A	+	A	A	A	+	+	+	+	+	I	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	A	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	A	A	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	A	A	+	A	A	+	A	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	A	A	+	A	A	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma				X																				
Intestine small, jejunum	+	A	A	+	A	A	+	A	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	A	A	+	A	A	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																		X			X			
Hepatoblastoma																								
Hepatocellular carcinoma		X	X		X				X												X			
Hepatocellular carcinoma, multiple						X	X	X						X										
Hepatocellular adenoma				X			X					X			X				X	X	X	X		
Hepatocellular adenoma, multiple																		X						X
Mesentery	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic, liver									X															
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic, liver									X															
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma															X									
Stomach, glandular	+	+	+	+	A	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth										+	+	+	+		+			+	+					
Cardiovascular System																								
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																								
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																								X
Subcapsular, adenoma																								
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																								
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																			X					
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	I	I	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																								
General Body System																								
Peritoneum	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic, liver									X															

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study of Diisopropylcarbodiimide: 10 mg/kg

Number of Days on Study	730	730	730	730	731	731	731	731	731	731	731	731	731	731	731	732	732	732	732	732	732	732	732	732	732	
Carcass ID Number	09090	09902	09905	09907	05454	05556	05557	05558	06404	06667	07505	08080	08081	08082	09096	05555	06161	07373	07766	08084	08636	09011	09944	09848	09909	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Adenoma																										1
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										2
Hepatoblastoma													X													1
Hepatocellular carcinoma	X		X														X									8
Hepatocellular carcinoma, multiple		X										X			X											7
Hepatocellular adenoma			X	X					X		X						X			X					X	15
Hepatocellular adenoma, multiple					X					X			X								X	X				7
Mesentery	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatocellular carcinoma, metastatic, liver																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma, metastatic, liver																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma																										1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Tooth						+			+									+				+				11
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Subcapsular, adenoma				X														X								2
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign																			X							1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, adenoma								X																		1
General Body System																										
Peritoneum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatocellular carcinoma, metastatic, liver																										1

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study of Diisopropylcarbodiimide: 10 mg/kg

Number of Days on Study	0 5 4	4 3 5	5 4 5	6 0 3	6 2 6	6 6 0	6 7 0	6 9 1	7 0 1	7 1 0	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0
Carcass ID Number	0 6 6	0 6 5	0 8 9	0 7 4	0 9 3	0 8 5	0 7 0	0 5 2	0 8 3	0 7 2	0 6 0	0 6 3	0 6 8	0 6 9	0 7 1	0 7 9	0 8 7	1 0 0	0 5 1	0 5 3	0 5 9	0 6 2	0 7 7	0 7 8	0 8 8
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node																									
Lymph node, mandibular	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	M	+	+	+	+	M	+	+	+	+	M	I	+	+	+	+	+	+	+	+	+	+	+
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibrosarcoma							X																		
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle									+																
Hepatocellular carcinoma, metastatic, liver									X																
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																				X					
Alveolar/bronchiolar adenoma, multiple																									
Alveolar/bronchiolar carcinoma											X							X							
Hepatocellular carcinoma, metastatic, liver								X	X					X											
Mediastinum, hepatocellular carcinoma, metastatic, liver									X																
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye	+	+	+	+	+	A	+	A	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma						X															X			X	
Carcinoma														X											

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study of Diisopropylcarbodiimide: 10 mg/kg

Number of Days on Study	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	
Carcass ID Number	0 0 9 0	0 0 9 2	0 0 9 5	0 0 9 7	0 0 5 4	0 0 5 6	0 0 5 7	0 0 5 8	0 0 6 4	0 0 6 7	0 0 7 5	0 0 8 0	0 0 8 1	0 0 8 2	0 0 9 6	0 0 5 5	0 0 6 1	0 0 7 3	0 0 7 6	0 0 8 4	0 0 8 6	0 0 9 1	0 0 9 4	0 0 9 8	0 0 9 9	Total Tissues/ Tumors
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node						+											+		+		+		+			5
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	I	+	+	+	+	+	+	+	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
Subcutaneous tissue, fibrosarcoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																					+					2
Hepatocellular carcinoma, metastatic, liver																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma										X				X				X							X	5
Alveolar/bronchiolar adenoma, multiple																							X			1
Alveolar/bronchiolar carcinoma					X																					3
Hepatocellular carcinoma, metastatic, liver		X										X			X											6
Mediastinum, hepatocellular carcinoma, metastatic, liver																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma						X		X						X		X				X	X					9
Carcinoma																										1

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study of Diisopropylcarbodiimide: 10 mg/kg

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

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study of Diisopropylcarbodiimide: 10 mg/kg

Number of Days on Study	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	
Carcass ID Number	0 9 0	0 9 2	0 9 5	0 9 7	0 5 4	0 5 6	0 5 7	0 5 8	0 6 4	0 6 7	0 7 5	0 8 0	0 8 1	0 8 2	0 9 6	0 5 5	0 6 1	0 7 3	0 7 6	0 8 4	0 8 6	0 9 1	0 9 4	0 9 8	0 9 9	Total Tissues/ Tumors
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Renal tubule, adenoma																									X	1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant										X	X															2

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study of Diisopropylcarbodiimide: 20 mg/kg

Number of Days on Study	0 4 8	0 5 5	4 9 3	4 9 6	5 9 7	6 2 5	6 5 3	6 6 9	6 8 1	6 9 0	7 1 3	7 1 5	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0
Carcass ID Number	1 2 2	1 2 3	1 4 2	1 3 7	1 5 0	1 0 5	1 1 5	1 1 7	1 2 5	1 4 5	1 0 2	1 4 4	1 0 8	1 1 2	1 1 4	1 1 8	1 2 1	1 2 4	1 2 8	1 2 9	1 3 2	1 3 4	1 4 3	1 0 1	1 0 4
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	A	I	+	A	+	+	A	A	+	A	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	A	+	A	+	A	+	+	A	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	A	+	A	+	A	+	+	A	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Carcinoma																									
Intestine small, jejunum	A	+	A	+	A	+	+	A	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma							X																		
Intestine small, ileum	A	+	A	+	A	+	+	A	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																					X				
Hepatocellular carcinoma					X		X		X		X						X								
Hepatocellular carcinoma, multiple				X				X		X															
Hepatocellular adenoma												X			X					X			X		
Hepatocellular adenoma, multiple			X							X						X								X	
Hepatocholangiocarcinoma																									
Mesentery	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic, liver								X																	
Pancreas	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Stomach, glandular	+	+	+	+	+	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth										+		+				+	+				+	+	+	+	+
Cardiovascular System																									
Blood vessel																									+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic, liver					X																				
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcapsular, adenoma											X											X			
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma						X																			
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	M	+	M	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars intermedia, adenoma																X									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study of Diisopropylcarbodiimide: 20 mg/kg

Number of Days on Study	730	730	730	730	730	730	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	732	732	732	
Carcass ID Number	10707	11019	11200	12207	13313	13636	10363	10066	10909	11010	11113	11616	12266	13330	13338	14040	14411	14616	14707	14818	14949	11111	13211	13355	13959	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Adenoma			X																							1
Carcinoma															X											1
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Carcinoma																										1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Carcinoma					X																					1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Hepatocellular carcinoma								X			X												X			8
Hepatocellular carcinoma, multiple																										3
Hepatocellular adenoma			X				X		X	X						X			X					X		11
Hepatocellular adenoma, multiple				X		X								X						X						8
Hepatocholangiocarcinoma						X																				1
Mesentery	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma, metastatic, liver																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma																X										1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Tooth				+					+		+			+						+					+	15
Cardiovascular System																										
Blood vessel														+												2
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma, metastatic, liver																										1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcapsular, adenoma	X			X								X													X	6
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma																										1
Parathyroid gland	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars intermedia, adenoma																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study of Diisopropylcarbodiimide: 20 mg/kg

Number of Days on Study	0 4 8	0 5 5	4 9 3	4 9 6	5 9 7	6 2 5	6 5 3	6 6 9	6 8 1	6 9 0	7 1 3	7 1 5	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0
Carcass ID Number	1 2 2	1 2 3	1 4 2	1 3 7	1 5 0	1 0 5	1 1 5	1 1 7	1 2 5	1 4 5	1 0 2	1 4 4	1 0 8	1 1 2	1 1 4	1 1 8	1 2 1	1 2 4	1 2 8	1 2 9	1 3 2	1 3 4	1 4 3	1 0 1	1 0 4
General Body System																									
Peritoneum	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tissue NOS					+			+																	
Abdominal, hepatocellular carcinoma, metastatic, liver					X																				
Mediastinum, hepatocellular carcinoma, metastatic, liver					X																				
Thoracic, hepatocellular carcinoma, metastatic, liver								X																	
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell, adenoma										X															
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Lymph node															+	+									
Lymph node, mandibular	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Thymus	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic, liver					X																				
Integumentary System																									
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle										+					+										
Hemangiosarcoma															X										
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve										+															
Spinal cord										+															

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study of Diisopropylcarbodiimide: 20 mg/kg

Number of Days on Study	730	730	730	730	730	730	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	732	732	732	
Carcass ID Number	10707	11909	12020	12207	13303	13636	10003	10006	10009	11003	11306	11606	12606	13008	13308	14001	14401	14606	14707	14808	14909	11101	13311	13505	13909	Total Tissues/ Tumors
General Body System																										
Peritoneum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Tissue NOS					+																					3
Abdominal, hepatocellular carcinoma, metastatic, liver																										1
Mediastinum, hepatocellular carcinoma, metastatic, liver																										1
Thoracic, hepatocellular carcinoma, metastatic, liver																										1
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell, adenoma																										1
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																							X			1
Lymph node						+		+							+											5
Lymph node, mandibular	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	47
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																							X			1
Thymus	+	+	+	+	+	I	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Hepatocellular carcinoma, metastatic, liver																										1
Integumentary System																										
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										2
Hemangiosarcoma																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Peripheral nerve																										1
Spinal cord																										1

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study of Diisopropylcarbodiimide: 20 mg/kg

Number of Days on Study	0 4 8	0 5 5	4 9 3	4 9 6	5 9 7	6 2 5	6 5 3	6 6 9	6 8 1	6 9 0	7 1 3	7 1 5	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0
Carcass ID Number	1 2 2	1 2 3	1 4 2	1 3 7	1 5 0	1 0 5	1 1 5	1 1 7	1 2 5	1 4 5	1 0 2	1 4 4	1 0 8	1 1 2	1 1 4	1 1 8	1 2 1	1 2 4	1 2 8	1 2 9	1 3 2	1 3 4	1 4 3	1 0 1	1 0 4
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma										X		X	X									X			X
Alveolar/bronchiolar carcinoma																				X					
Alveolar/bronchiolar carcinoma, multiple																									
Hepatocellular carcinoma, metastatic, liver					X		X	X	X																
Mediastinum, hepatocellular carcinoma, metastatic, liver								X																	
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye	+	+	A	+	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma						X				X											X				
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic, liver					X																				
Urinary bladder	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																									
Serosa, hemangiosarcoma																									
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant																X									

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study of Diisopropylcarbodiimide: 20 mg/kg

Number of Days on Study	730	730	730	730	730	730	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	732	732	732	
Carcass ID Number	10107	10119	10120	10227	10233	10236	10243	10006	10209	10210	10213	10216	10226	10230	10238	10240	10241	10246	10247	10248	10249	10311	10315	10329	10339	Total Tissues/ Tumors
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma			X													X										7
Alveolar/bronchiolar carcinoma					X																					2
Alveolar/bronchiolar carcinoma, multiple													X												X	2
Hepatocellular carcinoma, metastatic, liver																										4
Mediastinum, hepatocellular carcinoma, metastatic, liver																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma	X	X					X	X				X	X											X		10
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma, metastatic, liver																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangioma																			X							1
Serosa, hemangiosarcoma											X															1
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant														X												2

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study of Diisopropylcarbodiimide: 40 mg/kg

Number of Days on Study	0 3 1	0 4 8	4 7 4	4 8 4	4 9 8	5 5 8	5 7 3	6 4 2	6 6 4	6 6 7	6 7 4	6 7 9	7 1 0	7 1 2	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0
Carcass ID Number	1 1 9 5	1 8 2	1 5 2	1 6 6	1 8 0	1 9 9	1 5 6	1 7 3	1 5 1	1 8 1	1 6 3	1 5 7	1 7 8	1 9 6	1 6 2	1 6 4	1 7 1	1 7 6	1 8 4	1 8 5	1 9 1	1 9 4	2 0 0	1 5 3	1 5 8
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	A	A	I	A	+	+	+	M	A	M	A	+	A	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	A	+	+	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	A	A	+	+	A	+	A	+	A	A	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Leiomyoma																									
Intestine small, duodenum	A	A	A	+	A	+	+	+	A	A	A	A	+	A	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	A	A	A	+	A	+	A	+	A	A	A	A	+	A	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Intestine small, ileum	A	A	A	+	A	+	A	+	A	A	A	A	+	A	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma											X														
Hepatocellular carcinoma			X	X								X	X												X
Hepatocellular carcinoma, multiple														X								X			
Hepatocellular adenoma					X		X									X								X	
Hepatocellular adenoma, multiple															X			X							
Squamous cell carcinoma, metastatic, stomach, forestomach																									
Mesentery	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, pancreas													X												
Sarcoma									X																
Schwannoma malignant, metastatic, uncertain primary site					X																				
Pancreas	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, metastatic, uncertain primary site									X																
Duct, carcinoma													X												
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma																									
Squamous cell papilloma																									
Serosa, carcinoma, metastatic, pancreas													X												
Stomach, glandular	+	+	+	+	+	+	+	+	+	A	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, pancreas													X												
Tooth							+		+							+				+				+	
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Subcapsular, adenoma								X											X						
Adrenal medulla	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant												X													
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Parathyroid gland	+	+	+	+	+	+	M	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma														X											

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study of Diisopropylcarbodiimide: 40 mg/kg

Number of Days on Study	730	730	730	730	730	730	730	730	730	730	730	730	730	731	731	731	731	731	731	732	732	732	732	732	732	
Carcass ID Number	16060	16061	16065	16067	16068	17074	17077	18083	18087	18088	19093	19097	15074	15075	15079	18089	19090	19092	16069	17070	17072	17075	17079	18086	19098	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	41
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Leiomyoma													X													1
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	40
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Carcinoma																							X			1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma																										1
Hepatocellular carcinoma					X																		X		X	8
Hepatocellular carcinoma, multiple																						X				3
Hepatocellular adenoma							X		X						X	X			X	X						10
Hepatocellular adenoma, multiple		X		X	X			X			X						X	X								9
Squamous cell carcinoma, metastatic, stomach, forestomach																X										1
Mesentery	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, pancreas																										1
Sarcoma																										1
Schwannoma malignant, metastatic, uncertain primary site																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Sarcoma, metastatic, uncertain primary site																										1
Duct, carcinoma																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma																X										1
Squamous cell papilloma													X													1
Serosa, carcinoma, metastatic, pancreas																										1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Carcinoma, metastatic, pancreas																										1
Tooth					+			+	+			+					+		+			+				12
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma															X											1
Subcapsular, adenoma								X														X				4
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma malignant																										1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																	X									1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, adenoma																										1

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study of Diisopropylcarbodiimide: 40 mg/kg

Number of Days on Study	0 3 1	0 4 8	4 7 4	4 8 4	4 9 8	5 5 8	5 7 3	6 4 2	6 6 4	6 6 7	6 7 4	6 7 9	7 1 0	7 1 2	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0
Carcass ID Number	1 9 5	1 8 2	1 5 2	1 6 6	1 8 0	1 9 9	1 5 6	1 7 3	1 5 1	1 8 1	1 6 3	1 5 7	1 7 8	1 9 6	1 6 2	1 6 4	1 7 1	1 7 6	1 8 4	1 8 5	1 9 1	1 9 4	2 0 0	1 5 3	1 5 8
General Body System																									
Peritoneum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, pancreas													X												
Sarcoma									X																
Tissue NOS	+											+													
Mediastinum, hepatocellular carcinoma, metastatic, liver												X													
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma						X																			
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, pancreas													X												
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell, adenoma																									
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma								X																	
Lymph node						+			+				+												
Mediastinal, carcinoma, metastatic, pancreas													X												
Mediastinal, sarcoma, metastatic, uncertain primary site									X																
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	I	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	M	A	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, metastatic, uncertain primary site									X																
Spleen	+	+	+	+	+	+	+	+	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma								X																	
Thymus	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic, liver												X													
Integumentary System																									
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	A	M	M	M	M	M	M	M	M	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, hemangiosarcoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle				+		+		+		+			+												
Alveolar/bronchiolar carcinoma, metastatic, lung										X															
Carcinoma, metastatic, pancreas													X												

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study of Diisopropylcarbodiimide: 40 mg/kg

Number of Days on Study	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	
Carcass ID Number	1 6 0	1 6 1	1 6 5	1 6 7	1 6 8	1 7 4	1 7 7	1 8 3	1 8 7	1 8 8	1 9 3	1 9 7	1 5 4	1 5 5	1 5 9	1 8 9	1 9 0	1 9 2	1 6 9	1 7 0	1 7 2	1 7 5	1 7 9	1 8 6	1 9 8	Total Tissues/ Tumors
General Body System																									
Peritoneum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, pancreas																									1
Sarcoma																									1
Tissue NOS																									2
Mediastinum, hepatocellular carcinoma, metastatic, liver																									1
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																									1
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, pancreas																									1
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell, adenoma																					X				1
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma											X														2
Lymph node											+														4
Mediastinal, carcinoma, metastatic, pancreas																									1
Mediastinal, sarcoma, metastatic, uncertain primary site																									1
Lymph node, mandibular	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Sarcoma, metastatic, uncertain primary site																									1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	47
Hemangiosarcoma											X														2
Thymus	+	+	I	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Hepatocellular carcinoma, metastatic, liver																									1
Integumentary System																									
Mammary gland	M	M	M	M	M	M	+	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, hemangiosarcoma											X														1
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																									5
Alveolar/bronchiolar carcinoma, metastatic, lung																									1
Carcinoma, metastatic, pancreas																									1

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study of Diisopropylcarbodiimide: 40 mg/kg

Number of Days on Study	0 3 1	0 4 8	4 7 4	4 8 4	4 9 8	5 5 8	5 7 3	6 4 2	6 6 4	6 6 7	6 7 4	6 7 9	7 1 0	7 1 2	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0
Carcass ID Number	1 9 5	1 8 2	1 5 2	1 6 6	1 8 0	1 9 9	1 5 6	1 7 3	1 5 1	1 8 1	1 6 3	1 5 7	1 7 8	1 9 6	1 6 2	1 6 4	1 7 1	1 7 6	1 8 4	1 8 5	1 9 1	1 9 4	2 0 0	1 5 3	1 5 8
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve				+			+	+																	
Schwannoma malignant							X																		
Spinal cord				+				+																	
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																								X	
Alveolar/bronchiolar adenoma, multiple																									
Alveolar/bronchiolar carcinoma										X															
Carcinoma, metastatic, pancreas													X												
Hepatocellular carcinoma, metastatic, liver												X		X								X			
Sarcoma, metastatic, uncertain primary site									X																
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pleura																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye	+	A	A	+	A	+	+	+	+	A	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma			X													X				X		X	X		
Carcinoma																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Schwannoma malignant, metastatic, uncertain primary site					X																				
Capsule, carcinoma, metastatic, pancreas													X												
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant																								X	

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study of Diisopropylcarbodiimide: 40 mg/kg

Number of Days on Study	730	730	730	730	730	730	730	730	730	730	730	730	730	731	731	731	731	731	731	732	732	732	732	732	732	732	
Carcass ID Number	160	161	165	167	168	174	177	183	187	188	193	197	254	255	259	289	290	292	296	700	722	725	779	786	798		Total Tissues/ Tumors
Nervous System																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Peripheral nerve																											3
Schwannoma malignant																											1
Spinal cord											+																3
Respiratory System																											
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Alveolar/bronchiolar adenoma					X	X							X	X	X			X									7
Alveolar/bronchiolar adenoma, multiple	X																										1
Alveolar/bronchiolar carcinoma											X																2
Carcinoma, metastatic, pancreas																											1
Hepatocellular carcinoma, metastatic, liver																											3
Sarcoma, metastatic, uncertain primary site																											1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Pleura		+																									1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Special Senses System																											
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		44
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Adenoma	X			X												X											8
Carcinoma						X			X										X								3
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		48
Schwannoma malignant, metastatic, uncertain primary site																											1
Capsule, carcinoma, metastatic, pancreas																											1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Lymphoma malignant						X					X																3

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Dermal Study of Diisopropylcarbodiimide

	Vehicle Control	10 mg/kg	20 mg/kg	40 mg/kg
Adrenal Cortex: Adenoma				
Overall rate[a]	5/50 (10%)	3/50 (6%)	6/50 (12%)	5/49 (10%)
Adjusted rate[b]	10.6%	6.5%	13.4%	11.6%
Terminal rate[c]	4/39 (10%)	3/40 (8%)	5/38 (13%)	4/36 (11%)
First incidence (days)	682	729 (T)	713	642
Poly-3 test[d]	P=0.391	P=0.368N	P=0.468	P=0.574
Harderian Gland: Adenoma				
Overall rate	9/50 (18%)	9/50 (18%)	10/50 (20%)	8/50 (16%)
Adjusted rate	19.2%	19.5%	22.1%	18.1%
Terminal rate	8/39 (21%)	8/40 (20%)	8/38 (21%)	7/36 (19%)
First incidence (days)	706	660	625	474
Poly-3 test	P=0.511N	P=0.590	P=0.467	P=0.554N
Harderian Gland: Carcinoma				
Overall rate	2/50 (4%)	1/50 (2%)	0/50 (0%)	3/50 (6%)
Adjusted rate	4.3%	2.2%	0.0%	6.9%
Terminal rate	1/39 (3%)	1/40 (3%)	0/38 (0%)	3/36 (8%)
First incidence (days)	725	729 (T)	—[e]	729 (T)
Poly-3 test	P=0.322	P=0.506N	P=0.247N	P=0.466
Harderian Gland: Adenoma or Carcinoma				
Overall rate	10/50 (20%)	10/50 (20%)	10/50 (20%)	11/50 (22%)
Adjusted rate	21.3%	21.6%	22.1%	24.9%
Terminal rate	8/39 (21%)	9/40 (23%)	8/38 (21%)	10/36 (28%)
First incidence (days)	706	660	625	474
Poly-3 test	P=0.378	P=0.585	P=0.566	P=0.438
Small Intestine (Duodenum, Jejunum, Ileum): Carcinoma				
Overall rate	0/50 (0%)	0/50 (0%)	3/50 (6%)	1/50 (2%)
Adjusted rate	0.0%	0.0%	6.7%	2.3%
Terminal rate	0/39 (0%)	0/40 (0%)	2/38 (5%)	1/36 (3%)
First incidence (days)	—	—[f]	653	729 (T)
Poly-3 test	P=0.215	—	P=0.112	P=0.485
Small Intestine (Duodenum, Jejunum, Ileum): Adenoma or Carcinoma				
Overall rate	1/50 (2%)	1/50 (2%)	4/50 (8%)	1/50 (2%)
Adjusted rate	2.1%	2.2%	8.9%	2.3%
Terminal rate	1/39 (3%)	0/40 (0%)	3/38 (8%)	1/36 (3%)
First incidence (days)	729 (T)	603	653	729 (T)
Poly-3 test	P=0.478	P=0.759	P=0.168	P=0.744
Liver: Hepatocellular Adenoma				
Overall rate	18/50 (36%)	22/50 (44%)	19/50 (38%)	19/49 (39%)
Adjusted rate	38.4%	47.1%	41.5%	43.3%
Terminal rate	18/39 (46%)	20/40 (50%)	16/38 (42%)	17/36 (47%)
First incidence (days)	729 (T)	603	493	498
Poly-3 test	P=0.442	P=0.260	P=0.463	P=0.399
Liver: Hepatocellular Carcinoma				
Overall rate	20/50 (40%)	15/50 (30%)	11/50 (22%)	11/49 (22%)
Adjusted rate	40.4%	30.9%	23.5%	24.7%
Terminal rate	12/39 (31%)	8/40 (20%)	4/38 (11%)	6/36 (17%)
First incidence (days)	515	435	496	474
Poly-3 test	P=0.057N	P=0.222N	P=0.058N	P=0.081N

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Dermal Study of Diisopropylcarbodiimide

	Vehicle Control	10 mg/kg	20 mg/kg	40 mg/kg
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rate	35/50 (70%)	33/50 (66%)[g]	29/50 (58%)	29/49 (59%)
Adjusted rate	70.7%	67.5%	60.9%	63.5%
Terminal rate	27/39 (69%)	25/40 (63%)	20/38 (53%)	22/36 (61%)
First incidence (days)	515	435	493	474
Poly-3 test	P=0.236N	P=0.449N	P=0.210N	P=0.297N
Liver: Hepatocellular Carcinoma or Hepatoblastoma				
Overall rate	20/50 (40%)	16/50 (32%)	11/50 (22%)	11/49 (22%)
Adjusted rate	40.4%	33.0%	23.5%	24.7%
Terminal rate	12/39 (31%)	9/40 (23%)	4/38 (11%)	6/36 (17%)
First incidence (days)	515	435	496	474
Poly-3 test	P=0.050N	P=0.292N	P=0.058N	P=0.081N
Lung: Alveolar/bronchiolar Adenoma				
Overall rate	6/50 (12%)	6/50 (12%)	7/50 (14%)	8/50 (16%)
Adjusted rate	12.7%	13.0%	15.5%	18.4%
Terminal rate	5/39 (13%)	6/40 (15%)	5/38 (13%)	8/36 (22%)
First incidence (days)	598	729 (T)	690	729 (T)
Poly-3 test	P=0.242	P=0.601	P=0.463	P=0.323
Lung: Alveolar/bronchiolar Carcinoma				
Overall rate	2/50 (4%)	3/50 (6%)	4/50 (8%)	2/50 (4%)
Adjusted rate	4.3%	6.5%	8.9%	4.6%
Terminal rate	2/39 (5%)	3/40 (8%)	4/38 (11%)	1/36 (3%)
First incidence (days)	729 (T)	729 (T)	729 (T)	667
Poly-3 test	P=0.559	P=0.492	P=0.317	P=0.669
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rate	8/50 (16%)	9/50 (18%)	11/50 (22%)	10/50 (20%)
Adjusted rate	16.9%	19.6%	24.4%	22.9%
Terminal rate	7/39 (18%)	9/40 (23%)	9/38 (24%)	9/36 (25%)
First incidence (days)	598	729 (T)	690	667
Poly-3 test	P=0.260	P=0.476	P=0.264	P=0.327
All Organs: Hemangiosarcoma				
Overall rate	0/50 (0%)	2/50 (4%)	4/50 (8%)	3/50 (6%)
Adjusted rate	0.0%	4.4%	8.9%	6.8%
Terminal rate	0/39 (0%)	2/40 (5%)	4/38 (11%)	1/36 (3%)
First incidence (days)	—	729 (T)	729 (T)	642
Poly-3 test	P=0.094	P=0.233	P=0.055	P=0.108
All Organs: Hemangioma or Hemangiosarcoma				
Overall rate	1/50 (2%)	2/50 (4%)	5/50 (10%)	3/50 (6%)
Adjusted rate	2.1%	4.4%	11.2%	6.8%
Terminal rate	1/39 (3%)	2/40 (5%)	5/38 (13%)	1/36 (3%)
First incidence (days)	729 (T)	729 (T)	729 (T)	642
Poly-3 test	P=0.185	P=0.494	P=0.092	P=0.283
All Organs: Malignant Lymphoma				
Overall rate	2/50 (4%)	2/50 (4%)	2/50 (4%)	3/50 (6%)
Adjusted rate	4.3%	4.4%	4.5%	6.9%
Terminal rate	1/39 (3%)	2/40 (5%)	2/38 (5%)	3/36 (8%)
First incidence (days)	672	729 (T)	729 (T)	729 (T)
Poly-3 test	P=0.353	P=0.686	P=0.676	P=0.464

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Dermal Study of Diisopropylcarbodiimide

	Vehicle Control	10 mg/kg	20 mg/kg	40 mg/kg
All Organs: Benign Neoplasms				
Overall rate	29/50 (58%)	31/50 (62%)	33/50 (66%)	31/50 (62%)
Adjusted rate	60.9%	66.1%	71.5%	67.7%
Terminal rate	25/39 (64%)	28/40 (70%)	28/38 (74%)	26/36 (72%)
First incidence (days)	598	603	493	474
Poly-3 test	P=0.269	P=0.376	P=0.188	P=0.315
All Organs: Malignant Neoplasms				
Overall rate	27/50 (54%)	21/50 (42%)	22/50 (44%)	24/50 (48%)
Adjusted rate	54.0%	43.3%	46.6%	50.0%
Terminal rate	16/39 (41%)	14/40 (35%)	14/38 (37%)	12/36 (33%)
First incidence (days)	515	435	496	474
Poly-3 test	P=0.473N	P=0.196N	P=0.299N	P=0.424N
All Organs: Benign or Malignant Neoplasms				
Overall rate	42/50 (84%)	42/50 (84%)	42/50 (84%)	41/50 (82%)
Adjusted rate	84.0%	85.9%	87.5%	85.4%
Terminal rate	31/39 (80%)	34/40 (85%)	32/38 (84%)	29/36 (81%)
First incidence (days)	515	435	493	474
Poly-3 test	P=0.478	P=0.510	P=0.419	P=0.534

(T) Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, liver, and lung; 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 is the P value corresponding to pairwise comparisons between the vehicle controls and that of the 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.
[g] One hepatoblastoma occurred in an animal that also had a hepatocellular adenoma.

TABLE C4
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Dermal Study of Diisopropylcarbodiimide[a]

	Vehicle Control	10 mg/kg	20 mg/kg	40 mg/kg
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Accidental death				1
Moribund	5	1	2	5
Natural deaths	6	9	10	8
Survivors				
Died last week of study	1			
Terminal sacrifice	38	40	38	36
Animals examined microscopically	50	50	50	50
Alimentary System				
Gallbladder	(45)	(42)	(43)	(41)
Cyst	1 (2%)	1 (2%)	2 (5%)	
Epithelium, degeneration, hyaline		1 (2%)	1 (2%)	
Epithelium, hyperplasia			1 (2%)	
Intestine small, duodenum	(46)	(44)	(44)	(40)
Ectopic tissue		1 (2%)		
Serosa, inflammation, chronic				1 (3%)
Intestine small, jejunum	(46)	(43)	(44)	(40)
Cyst				1 (3%)
Inflammation, focal		1 (2%)	1 (2%)	
Necrosis	1 (2%)			
Peyer's patch, hyperplasia, lymphoid	1 (2%)	1 (2%)		1 (3%)
Intestine small, ileum	(46)	(44)	(44)	(40)
Peyer's patch, hyperplasia, lymphoid	1 (2%)			
Liver	(50)	(50)	(50)	(49)
Atrophy	1 (2%)			
Basophilic focus	1 (2%)			
Clear cell focus	2 (4%)	1 (2%)	1 (2%)	2 (4%)
Eosinophilic focus	2 (4%)	1 (2%)	1 (2%)	4 (8%)
Fibrosis, focal	1 (2%)			
Hemorrhage, focal				1 (2%)
Hepatodiaphragmatic nodule				1 (2%)
Hyperplasia, focal, histiocytic		1 (2%)		
Infarct			1 (2%)	1 (2%)
Infiltration cellular, polymorphonuclear	1 (2%)			
Infiltration cellular, mixed cell	8 (16%)	5 (10%)	5 (10%)	6 (12%)
Inflammation, focal, granulomatous				1 (2%)
Pigmentation, focal		1 (2%)		
Thrombosis			1 (2%)	
Bile duct, hyperplasia	1 (2%)		1 (2%)	
Capsule, inflammation, chronic				1 (2%)
Hepatocyte, clear cell focus	19 (38%)	17 (34%)	12 (24%)	8 (16%)
Hepatocyte, eosinophilic focus	2 (4%)			
Hepatocyte, mixed cell focus	1 (2%)	2 (4%)		2 (4%)
Hepatocyte, necrosis, focal	5 (10%)	3 (6%)	2 (4%)	7 (14%)
Hepatocyte, vacuolization cytoplasmic	18 (36%)	17 (34%)	17 (34%)	18 (37%)
Mesentery	(49)	(49)	(50)	(50)
Fibrosis, focal			1 (2%)	
Inflammation		1 (2%)		1 (2%)
Inflammation, chronic				1 (2%)
Artery, inflammation		1 (2%)		
Fat, necrosis, focal	4 (8%)	2 (4%)	4 (8%)	4 (8%)

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

TABLE C4
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Dermal Study of Diisopropylcarbodiimide

	Vehicle Control	10 mg/kg	20 mg/kg	40 mg/kg
Alimentary System (continued)				
Pancreas	(49)	(50)	(49)	(49)
Inflammation, focal			1 (2%)	
Necrosis, focal		1 (2%)	1 (2%)	
Acinus, atrophy, focal				3 (6%)
Serosa, inflammation, chronic				1 (2%)
Salivary glands	(50)	(50)	(50)	(50)
Atrophy			1 (2%)	
Stomach, forestomach	(50)	(50)	(50)	(50)
Diverticulum				1 (2%)
Erosion		1 (2%)		
Inflammation, focal			1 (2%)	1 (2%)
Ulcer		1 (2%)		
Epithelium, cyst				1 (2%)
Epithelium, hyperplasia	2 (4%)	2 (4%)	3 (6%)	2 (4%)
Stomach, glandular	(50)	(47)	(48)	(47)
Erosion	4 (8%)	1 (2%)	1 (2%)	
Tooth	(18)	(11)	(15)	(12)
Malformation	18 (100%)	11 (100%)	15 (100%)	12 (100%)
Peridontal tissue, inflammation, chronic			1 (7%)	
Pulp, inflammation			1 (7%)	
Cardiovascular System				
Heart	(50)	(50)	(50)	(50)
Cardiomyopathy			1 (2%)	1 (2%)
Infiltration cellular, mixed cell				1 (2%)
Inflammation, chronic, focal			1 (2%)	
Thrombosis		1 (2%)		
Artery, inflammation, chronic		1 (2%)		
Endocrine System				
Adrenal cortex	(50)	(50)	(50)	(49)
Accessory adrenal cortical nodule	3 (6%)	2 (4%)	2 (4%)	2 (4%)
Cytoplasmic alteration, focal	9 (18%)	5 (10%)	7 (14%)	4 (8%)
Degeneration, cystic				1 (2%)
Hyperplasia, focal, histiocytic		1 (2%)		
Hypertrophy			1 (2%)	
Vacuolization cytoplasmic, focal	1 (2%)			
Adrenal medulla	(49)	(50)	(50)	(49)
Angiectasis	1 (2%)			
Hyperplasia, focal			1 (2%)	
Islets, pancreatic	(49)	(50)	(49)	(50)
Hyperplasia	2 (4%)	2 (4%)	2 (4%)	1 (2%)
Parathyroid gland	(49)	(50)	(46)	(47)
Cyst	1 (2%)		2 (4%)	1 (2%)
Pituitary gland	(48)	(47)	(50)	(49)
Cyst	1 (2%)	2 (4%)	3 (6%)	3 (6%)
Pars distalis, cytoplasmic alteration, focal	1 (2%)		5 (10%)	
Pars distalis, hyperplasia, focal	1 (2%)			
Thyroid gland	(49)	(50)	(50)	(50)
C-cell, hyperplasia	1 (2%)	3 (6%)		
Follicle, degeneration, cystic, focal	4 (8%)	6 (12%)	8 (16%)	6 (12%)
Follicular cell, hyperplasia, focal	7 (14%)	7 (14%)	8 (16%)	3 (6%)

TABLE C4
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Dermal Study of Diisopropylcarbodiimide

	Vehicle Control	10 mg/kg	20 mg/kg	40 mg/kg
General Body System				
Tissue NOS			(3)	(2)
Hemorrhage				1 (50%)
Abdominal, cyst			1 (33%)	
Genital System				
Epididymis	(50)	(50)	(50)	(50)
Granuloma sperm			1 (2%)	1 (2%)
Inflammation, chronic			1 (2%)	1 (2%)
Spermatocele		1 (2%)		
Preputial gland	(50)	(50)	(50)	(50)
Cyst				2 (4%)
Degeneration, cystic	3 (6%)	1 (2%)	1 (2%)	4 (8%)
Hyperplasia, lymphoid		1 (2%)		
Inflammation, chronic	11 (22%)	8 (16%)	10 (20%)	6 (12%)
Prostate	(50)	(50)	(50)	(50)
Inflammation		1 (2%)		2 (4%)
Epithelium, hyperplasia, focal	2 (4%)	1 (2%)		
Seminal vesicle	(50)	(50)	(50)	(50)
Cyst		1 (2%)		
Testes	(50)	(50)	(50)	(50)
Atrophy		1 (2%)	1 (2%)	
Interstitial cell, hyperplasia, focal			1 (2%)	
Hematopoietic System				
Bone marrow	(49)	(50)	(50)	(50)
Hyperplasia	9 (18%)	13 (26%)	12 (24%)	7 (14%)
Thrombosis				1 (2%)
Lymph node	(6)	(5)	(5)	(4)
Bronchial, hyperplasia, lymphoid		1 (20%)		
Iliac, hyperplasia, lymphoid				1 (25%)
Inguinal, hyperplasia, lymphoid	2 (33%)	3 (60%)	4 (80%)	1 (25%)
Mediastinal, hyperplasia, lymphoid			1 (20%)	
Pancreatic, hyperplasia, lymphoid		1 (20%)	1 (20%)	1 (25%)
Lymph node, mandibular	(47)	(48)	(47)	(47)
Hyperplasia, histiocytic				1 (2%)
Hyperplasia, lymphoid		1 (2%)		1 (2%)
Lymph node, mesenteric	(50)	(48)	(49)	(48)
Ectasia			1 (2%)	
Hematopoietic cell proliferation		1 (2%)		
Hemorrhage	3 (6%)	1 (2%)	3 (6%)	
Hyperplasia, lymphoid	3 (6%)	2 (4%)	4 (8%)	2 (4%)
Spleen	(49)	(50)	(50)	(47)
Atrophy	1 (2%)		1 (2%)	
Fibrosis, focal				1 (2%)
Hematopoietic cell proliferation	15 (31%)	13 (26%)	14 (28%)	13 (28%)
Hyperplasia, lymphoid	2 (4%)	5 (10%)	1 (2%)	1 (2%)
Thrombosis				1 (2%)
Capsule, inflammation, chronic				1 (2%)
Thymus	(47)	(44)	(47)	(46)
Cyst	2 (4%)	1 (2%)	2 (4%)	
Hyperplasia, lymphoid	1 (2%)			

TABLE C4
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Dermal Study of Diisopropylcarbodiimide

	Vehicle Control	10 mg/kg	20 mg/kg	40 mg/kg
Integumentary System				
Skin	(50)	(50)	(50)	(50)
Ulcer	1 (2%)			
Epidermis, hyperplasia, focal	1 (2%)		1 (2%)	
Site of application, dermis, inflammation, focal	2 (4%)	2 (4%)	9 (18%)	1 (2%)
Site of application, epidermis, hyperplasia	2 (4%)	3 (6%)	10 (20%)	1 (2%)
Site of application, ulcer		1 (2%)	1 (2%)	
Subcutaneous tissue, angiectasis, focal			1 (2%)	
Subcutaneous tissue, edema				2 (4%)
Subcutaneous tissue, inflammation, chronic, focal			1 (2%)	
Subcutaneous tissue, thrombosis			1 (2%)	
Subcutaneous tissue, site of application, infiltration cellular				1 (2%)
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Hyperostosis	2 (4%)	2 (4%)	1 (2%)	
Skeletal muscle	(2)	(2)	(2)	(5)
Inflammation, chronic				1 (20%)
Nervous System				
None				
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Congestion	1 (2%)		1 (2%)	
Hyperplasia, histiocytic	1 (2%)	1 (2%)	4 (8%)	
Hyperplasia, lymphoid	1 (2%)	1 (2%)		
Inflammation, chronic, focal	1 (2%)			
Alveolar epithelium, hyperplasia, focal	4 (8%)	2 (4%)	1 (2%)	3 (6%)
Mediastinum, hyperplasia, lymphoid	1 (2%)			
Nose	(49)	(50)	(50)	(50)
Inflammation	2 (4%)		1 (2%)	
Nasolacrimal duct, cyst		1 (2%)		
Nasolacrimal duct, hyperplasia, focal	1 (2%)	2 (4%)	1 (2%)	
Nasolacrimal duct, inflammation	1 (2%)		2 (4%)	3 (6%)
Special Senses System				
Eye	(46)	(46)	(47)	(44)
Atrophy	1 (2%)			
Inflammation	1 (2%)			
Cornea, hyperplasia, squamous		1 (2%)		1 (2%)
Cornea, inflammation, chronic	2 (4%)	3 (7%)	1 (2%)	3 (7%)
Cornea, necrosis, focal		1 (2%)		1 (2%)
Retrobulbar, inflammation				1 (2%)
Harderian gland	(50)	(50)	(50)	(50)
Degeneration, cystic, focal		1 (2%)		
Inflammation	1 (2%)			1 (2%)
Epithelium, hyperplasia, focal	3 (6%)		3 (6%)	1 (2%)

TABLE C4
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Dermal Study of Diisopropylcarbodiimide

	Vehicle Control	10 mg/kg	20 mg/kg	40 mg/kg
Urinary System				
Kidney	(48)	(48)	(50)	(48)
Cyst	3 (6%)	10 (21%)	5 (10%)	3 (6%)
Hydronephrosis	2 (4%)	1 (2%)		
Infarct	2 (4%)	3 (6%)	1 (2%)	1 (2%)
Infiltration cellular, mixed cell			1 (2%)	
Inflammation				3 (6%)
Metaplasia, focal, osseous	4 (8%)	2 (4%)	1 (2%)	
Nephropathy	46 (96%)	44 (92%)	41 (82%)	40 (83%)
Pelvis, dilatation				1 (2%)
Renal tubule, hyperplasia, focal	2 (4%)	3 (6%)		1 (2%)
Urinary bladder	(50)	(50)	(49)	(50)
Inflammation		1 (2%)		2 (4%)

APPENDIX D
SUMMARY OF LESIONS
IN FEMALE MICE IN THE 2-YEAR DERMAL STUDY
OF DIISOPROPYLCARBODIIMIDE

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

	Vehicle Control	10 mg/kg	20 mg/kg	40 mg/kg
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Accidental deaths		1	1	1
Moribund	12	11	4	5
Natural deaths	5	5	6	4
Survivors				
Died last week of study		1	1	
Terminal sacrifice	33	32	38	40
Animals examined microscopically	50	50	50	50
Alimentary System				
Esophagus	(50)	(50)	(49)	(50)
Gallbladder	(42)	(47)	(42)	(47)
Intestine large, colon	(49)	(48)	(48)	(48)
Intestine large, cecum	(46)	(45)	(44)	(47)
Intestine small, duodenum	(46)	(46)	(44)	(47)
Adenoma	1 (2%)			
Intestine small, jejunum	(47)	(45)	(44)	(46)
Adenoma		1 (2%)		
Carcinoma			1 (2%)	1 (2%)
Intestine small, ileum	(46)	(44)	(45)	(47)
Liver	(50)	(50)	(50)	(50)
Hemangiosarcoma	1 (2%)	1 (2%)		1 (2%)
Hepatocellular carcinoma	8 (16%)	2 (4%)	7 (14%)	3 (6%)
Hepatocellular carcinoma, multiple	2 (4%)		1 (2%)	
Hepatocellular adenoma	13 (26%)	16 (32%)	10 (20%)	9 (18%)
Hepatocellular adenoma, multiple	8 (16%)	11 (22%)	11 (22%)	9 (18%)
Hepatocholangiocarcinoma, multiple				1 (2%)
Histiocytic sarcoma	3 (6%)		2 (4%)	1 (2%)
Liposarcoma, metastatic, tissue NOS		1 (2%)		
Mesentery	(23)	(20)	(14)	(18)
Hemangiosarcoma, metastatic, liver				1 (6%)
Histiocytic sarcoma	1 (4%)		2 (14%)	2 (11%)
Liposarcoma				1 (6%)
Pancreas	(50)	(48)	(50)	(50)
Histiocytic sarcoma	1 (2%)		1 (2%)	
Salivary glands	(50)	(50)	(50)	(49)
Stomach, forestomach	(50)	(49)	(50)	(50)
Squamous cell carcinoma			1 (2%)	
Squamous cell papilloma	1 (2%)	1 (2%)	1 (2%)	2 (4%)
Stomach, glandular	(49)	(48)	(47)	(50)
Tooth	(1)	(1)	(1)	(2)
Peridontal tissue, histiocytic sarcoma, metastatic, uncertain primary site	1 (100%)			
Peridontal tissue, histiocytic sarcoma, metastatic, nose				1 (50%)
Cardiovascular System				
Heart	(50)	(50)	(49)	(50)
Hepatocholangiocarcinoma, metastatic, liver				1 (2%)
Histiocytic sarcoma			1 (2%)	

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Dermal Study of Diisopropylcarbodiimide

	Vehicle Control	10 mg/kg	20 mg/kg	40 mg/kg
Endocrine System				
Adrenal cortex	(50)	(50)	(49)	(50)
Histiocytic sarcoma	1 (2%)		1 (2%)	
Subcapsular, adenoma				1 (2%)
Adrenal medulla	(49)	(50)	(49)	(49)
Histiocytic sarcoma			1 (2%)	
Pheochromocytoma benign		1 (2%)		1 (2%)
Islets, pancreatic	(50)	(49)	(50)	(50)
Adenoma		2 (4%)		
Pituitary gland	(48)	(50)	(50)	(46)
Pars distalis, adenoma	4 (8%)	12 (24%)	3 (6%)	10 (22%)
Pars distalis, carcinoma	1 (2%)			
Pars intermedia, adenoma		2 (4%)	1 (2%)	1 (2%)
Thyroid gland	(50)	(50)	(50)	(50)
Bilateral, follicular cell, adenoma	1 (2%)			
Follicular cell, adenoma	2 (4%)			2 (4%)
General Body System				
Tissue NOS	(5)	(8)	(3)	(4)
Abdominal, pelvic, liposarcoma		1 (13%)		
Mediastinum, hepatocholangiocarcinoma, metastatic, liver				1 (25%)
Mediastinum, histiocytic sarcoma	1 (20%)		1 (33%)	
Thoracic, hepatocholangiocarcinoma, metastatic, liver				1 (25%)
Genital System				
Ovary	(49)	(50)	(49)	(49)
Cystadenoma	1 (2%)	2 (4%)	2 (4%)	2 (4%)
Granulosa cell tumor benign	1 (2%)			
Hemangiosarcoma	1 (2%)			
Histiocytic sarcoma	1 (2%)		1 (2%)	1 (2%)
Teratoma benign			1 (2%)	
Oviduct	(3)	(1)		
Uterus	(50)	(50)	(50)	(50)
Adenoma	1 (2%)			1 (2%)
Histiocytic sarcoma	3 (6%)	1 (2%)	2 (4%)	2 (4%)
Leiomyosarcoma				2 (4%)
Endometrium, carcinoma		1 (2%)		
Endometrium, polyp stromal	4 (8%)	2 (4%)	5 (10%)	
Endometrium, sarcoma stromal			1 (2%)	
Vagina				(1)
Histiocytic sarcoma				1 (100%)
Hematopoietic System				
Bone marrow	(49)	(50)	(50)	(49)
Hemangiosarcoma	1 (2%)			
Histiocytic sarcoma			2 (4%)	1 (2%)
Liposarcoma, metastatic, tissue NOS		1 (2%)		

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Dermal Study of Diisopropylcarbodiimide

	Vehicle Control	10 mg/kg	20 mg/kg	40 mg/kg
Hematopoietic System (continued)				
Lymph node	(11)	(13)	(10)	(10)
Bronchial, alveolar/bronchiolar carcinoma, metastatic, lung			1 (10%)	
Iliac, carcinoma, metastatic, uterus		1 (8%)		
Iliac, histiocytic sarcoma			1 (10%)	
Mediastinal, histiocytic sarcoma	1 (9%)		1 (10%)	1 (10%)
Pancreatic, histiocytic sarcoma			1 (10%)	
Pancreatic, squamous cell carcinoma, metastatic, stomach, forestomach			1 (10%)	
Renal, histiocytic sarcoma			1 (10%)	
Lymph node, mandibular	(47)	(49)	(49)	(48)
Carcinoma, metastatic, harderian gland			1 (2%)	
Histiocytic sarcoma	1 (2%)		1 (2%)	1 (2%)
Lymph node, mesenteric	(47)	(48)	(49)	(50)
Hemangioma		1 (2%)		
Histiocytic sarcoma	1 (2%)		1 (2%)	1 (2%)
Spleen	(49)	(49)	(50)	(50)
Hemangiosarcoma	1 (2%)	1 (2%)		
Histiocytic sarcoma	1 (2%)		2 (4%)	2 (4%)
Thymus	(46)	(48)	(44)	(47)
Histiocytic sarcoma			1 (2%)	
Integumentary System				
Mammary gland	(50)	(50)	(49)	(49)
Carcinoma	1 (2%)		2 (4%)	
Skin	(50)	(50)	(50)	(50)
Basosquamous tumor benign			1 (2%)	
Squamous cell carcinoma			1 (2%)	
Site of application, basal cell adenoma			1 (2%)	
Subcutaneous tissue, fibroma		1 (2%)		
Subcutaneous tissue, fibrosarcoma	1 (2%)			
Subcutaneous tissue, hemangioma	2 (4%)	1 (2%)		1 (2%)
Subcutaneous tissue, hemangiosarcoma	2 (4%)	1 (2%)		
Subcutaneous tissue, melanoma malignant		1 (2%)	1 (2%)	
Subcutaneous tissue, squamous cell carcinoma				1 (2%)
Subcutaneous tissue, site of application, melanoma benign				1 (2%)
Subcutaneous tissue, site of application, myxoma		1 (2%)		
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Osteosarcoma		1 (2%)		
Cranium, osteosarcoma				1 (2%)
Skeletal muscle		(4)	(1)	(1)
Lipoma		1 (25%)		
Rhabdomyosarcoma			1 (100%)	
Nervous System				
Brain	(50)	(50)	(50)	(50)
Histiocytic sarcoma				1 (2%)
Osteosarcoma, metastatic, bone				1 (2%)
Spinal cord	(1)	(3)		(2)

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Dermal Study of Diisopropylcarbodiimide

	Vehicle Control	10 mg/kg	20 mg/kg	40 mg/kg
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Alveolar/bronchiolar adenoma	3 (6%)	2 (4%)	2 (4%)	1 (2%)
Alveolar/bronchiolar adenoma, multiple	1 (2%)		1 (2%)	
Alveolar/bronchiolar carcinoma		1 (2%)	1 (2%)	4 (8%)
Alveolar/bronchiolar carcinoma, multiple		1 (2%)	1 (2%)	1 (2%)
Carcinoma, metastatic, harderian gland	1 (2%)		1 (2%)	
Carcinoma, metastatic, mammary gland			1 (2%)	
Hepatocellular carcinoma, metastatic, liver	1 (2%)		4 (8%)	
Hepatocholangiocarcinoma, metastatic, liver				1 (2%)
Histiocytic sarcoma			2 (4%)	1 (2%)
Liposarcoma, metastatic, tissue NOS		1 (2%)		
Osteosarcoma, metastatic, uncertain primary site		1 (2%)		
Sarcoma stromal, metastatic, uterus			1 (2%)	
Nose	(50)	(50)	(49)	(50)
Histiocytic sarcoma				1 (2%)
Special Senses System				
Eye	(47)	(48)	(49)	(49)
Carcinoma, metastatic, harderian gland			1 (2%)	
Histiocytic sarcoma			1 (2%)	1 (2%)
Retrobulbar, carcinoma, metastatic, harderian gland	1 (2%)			
Retrobulbar, sarcoma			1 (2%)	
Harderian gland	(50)	(49)	(50)	(50)
Adenoma	9 (18%)	5 (10%)	5 (10%)	3 (6%)
Carcinoma	1 (2%)		4 (8%)	1 (2%)
Zymbal's gland		(1)		
Carcinoma		1 (100%)		
Urinary System				
Kidney	(49)	(49)	(50)	(49)
Histiocytic sarcoma	1 (2%)		2 (4%)	1 (2%)
Ureter		(1)		(1)
Histiocytic sarcoma				1 (100%)
Urinary bladder	(50)	(50)	(49)	(50)
Histiocytic sarcoma			1 (2%)	1 (2%)
Systemic Lesions				
Multiple organs[b]	(50)	(50)	(50)	(50)
Histiocytic sarcoma	3 (6%)	1 (2%)	2 (4%)	2 (4%)
Lymphoma malignant	10 (20%)	9 (18%)	7 (14%)	7 (14%)

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Dermal Study of Diisopropylcarbodiimide

	Vehicle Control	10 mg/kg	20 mg/kg	40 mg/kg
Neoplasm Summary				
Total animals with primary neoplasms[c]	47	43	41	41
Total primary neoplasms	85	84	76	70
Total animals with benign neoplasms	35	38	28	31
Total benign neoplasms	52	62	44	44
Total animals with malignant neoplasms	26	19	26	18
Total malignant neoplasms	33	22	32	26
Total animals with metastatic neoplasms	3	3	9	4
Total metastatic neoplasms	4	5	11	7
Total animals with malignant neoplasms of uncertain primary site	1	1		

[a] Number of animals examined microscopically at the site and the number of animals with neoplasms
[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 Dermal Study of Diisopropylcarbodiimide: Vehicle Control

Number of Days on Study	0 4 4	3 0 5	3 6 5	4 8 8	5 0 6	5 2 1	6 0 3	6 0 3	6 1 9	6 5 3	6 5 4	6 8 1	6 8 3	6 9 7	6 9 8	7 1 5	7 2 0	7 3 2	7 3 2	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3
Carcass ID Number	2 0 4	2 4 4	2 4 6	2 3 2	2 2 7	2 1 4	2 1 0	2 2 2	2 3 9	2 1 7	2 3 8	2 1 2	2 4 5	2 2 1	2 3 1	2 2 5	2 4 7	2 3 4	2 4 0	2 5 0	2 0 2	2 0 8	2 0 9	2 1 8	2 1 9
Alimentary System																								
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	I	+	+	+	A	+	+	+	+	+	A	A	+	A	+	+	M	+	+	+	+	+	M	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	A	+	+	+	+	+	A	A	+	A	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	A	+	+	+	+	+	A	A	+	A	+	+	+	+	+	+	+	+	+	+
Adenoma																								
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	A	A	+	A	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	A	+	+	+	+	+	A	A	+	A	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																								X
Hepatocellular carcinoma									X			X				X						X		
Hepatocellular carcinoma, multiple																	X							X
Hepatocellular adenoma								X			X								X	X	X			
Hepatocellular adenoma, multiple																							X	X
Histiocytic sarcoma				X																			X	
Mesentery			+	+	+		+		+					+	+	+		+		+		+	+	+
Histiocytic sarcoma				X																				
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma				X																				
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																								
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth				+																				
Peridontal tissue, histiocytic sarcoma, metastatic, uncertain primary site				X																				
Cardiovascular System																								
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																								
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma				X																				
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma						X																		
Pars distalis, carcinoma															X									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, follicular cell, adenoma																								
Follicular cell, adenoma																								X

+: 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 Dermal Study of Diisopropylcarbodiimide: Vehicle Control

Number of Days on Study	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	2 2 0	2 2 4	2 2 6	2 3 0	2 3 6	2 3 7	2 4 8	2 0 1	2 0 3	2 0 5	2 0 7	2 1 1	2 1 3	2 1 5	2 1 6	2 2 3	2 3 3	2 4 1	2 4 2	2 0 6	2 2 8	2 2 9	2 3 5	2 4 3	2 4 9	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	42
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Adenoma									X																	1
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Hepatocellular carcinoma											X	X					X	X								8
Hepatocellular carcinoma, multiple																										2
Hepatocellular adenoma					X	X		X		X								X	X			X		X		13
Hepatocellular adenoma, multiple	X		X				X						X	X									X			8
Histiocytic sarcoma			X																							3
Mesentery			+		+								+	+			+		+	+			+		+	23
Histiocytic sarcoma																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma				X																						1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Tooth																										1
Peridontal tissue, histiocytic sarcoma, metastatic, uncertain primary site																										1
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	49
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	46
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	48
Pars distalis, adenoma												X			X						X					4
Pars distalis, carcinoma																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, follicular cell, adenoma																					X					1
Follicular cell, adenoma																		X								2

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Diisopropylcarbodiimide: Vehicle Control

Number of Days on Study	0 4 4	3 0 5	3 6 5	4 8 8	5 0 6	5 2 1	6 0 3	6 0 3	6 1 9	6 5 3	6 5 4	6 8 1	6 8 3	6 9 7	6 9 8	7 1 5	7 2 0	7 3 2	7 3 2	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3
Carcass ID Number	2 0 4	2 4 4	2 4 6	2 3 2	2 2 7	2 1 4	2 1 0	2 2 2	2 3 9	2 1 7	2 3 8	2 1 2	2 4 5	2 2 1	2 3 1	2 2 5	2 4 7	2 3 4	2 4 0	2 5 0	2 0 2	2 0 8	2 0 9	2 1 8	2 1 9
General Body System																								
Tissue NOS			+	+	+									+				+						
Mediastinum, histiocytic sarcoma				X																				
Genital System																								
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	M	+	+	I	+	M	+	+	+	+	+	+	+
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma																								
Granulosa cell tumor benign												X												
Hemangiosarcoma																						X		
Histiocytic sarcoma				X																				
Oviduct																								
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																								
Histiocytic sarcoma				X																			X	
Endometrium, polyp stromal											X													
Hematopoietic System																								
Bone marrow	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma													X											
Lymph node				+	+		+			+				+		+		+						
Mediastinal, histiocytic sarcoma				X																				
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+
Histiocytic sarcoma				X																				
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	M	+	+	+	+	+	+	+
Histiocytic sarcoma				X																				
Spleen	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma													X											
Histiocytic sarcoma				X																				
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	I	+	+
Integumentary System																								
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma															X									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibrosarcoma										X														
Subcutaneous tissue, hemangioma								X																
Subcutaneous tissue, hemangiosarcoma												X	X											
Musculoskeletal System																								
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																								
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve																	+							
Spinal cord																	+							

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Diisopropylcarbodiimide: Vehicle Control

Number of Days on Study	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	2 2 0	2 2 4	2 2 6	2 3 0	2 3 6	2 3 7	2 4 8	2 0 1	2 0 3	2 0 5	2 0 7	2 1 1	2 1 3	2 1 5	2 1 6	2 2 3	2 3 3	2 4 1	2 4 2	2 0 6	2 2 8	2 2 9	2 3 5	2 4 3	2 4 9	Total Tissues/ Tumors
General Body System																										
Tissue NOS																						M				5
Mediastinum, histiocytic sarcoma																										1
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	46
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	49
Cystadenoma						X																				1
Granulosa cell tumor benign																										1
Hemangiosarcoma																										1
Histiocytic sarcoma																										1
Oviduct				+												+									+	3
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																					X					1
Histiocytic sarcoma			X																							3
Endometrium, polyp stromal				X		X					X															4
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma																										1
Lymph node														+		+	+					+				11
Mediastinal, histiocytic sarcoma																										1
Lymph node, mandibular	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	47
Histiocytic sarcoma																										1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	47
Histiocytic sarcoma																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma																										1
Histiocytic sarcoma																										1
Thymus	+	+	+	M	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	46
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																										1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, fibrosarcoma																										1
Subcutaneous tissue, hemangioma		X																								2
Subcutaneous tissue, hemangiosarcoma																										2
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Peripheral nerve																										1
Spinal cord																										1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Diisopropylcarbodiimide: Vehicle Control

Number of Days on Study	0 4 4	3 0 5	3 6 5	4 8 8	5 0 6	5 2 1	6 0 3	6 0 3	6 1 9	6 5 3	6 5 4	6 8 1	6 8 3	6 9 7	6 9 8	7 1 5	7 2 0	7 3 2	7 3 2	7 3 2	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3
Carcass ID Number	2 0 4	2 4 4	2 4 6	2 3 2	2 2 7	2 1 4	2 1 0	2 2 2	2 3 9	2 1 7	2 3 8	2 1 2	2 4 5	2 2 1	2 3 1	2 2 5	2 4 7	2 3 4	2 4 0	2 5 0	2 0 2	2 0 8	2 0 9	2 1 8	2 1 9
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma														X											X
Alveolar/bronchiolar adenoma, multiple								X																	
Carcinoma, metastatic, harderian gland								X																	
Hepatocellular carcinoma, metastatic, liver																	X								
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye	+	+	+	+	A	+	+	+	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+
Retrobulbar, carcinoma, metastatic, harderian gland								X																	
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma									X																X
Carcinoma								X																	
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma				X																					
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma				X																				X	
Lymphoma malignant			X		X		X							X											

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Diisopropylcarbodiimide: Vehicle Control

Number of Days on Study	733	733	733	733	733	733	733	736	736	736	736	736	736	736	736	736	736	736	736	737	737	737	737	737	737	
Carcass ID Number	22020	22044	22266	23000	23366	23737	24048	20101	20003	20005	20007	21101	21103	21105	21106	21233	23303	24141	24212	20006	22208	22299	23355	24343	24449	Total Tissues/ Tumors
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																				X						3
Alveolar/bronchiolar adenoma, multiple																										1
Carcinoma, metastatic, harderian gland																										1
Hepatocellular carcinoma, metastatic, liver																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Retrobulbar, carcinoma, metastatic, harderian gland																										1
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma			X		X					X							X				X		X		X	9
Carcinoma																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma			X																							3
Lymphoma malignant		X												X	X	X	X					X				10

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Diisopropylcarbodiimide: 10 mg/kg

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

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Diisopropylcarbodiimide: 10 mg/kg

Number of Days on Study	7 3 3	7 3 3	7 3 3	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	2 9 0	2 9 2	2 9 4	2 6 7	2 6 9	2 7 0	2 7 1	2 7 6	2 7 7	2 8 2	2 8 6	2 8 9	2 9 3	3 0 0	2 5 2	2 5 5	2 5 6	2 6 2	2 6 3	2 7 9	2 8 4	2 8 7	2 8 8	2 9 5	2 9 9	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Adenoma																										1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Hepatocellular carcinoma																										2
Hepatocellular adenoma	X		X			X		X		X						X						X		X	X	16
Hepatocellular adenoma, multiple									X		X			X	X		X	X	X				X			11
Liposarcoma, metastatic, tissue NOS																										1
Mesentery	+				+									+	+		+	+			+	+		+		20
Oral mucosa																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Squamous cell papilloma																										1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Tooth																										1
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign																			X							1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma							X																			2
Parathyroid gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	43
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma	X						X	X						X				X		X	X					12
Pars intermedia, adenoma																		X								2
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
General Body System																										
Tissue NOS																				+	+					8
Abdominal, pelvic, liposarcoma																										1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Diisopropylcarbodiimide: 10 mg/kg

Number of Days on Study	0 1 2	5 4 0	5 5 5	5 6 8	5 7 9	5 8 8	6 1 7	6 1 9	6 2 5	6 5 3	6 5 3	6 5 3	6 8 3	6 8 4	6 9 0	6 9 5	7 0 7	7 3 2	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3
Carcass ID Number	2 6 0	2 9 1	2 8 0	2 5 3	2 8 5	2 6 6	2 9 7	2 8 1	2 6 4	2 5 7	2 9 6	2 9 8	2 5 4	2 6 1	2 6 8	2 5 9	2 6 5	2 8 3	2 5 1	2 5 8	2 7 2	2 7 3	2 7 4	2 7 5	2 7 8
Genital System																								
Clitoral gland	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma																								
Oviduct				+																				
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma											X													
Endometrium, carcinoma									X															
Endometrium, polyp stromal																								
Hematopoietic System																								
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liposarcoma, metastatic, tissue NOS			X																					
Lymph node				+			+	+	+		+	+			+		+				+			
Iliac, carcinoma, metastatic, uterus									X															
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	I	+	+	+
Hemangioma																				X				
Spleen	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																X								
Thymus	+	I	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																								
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibroma																								
Subcutaneous tissue, hemangioma																			X					
Subcutaneous tissue, hemangiosarcoma										X														
Subcutaneous tissue, melanoma, malignant																								
Subcutaneous tissue, site of application, myxoma																							X	
Musculoskeletal System																								
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma																								
Skeletal muscle							+		+					+										
Lipoma																								
Nervous System																								
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve							+		+					+										
Spinal cord							+		+					+										

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Diisopropylcarbodiimide: 10 mg/kg

Number of Days on Study	733	733	733	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	29090	29902	29904	26267	26469	26770	27701	27716	27717	28202	28486	28489	29093	30060	25502	25555	25556	26262	26363	26779	28284	28287	28288	29595	29599	Total Tissues/ Tumors
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cystadenoma						X																X				2
Oviduct																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Endometrium, carcinoma																										1
Endometrium, polyp stromal													X										X			2
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liposarcoma, metastatic, tissue NOS																										1
Lymph node					+									+							+	+				13
Iliac, carcinoma, metastatic, uterus																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Hemangioma																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma																										1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, fibroma				X																						1
Subcutaneous tissue, hemangioma																										1
Subcutaneous tissue, hemangiosarcoma																										1
Subcutaneous tissue, melanoma malignant											X															1
Subcutaneous tissue, site of application, myxoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma			X																							1
Skeletal muscle																						+				4
Lipoma																						X				1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Peripheral nerve																										3
Spinal cord																										3

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Diisopropylcarbodiimide: 10 mg/kg

Number of Days on Study	0 1 2	5 4 0	5 5 5	5 6 8	5 7 9	5 8 8	6 1 7	6 1 9	6 2 5	6 5 3	6 5 3	6 5 3	6 8 3	6 8 4	6 9 0	6 9 5	7 0 7	7 3 2	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3
Carcass ID Number	26 00	29 01	28 00	25 33	28 55	26 66	29 67	28 11	26 44	25 77	29 66	29 88	25 44	26 11	26 88	25 99	26 55	28 33	25 11	25 88	27 22	27 33	27 44	27 55	27 88
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma												X													
Alveolar/bronchiolar carcinoma																									
Alveolar/bronchiolar carcinoma, multiple										X															
Liposarcoma, metastatic, tissue NOS			X																						
Osteosarcoma, metastatic, uncertain primary site																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	I	+	+	+	+
Harderian gland	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																					X				
Zymbal's gland					+																				
Carcinoma					X																				
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ureter																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma											X														
Lymphoma malignant				X			X	X			X	X													

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Diisopropylcarbodiimide: 10 mg/kg

Number of Days on Study	733	733	733	736	736	736	736	736	736	736	736	736	736	736	737	737	737	737	737	737	737	737	737	737	737	737	
Carcass ID Number	29090	29092	29094	26067	26069	27070	27071	27076	27077	28082	28086	28089	29093	30300	25502	25555	25566	26262	26363	27079	28084	28477	28788	29595	29599	Total Tissues/ Tumors
Respiratory System																											
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma													X														2
Alveolar/bronchiolar carcinoma																	X										1
Alveolar/bronchiolar carcinoma, multiple																											1
Liposarcoma, metastatic, tissue NOS																											1
Osteosarcoma, metastatic, uncertain primary site						X																					1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																											
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma			X	X	X						X																5
Zymbal's gland																											1
Carcinoma																											1
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Ureter					+																						1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																											1
Lymphoma malignant					X											X				X	X						9

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Diisopropylcarbodiimide: 20 mg/kg

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

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Diisopropylcarbodiimide: 20 mg/kg

Number of Days on Study	7 3 3	7 3 3	7 3 3	7 3 4	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	3 4 2	3 4 5	3 4 9	3 1 0	3 0 3	3 0 9	3 1 2	3 2 0	3 2 7	3 3 7	3 4 3	3 4 4	3 4 4	3 0 4	3 0 7	3 1 1	3 1 3	3 1 4	3 1 8	3 2 1	3 2 3	3 2 5	3 3 9	3 4 1	3 4 7	3 5 0	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	49
Gallbladder	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Carcinoma																											1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma			X										X														7
Hepatocellular carcinoma, multiple				X																							1
Hepatocellular adenoma	X		X			X			X						X				X							X	10
Hepatocellular adenoma, multiple		X			X			X		X		X	X					X						X	X		11
Histiocytic sarcoma																											2
Mesentery				+	+	+		+			+							+			+	+				14
Histiocytic sarcoma																											2
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																											1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma												X															1
Squamous cell papilloma													X														1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Tooth																											1
Cardiovascular System																											
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma																											1
Endocrine System																											
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma																											1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma																											1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma														X													3
Pars intermedia, adenoma										X																	1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
General Body System																											
Tissue NOS										+																	3
Mediastinum, histiocytic sarcoma																											1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Diisopropylcarbodiimide: 20 mg/kg

Number of Days on Study	0 1 5	0 6 7	4 1 7	5 6 0	5 7 9	5 8 4	6 0 3	6 1 4	6 5 3	6 8 7	6 9 0	7 3 2	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3
Carcass ID Number	3 2 9	3 0 1	3 3 8	3 0 6	3 3 5	3 1 6	3 1 7	3 3 4	3 4 8	3 0 5	3 4 6	3 3 2	3 0 2	3 0 8	3 1 5	3 1 9	3 2 2	3 2 4	3 2 6	3 2 8	3 3 0	3 3 1	3 3 3	3 3 6	3 4 0
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+
Ovary	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma																			X						
Histiocytic sarcoma				X																					
Teratoma benign		X																							
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma				X		X																			
Endometrium, polyp stromal							X											X						X	
Endometrium, sarcoma stromal																		X							
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma				X		X																			
Lymph node				+			+			+								+	+				+		+
Bronchial, alveolar/bronchiolar carcinoma, metastatic, lung							X																		
Iliac, histiocytic sarcoma				X																					
Mediastinal, histiocytic sarcoma				X																					
Pancreatic, histiocytic sarcoma				X																					
Pancreatic, squamous cell carcinoma, metastatic, stomach, forestomach																									
Renal, histiocytic sarcoma				X																					
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, harderian gland								X																	
Histiocytic sarcoma				X																					
Lymph node, mesenteric	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma				X																					
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma				X		X																			
Thymus	+	+	+	+	+	I	+	+	+	A	+	+	+	+	I	+	I	+	+	+	+	+	+	+	+
Histiocytic sarcoma				X																					
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma									X																
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basosquamous tumor benign																									
Squamous cell carcinoma																									
Site of application, basal cell adenoma																									
Subcutaneous tissue, melanoma, malignant																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle														+											
Rhabdomyosarcoma														X											

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Diisopropylcarbodiimide: 20 mg/kg

Number of Days on Study	7 3 3	7 3 3	7 3 3	7 3 4	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	3 4 2	3 4 5	3 4 9	3 1 0	3 0 3	3 0 9	3 1 2	3 2 0	3 2 7	3 3 7	3 4 3	3 4 4	3 4 4	3 0 4	3 0 7	3 1 1	3 1 3	3 1 4	3 1 8	3 2 1	3 2 3	3 2 5	3 3 9	3 4 1	3 4 7	3 5 0	Total Tissues/ Tumors
Genital System																										
Clitoral gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cystadenoma							X																			2
Histiocytic sarcoma																										1
Teratoma benign																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										2
Endometrium, polyp stromal																			X				X			5
Endometrium, sarcoma stromal																										1
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										2
Lymph node												+									+			+		10
Bronchial, alveolar/bronchiolar carcinoma, metastatic, lung																										1
Iliac, histiocytic sarcoma																										1
Mediastinal, histiocytic sarcoma																										1
Pancreatic, histiocytic sarcoma																										1
Pancreatic, squamous cell carcinoma, metastatic, stomach, forestomach												X														1
Renal, histiocytic sarcoma																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma, metastatic, harderian gland																										1
Histiocytic sarcoma																										1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										2
Thymus	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	44
Histiocytic sarcoma																										1
Integumentary System																										
Mammary gland	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma																									X	2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basosquamous tumor benign								X																		1
Squamous cell carcinoma												X														1
Site of application, basal cell adenoma																									X	1
Subcutaneous tissue, melanoma, malignant										X																1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										1
Rhabdomyosarcoma																										1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Diisopropylcarbodiimide: 20 mg/kg

Number of Days on Study	0 1 5	0 6 7	4 1 7	5 6 0	5 7 9	5 8 4	6 0 3	6 1 4	6 5 3	6 8 7	6 9 0	7 3 2	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3
Carcass ID Number	3 2 9	3 0 1	3 3 8	3 0 6	3 3 5	3 1 6	3 1 7	3 3 4	3 4 8	3 0 5	3 4 6	3 3 2	3 0 2	3 0 8	3 1 5	3 1 9	3 2 2	3 2 4	3 2 6	3 2 8	3 3 0	3 3 1	3 3 3	3 3 6	3 4 0
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar adenoma, multiple																									
Alveolar/bronchiolar carcinoma							X																		
Alveolar/bronchiolar carcinoma, multiple											X														
Carcinoma, metastatic, harderian gland								X																	
Carcinoma, metastatic, mammary gland									X																
Hepatocellular carcinoma, metastatic, liver			X														X						X		
Histiocytic sarcoma				X		X																			
Sarcoma stromal, metastatic, uterus																		X							
Nose	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, harderian gland								X																	
Histiocytic sarcoma				X																					
Retrobulbar, sarcoma																									
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																		X				X	X		
Carcinoma								X																	
Lacrimal gland	+																								
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma				X		X																			
Urinary bladder	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma				X																					
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma				X		X																			
Lymphoma malignant										X															X

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Diisopropylcarbodiimide: 20 mg/kg

Number of Days on Study	7 3 3	7 3 3	7 3 3	7 3 4	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	3 4 2	3 4 5	3 4 9	3 1 0	3 0 3	3 0 9	3 1 2	3 2 0	3 2 7	3 3 7	3 4 3	3 4 4	3 0 4	3 0 7	3 1 1	3 1 3	3 1 4	3 1 8	3 2 1	3 2 3	3 2 5	3 3 9	3 4 1	3 4 7	3 5 0	Total Tissues/ Tumors
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma														X		X										2
Alveolar/bronchiolar adenoma, multiple																						X				1
Alveolar/bronchiolar carcinoma																										1
Alveolar/bronchiolar carcinoma, multiple																										1
Carcinoma, metastatic, harderian gland																										1
Carcinoma, metastatic, mammary gland																										1
Hepatocellular carcinoma, metastatic, liver				X																						4
Histiocytic sarcoma																										2
Sarcoma stromal, metastatic, uterus																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma, metastatic, harderian gland																										1
Histiocytic sarcoma																										1
Retrobulbar, sarcoma																									X	1
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma			X					X																		5
Carcinoma			X								X														X	4
Lacrimal gland																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										2
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma																										1
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										2
Lymphoma malignant		X			X					X										X			X			7

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Diisopropylcarbodiimide: 40 mg/kg

Number of Days on Study	1 0 5	4 8 1	5 2 8	5 5 1	5 8 2	6 0 4	6 1 7	6 1 9	6 6 9	7 1 8	7 2 9	7 2 9	7 2 9	7 2 9	7 3 2	7 3 2	7 3 2	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3
Carcass ID Number	3 5 4	3 5 5	3 9 7	3 6 5	4 0 0	3 7 0	3 6 4	3 9 6	3 5 9	3 7 9	3 6 1	3 6 8	3 9 3	3 9 5	3 9 8	3 7 2	3 7 3	3 7 4	3 5 7	3 7 7	3 8 1	3 8 8	3 8 9	3 9 0	3 9 2
Alimentary System																								
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	I	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	A	+	+	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	A	+	+	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	A	+	+	+	A	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																								
Intestine small, ileum	+	A	+	+	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																			X					
Hepatocellular carcinoma										X														
Hepatocellular adenoma								X					X	X								X		X
Hepatocellular adenoma, multiple										X						X	X						X	X
Hepatocholangiocarcinoma, multiple									X															
Histiocytic sarcoma						X																		
Mesentery				+	+	+		+		+						+			+	+	+		+	
Hemangiosarcoma, metastatic, liver																			X					
Histiocytic sarcoma						X		X																
Liposarcoma										X														
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma															X									
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth						+						+												
Peridontal tissue, histiocytic sarcoma, metastatic, nose						X																		
Cardiovascular System																								
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocholangiocarcinoma, metastatic, liver									X															
Endocrine System																								
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcapsular, adenoma																								
Adrenal medulla	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																								X
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	I	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma														X				X		X	X			
Pars intermedia, adenoma																						X		
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma												X					X							

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Diisopropylcarbodiimide: 40 mg/kg

Number of Days on Study	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	3 5 2	3 5 3	3 5 6	3 5 8	3 6 0	3 6 2	3 6 7	3 7 6	3 8 0	3 8 3	3 8 4	3 8 5	3 9 1	3 5 1	3 6 3	3 6 6	3 6 9	3 7 1	3 7 5	3 7 8	3 8 2	3 8 6	3 8 7	3 9 4	3 9 9	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Carcinoma													X													1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Hepatocellular carcinoma								X				X														3
Hepatocellular adenoma	X				X					X											X					9
Hepatocellular adenoma, multiple		X		X			X															X				9
Hepatocholangiocarcinoma, multiple																										1
Histiocytic sarcoma																										1
Mesentery		+			+			+			+	+			+							+		+		18
Hemangiosarcoma, metastatic, liver																										1
Histiocytic sarcoma																										2
Liposarcoma																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma				X																						2
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tooth																										2
Peridontal tissue, histiocytic sarcoma, metastatic, nose																										1
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocholangiocarcinoma, metastatic, liver																										1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcapsular, adenoma	X																									1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma benign																										1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	49
Pituitary gland	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	46
Pars distalis, adenoma	X			X		X								X			X						X			10
Pars intermedia, adenoma																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, adenoma																										2

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Diisopropylcarbodiimide: 40 mg/kg

Number of Days on Study	1 0 5	4 8 1	5 2 8	5 5 1	5 8 2	6 0 4	6 1 7	6 1 9	6 6 9	7 1 8	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 2	7 3 2	7 3 2	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3
Carcass ID Number	3 5 4	3 5 5	3 9 7	3 6 5	4 0 0	3 7 0	3 6 4	3 9 6	3 5 9	3 7 9	3 6 1	3 6 8	3 9 3	3 9 5	3 9 8	3 7 2	3 7 3	3 7 4	3 5 7	3 7 7	3 8 1	3 8 8	3 8 9	3 9 0	3 9 2
General Body System																								
Tissue NOS		+							+															
Mediastinum, hepatocholangiocarcinoma, metastatic, liver									X															
Thoracic, hepatocholangiocarcinoma, metastatic, liver									X															
Genital System																								
Clitoral gland	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+
Ovary	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma																								
Histiocytic sarcoma						X																		
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																								
Histiocytic sarcoma						X		X																
Leiomyosarcoma																								
Vagina								+																
Histiocytic sarcoma								X																
Hematopoietic System																								
Bone marrow	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma						X																		
Lymph node						+				+							+	+						
Mediastinal, histiocytic sarcoma						X																		
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Histiocytic sarcoma						X																		
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma						X																		
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma						X		X																
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Integumentary System																								
Mammary gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, hemangioma																						X		
Subcutaneous tissue, squamous cell carcinoma																								
Subcutaneous tissue, site of application, melanoma benign																						X		
Musculoskeletal System																								
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cranium, osteosarcoma				X																				
Skeletal muscle			+																					

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Diisopropylcarbodiimide: 40 mg/kg

Number of Days on Study	7 3 3 6	7 3 6 6	7 3 6 6	7 3 3 6	7 3 3 6	7 3 6 6	7 3 3 6	7 3 3 6	7 3 3 6	7 3 3 6	7 3 3 6	7 3 3 6	7 3 3 6	7 3 6 6	7 3 3 7	7 3 3 7	7 3 3 7	7 3 3 7	7 3 3 7	7 3 3 7	7 3 3 7	7 3 3 7	7 3 3 7	7 3 3 7	7 3 3 7	
Carcass ID Number	3 5 5 2	3 5 3 3	3 5 5 6	3 5 5 8	3 5 6 0	3 6 6 2	3 6 6 7	3 7 7 6	3 7 8 0	3 8 8 3	3 8 8 4	3 8 8 5	3 8 9 1	3 5 1 1	3 6 6 3	3 6 6 6	3 6 6 9	3 7 7 1	3 7 7 5	3 7 7 8	3 8 8 2	3 8 8 6	3 8 8 7	3 9 9 4	3 9 9 9	Total Tissues/ Tumors
General Body System																										
Tissue NOS		+							+																	4
Mediastinum, hepatocholangiocarcinoma, metastatic, liver																										1
Thoracic, hepatocholangiocarcinoma, metastatic, liver																										1
Genital System																										
Clitoral gland	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	47
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cystadenoma									X						X											2
Histiocytic sarcoma																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																							X			1
Histiocytic sarcoma																										2
Leiomyosarcoma												X	X													2
Vagina																										1
Histiocytic sarcoma																										1
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma																										1
Lymph node		+	+										+				+	+	+							10
Mediastinal, histiocytic sarcoma																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	48
Histiocytic sarcoma																										1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										2
Thymus	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	I	+	47
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, hemangioma																										1
Subcutaneous tissue, squamous cell carcinoma																									X	1
Subcutaneous tissue, site of application, melanoma benign																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cranium, osteosarcoma																										1
Skeletal muscle																										1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Diisopropylcarbodiimide: 40 mg/kg

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

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Diisopropylcarbodiimide: 40 mg/kg

Number of Days on Study	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	3 5 2	3 5 3	3 5 6	3 5 8	3 6 0	3 6 2	3 6 7	3 7 6	3 8 0	3 8 3	3 8 4	3 8 5	3 9 1	3 5 1	3 6 3	3 6 6	3 6 9	3 7 1	3 7 5	3 7 8	3 8 2	3 8 6	3 8 7	3 9 4	3 9 9	Total Tissues/ Tumors
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Osteosarcoma, metastatic, bone																										1
Peripheral nerve																										1
Spinal cord																										2
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																										1
Alveolar/bronchiolar carcinoma	X										X															4
Alveolar/bronchiolar carcinoma, multiple		X																								1
Hepatocholangiocarcinoma, metastatic, liver																										1
Histiocytic sarcoma																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma																										1
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										3
Carcinoma																		X								1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma																										1
Ureter																										1
Histiocytic sarcoma																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										2
Lymphoma malignant					X								X					X	X						X	7

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Dermal Study of Diisopropylcarbodiimide

	Vehicle Control	10 mg/kg	20 mg/kg	40 mg/kg
Harderian Gland: Adenoma				
Overall rate[a]	9/50 (18%)	5/50 (10%)	5/50 (10%)	3/50 (6%)
Adjusted rate[b]	20.9%	11.5%	11.3%	6.5%
Terminal rate[c]	8/33 (24%)	5/33 (15%)	5/39 (13%)	1/40 (3%)
First incidence (days)	619	729 (T)	729 (T)	582
Poly-3 test[d]	P=0.042N	P=0.183N	P=0.176N	P=0.045N
Harderian Gland: Carcinoma				
Overall rate	1/50 (2%)	0/50 (0%)	4/50 (8%)	1/50 (2%)
Adjusted rate	2.3%	0.0%	9.0%	2.2%
Terminal rate	0/33 (0%)	0/33 (0%)	3/39 (8%)	1/40 (3%)
First incidence (days)	603	—[e]	614	729 (T)
Poly-3 test	P=0.470	P=0.498N	P=0.189	P=0.750N
Harderian Gland: Adenoma or Carcinoma				
Overall rate	10/50 (20%)	5/50 (10%)	8/50 (16%)	4/50 (8%)
Adjusted rate	23.0%	11.5%	17.9%	8.7%
Terminal rate	8/33 (24%)	5/33 (15%)	7/39 (18%)	2/40 (5%)
First incidence (days)	603	729 (T)	614	582
Poly-3 test	P=0.076N	P=0.125N	P=0.373N	P=0.056N
Liver: Hepatocellular Adenoma				
Overall rate	21/50 (42%)	27/50 (54%)	21/50 (42%)	18/50 (36%)
Adjusted rate	48.4%	60.1%	47.0%	39.5%
Terminal rate	19/33 (58%)	22/33 (67%)	20/39 (51%)	16/40 (40%)
First incidence (days)	603	579	603	619
Poly-3 test	P=0.100N	P=0.181	P=0.534N	P=0.262N
Liver: Hepatocellular Carcinoma				
Overall rate	10/50 (20%)	2/50 (4%)	8/50 (16%)	3/50 (6%)
Adjusted rate	23.1%	4.6%	17.8%	6.6%
Terminal rate	6/33 (18%)	2/33 (6%)	7/39 (18%)	2/40 (5%)
First incidence (days)	619	729 (T)	417	718
Poly-3 test	P=0.067N	P=0.012N	P=0.362N	P=0.028N
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rate	29/50 (58%)	29/50 (58%)	26/50 (52%)	20/50 (40%)
Adjusted rate	65.8%	64.5%	57.2%	43.9%
Terminal rate	23/33 (70%)	24/33 (73%)	24/39 (62%)	18/40 (45%)
First incidence (days)	603	579	417	619
Poly-3 test	P=0.011N	P=0.538N	P=0.262N	P=0.026N
Lung: Alveolar/bronchiolar Adenoma				
Overall rate	4/50 (8%)	2/50 (4%)	3/50 (6%)	1/50 (2%)
Adjusted rate	9.3%	4.6%	6.8%	2.2%
Terminal rate	2/33 (6%)	1/33 (3%)	3/39 (8%)	1/40 (3%)
First incidence (days)	603	653	729 (T)	729 (T)
Poly-3 test	P=0.151N	P=0.330N	P=0.488N	P=0.166N
Lung: Alveolar/bronchiolar Carcinoma				
Overall rate	0/50 (0%)	2/50 (4%)	2/50 (4%)	5/50 (10%)
Adjusted rate	0.0%	4.6%	4.5%	11.1%
Terminal rate	0/33 (0%)	1/33 (3%)	0/39 (0%)	5/40 (13%)
First incidence (days)	—	653	603	729 (T)
Poly-3 test	P=0.019	P=0.243	P=0.248	P=0.035

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Dermal Study of Diisopropylcarbodiimide

	Vehicle Control	10 mg/kg	20 mg/kg	40 mg/kg
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rate	4/50 (8%)	4/50 (8%)	5/50 (10%)	6/50 (12%)
Adjusted rate	9.3%	9.1%	11.2%	13.3%
Terminal rate	2/33 (6%)	2/33 (6%)	3/39 (8%)	6/40 (15%)
First incidence (days)	603	653	603	729 (T)
Poly-3 test	P=0.294	P=0.632N	P=0.522	P=0.396
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	4/48 (8%)	12/50 (24%)	3/50 (6%)	10/46 (22%)
Adjusted rate	9.7%	26.9%	6.8%	23.7%
Terminal rate	3/32 (9%)	9/33 (27%)	3/39 (8%)	10/38 (26%)
First incidence (days)	521	540	729 (T)	729 (T)
Poly-3 test	P=0.187	P=0.035	P=0.465N	P=0.074
Pituitary Gland (Pars Distalis): Adenoma or Carcinoma				
Overall rate	5/48 (10%)	12/50 (24%)	3/50 (6%)	10/46 (22%)
Adjusted rate	12.0%	26.9%	6.8%	23.7%
Terminal rate	3/32 (9%)	9/33 (27%)	3/39 (8%)	10/38 (26%)
First incidence (days)	521	540	729 (T)	729 (T)
Poly-3 test	P=0.261	P=0.070	P=0.322N	P=0.132
Skin: Benign Basosquamous Tumor, Basal Cell Adenoma, or Squamous Cell Carcinoma				
Overall rate	0/50 (0%)	0/50 (0%)	3/50 (6%)	1/50 (2%)
Adjusted rate	0.0%	0.0%	6.8%	2.2%
Terminal rate	0/33 (0%)	0/33 (0%)	3/39 (8%)	1/40 (3%)
First incidence (days)	—	—[f]	729 (T)	729 (T)
Poly-3 test	P=0.269	—	P=0.125	P=0.511
Thyroid Gland (Follicular Cell): Adenoma				
Overall rate	3/50 (6%)	0/50 (0%)	0/50 (0%)	2/50 (4%)
Adjusted rate	7.0%	0.0%	0.0%	4.4%
Terminal rate	3/33 (9%)	0/33 (0%)	0/39 (0%)	2/40 (5%)
First incidence (days)	729 (T)	—	—	729 (T)
Poly-3 test	P=0.532N	P=0.114N	P=0.112N	P=0.475N
Uterus: Stromal Polyp				
Overall rate	4/50 (8%)	2/50 (4%)	5/50 (10%)[g]	0/50 (0%)
Adjusted rate	9.3%	4.6%	11.2%	0.0%
Terminal rate	3/33 (9%)	2/33 (6%)	4/39 (10%)	0/40 (0%)
First incidence (days)	654	729 (T)	603	—
Poly-3 test	P=0.081N	P=0.330N	P=0.524	P=0.054N
All Organs: Hemangiosarcoma				
Overall rate	4/50 (8%)	2/50 (4%)	0/50 (0%)	1/50 (2%)
Adjusted rate	9.3%	4.5%	0.0%	2.2%
Terminal rate	2/33 (6%)	0/33 (0%)	0/39 (0%)	1/40 (3%)
First incidence (days)	681	653	—	729 (T)
Poly-3 test	P=0.082N	P=0.326N	P=0.057N	P=0.164N
All Organs: Hemangioma or Hemangiosarcoma				
Overall rate	6/50 (12%)	4/50 (8%)	0/50 (0%)	2/50 (4%)
Adjusted rate	13.8%	9.1%	0.0%	4.4%
Terminal rate	3/33 (9%)	2/33 (6%)	0/39 (0%)	2/40 (5%)
First incidence (days)	603	653	—	729 (T)
Poly-3 test	P=0.049N	P=0.361N	P=0.014N	P=0.121N

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Dermal Study of Diisopropylcarbodiimide

	Vehicle Control	10 mg/kg	20 mg/kg	40 mg/kg
All Organs: Histiocytic Sarcoma				
Overall rate	3/50 (6%)	1/50 (2%)	2/50 (4%)	2/50 (4%)
Adjusted rate	6.9%	2.3%	4.4%	4.4%
Terminal rate	2/33 (6%)	0/33 (0%)	0/39 (0%)	0/40 (0%)
First incidence (days)	488	653	560	604
Poly-3 test	P=0.481N	P=0.301N	P=0.481N	P=0.474N
All Organs: Malignant Lymphoma				
Overall rate	10/50 (20%)	9/50 (18%)	7/50 (14%)	7/50 (14%)
Adjusted rate	22.3%	19.8%	15.8%	15.5%
Terminal rate	6/33 (18%)	4/33 (12%)	6/39 (15%)	6/40 (15%)
First incidence (days)	365	568	687	718
Poly-3 test	P=0.226N	P=0.485N	P=0.302N	P=0.289N
All Organs: Benign Neoplasms				
Overall rate	35/50 (70%)	38/50 (76%)	28/50 (56%)	31/50 (62%)
Adjusted rate	78.3%	82.1%	61.3%	67.3%
Terminal rate	29/33 (88%)	30/33 (91%)	26/39 (67%)	28/40 (70%)
First incidence (days)	521	540	67	582
Poly-3 test	P=0.057N	P=0.419	P=0.055N	P=0.166N
All Organs: Malignant Neoplasms				
Overall rate	26/50 (52%)	20/50 (40%)	26/50 (52%)	18/50 (36%)
Adjusted rate	55.1%	42.3%	54.7%	38.5%
Terminal rate	13/33 (39%)	10/33 (30%)	18/39 (46%)	13/40 (33%)
First incidence (days)	365	555	417	551
Poly-3 test	P=0.116N	P=0.146N	P=0.566N	P=0.077N
All Organs: Benign or Malignant Neoplasms				
Overall rate	47/50 (94%)	43/50 (86%)	41/50 (82%)	41/50 (82%)
Adjusted rate	97.8%	89.2%	84.5%	86.7%
Terminal rate	32/33 (97%)	30/33 (91%)	32/39 (82%)	35/40 (88%)
First incidence (days)	365	540	67	551
Poly-3 test	P=0.058N	P=0.088N	P=0.023N	P=0.041N

(T) Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for liver, lung, pituitary gland, and thyroid gland; for other tissues, denominator is number of animals necropsied.
[b] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the vehicle control group is the P value associated with the trend test. Beneath the dosed group incidence is the P value corresponding to pairwise comparisons between the vehicle controls and that of the 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 could not be computed
[g] One stromal sarcoma occurred in an animal that also had a stromal polyp

TABLE D4
Historical Incidence of Alveolar/bronchiolar Carcinoma in Control Female B6C3F$_1$ Mice[a]

Study	Incidence in Controls
Historical Incidence: All Routes	
Acrylonitrile (gavage)	2/50
Benzophenone (feed)	1/50
Bromodichloromethane (drinking water)	1/50
trans-Cinnamaldehyde (feed)	2/100
Citral (feed)	6/99
Decalin (inhalation)	6/49
Dibromoacetic acid (drinking water)	1/50
p,p′-Dichlorodiphenyl sulfone (feed)	0/50
Diisopropylcarbodiimide (dermal)	0/50
Dipropylene glycol (drinking water)	2/50
Divinylbenzene (inhalation)	2/50
Elmiron® (gavage)	1/50
2,4-Hexadienal (gavage)	0/49
Indium phosphide (inhalation)	1/50
60-Hz Magnetic fields (whole body exposure)	2/95
Methacrylonitrile (gavage)	1/50
Methyl isobutyl ketone (inhalation)	0/50
2-Methylimidazole (feed)	0/50
4-Methylimidazole (feed)	3/50
o-Nitrotoluene (feed)	3/60
p-Nitrotoluene (feed)	1/50
Propylene glycol mono-*t*-butyl ether (inhalation)	1/50
Riddelliine (gavage)	1/50
Sodium chlorate (drinking water)	1/50
Sodium nitrite (drinking water)	0/50
Stoddard Solvent IIC (inhalation)	0/50
Triethanolamine (dermal)	2/50
Vanadium pentoxide (inhalation)	0/50
Overall Historical Incidence: All Routes	
Total (%)	40/1,552 (2.6%)
Mean ± standard deviation	2.5% ± 2.6%
Range	0%-12%

[a] Data as of January 28, 2005; there are only two dermal studies (one is the current study of diisopropylcarbodiimide) in the historical database, each using a different vehicle

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Dermal Study of Diisopropylcarbodiimide[a]

	Vehicle Control	10 mg/kg	20 mg/kg	40 mg/kg
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Accidental deaths		1	1	1
Moribund	12	11	4	5
Natural deaths	5	5	6	4
Survivors				
Died last week of study		1	1	
Terminal sacrifice	33	32	38	40
Animals examined microscopically	50	50	50	50
Alimentary System				
Gallbladder	(42)	(47)	(42)	(47)
Cyst		1 (2%)		
Intestine large, cecum	(46)	(45)	(44)	(47)
Cyst	1 (2%)			
Edema				1 (2%)
Intestine small, duodenum	(46)	(46)	(44)	(47)
Hyperplasia, lymphoid		1 (2%)		
Perforation			1 (2%)	
Intestine small, jejunum	(47)	(45)	(44)	(46)
Inflammation, focal		1 (2%)		
Epithelium, hyperplasia, focal				1 (2%)
Peyer's patch, hyperplasia, lymphoid		1 (2%)		
Intestine small, ileum	(46)	(44)	(45)	(47)
Peyer's patch, hyperplasia, lymphoid	1 (2%)			
Liver	(50)	(50)	(50)	(50)
Angiectasis, focal	1 (2%)	2 (4%)		
Clear cell focus				1 (2%)
Congestion	1 (2%)			
Eosinophilic focus	6 (12%)	1 (2%)	6 (12%)	
Hematopoietic cell proliferation		2 (4%)		1 (2%)
Hyperplasia, focal, lymphoid		1 (2%)	2 (4%)	
Infiltration cellular, polymorphonuclear		1 (2%)		1 (2%)
Infiltration cellular, mixed cell	16 (32%)	9 (18%)	10 (20%)	22 (44%)
Mineralization, focal		1 (2%)		
Necrosis, focal			1 (2%)	
Hepatocyte, basophilic focus	1 (2%)		1 (2%)	1 (2%)
Hepatocyte, clear cell focus	3 (6%)	2 (4%)		1 (2%)
Hepatocyte, eosinophilic focus			4 (8%)	
Hepatocyte, karyomegaly	1 (2%)			
Hepatocyte, mixed cell focus	2 (4%)		1 (2%)	6 (12%)
Hepatocyte, necrosis, focal	3 (6%)	3 (6%)	1 (2%)	1 (2%)
Hepatocyte, vacuolization cytoplasmic	5 (10%)	3 (6%)	1 (2%)	5 (10%)
Mesentery	(23)	(20)	(14)	(18)
Hemorrhage			1 (7%)	
Infiltration cellular, lymphoid	1 (4%)			
Infiltration cellular, mixed cell	1 (4%)			
Inflammation	3 (13%)	5 (25%)		1 (6%)
Artery, inflammation				1 (6%)
Fat, necrosis, focal	17 (74%)	13 (65%)	9 (64%)	15 (83%)

[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 Dermal Study of Diisopropylcarbodiimide

	Vehicle Control	10 mg/kg	20 mg/kg	40 mg/kg
Alimentary System (continued)				
Pancreas	(50)	(48)	(50)	(50)
Inflammation, focal	1 (2%)			
Acinus, atrophy, diffuse		2 (4%)		
Acinus, atrophy, focal	1 (2%)	2 (4%)	1 (2%)	3 (6%)
Duct, cyst, focal, multiple		2 (4%)		1 (2%)
Stomach, forestomach	(50)	(49)	(50)	(50)
Diverticulum			1 (2%)	1 (2%)
Erosion	2 (4%)		2 (4%)	
Inflammation, focal	1 (2%)		1 (2%)	1 (2%)
Ulcer	1 (2%)	1 (2%)		2 (4%)
Epithelium, hyperplasia	4 (8%)	4 (8%)	2 (4%)	1 (2%)
Stomach, glandular	(49)	(48)	(47)	(50)
Erosion				1 (2%)
Glands, hyperplasia, focal		1 (2%)		
Tooth	(1)	(1)	(1)	(2)
Malformation		1 (100%)		1 (50%)
Peridontal tissue, inflammation, chronic			1 (100%)	
Cardiovascular System				
Heart	(50)	(50)	(49)	(50)
Cardiomyopathy		3 (6%)	1 (2%)	1 (2%)
Infiltration cellular, polymorphonuclear		1 (2%)		
Infiltration cellular, mixed cell	1 (2%)			
Inflammation, chronic, focal		1 (2%)		
Thrombosis	4 (8%)		2 (4%)	
Artery, inflammation, chronic	1 (2%)		1 (2%)	
Endocrine System				
Adrenal cortex	(50)	(50)	(49)	(50)
Accessory adrenal cortical nodule	2 (4%)	1 (2%)	1 (2%)	3 (6%)
Angiectasis		1 (2%)		
Cytoplasmic alteration, focal	1 (2%)	2 (4%)	1 (2%)	
Degeneration, cystic	1 (2%)		1 (2%)	1 (2%)
Infiltration cellular, polymorphonuclear	1 (2%)			
Inflammation, suppurative		1 (2%)		
Necrosis, focal				1 (2%)
Adrenal medulla	(49)	(50)	(49)	(49)
Angiectasis		1 (2%)		
Hyperplasia				1 (2%)
Inflammation, suppurative		1 (2%)		
Islets, pancreatic	(50)	(49)	(50)	(50)
Hyperplasia		2 (4%)	1 (2%)	
Parathyroid gland	(46)	(43)	(49)	(49)
Cyst	2 (4%)	2 (5%)		1 (2%)
Pituitary gland	(48)	(50)	(50)	(46)
Angiectasis	3 (6%)	1 (2%)	1 (2%)	3 (7%)
Cyst			1 (2%)	
Hemorrhage			1 (2%)	
Pars distalis, cytoplasmic alteration, focal	2 (4%)		4 (8%)	1 (2%)
Pars distalis, degeneration, cystic, focal	1 (2%)			
Pars distalis, hyperplasia, focal	3 (6%)	2 (4%)	7 (14%)	3 (7%)
Pars intermedia, hyperplasia, focal			1 (2%)	

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Dermal Study of Diisopropylcarbodiimide

	Vehicle Control	10 mg/kg	20 mg/kg	40 mg/kg
Endocrine System (continued)				
Thyroid gland	(50)	(50)	(50)	(50)
Cyst		2 (4%)	3 (6%)	1 (2%)
Inflammation, chronic, focal			1 (2%)	
C-cell, hyperplasia		2 (4%)		
Follicle, degeneration, cystic, focal	14 (28%)	14 (28%)	18 (36%)	12 (24%)
Follicular cell, hyperplasia, focal	1 (2%)	11 (22%)	9 (18%)	4 (8%)
Follicular cell, vacuolization cytoplasmic, focal				1 (2%)
General Body System				
Tissue NOS	(5)	(8)	(3)	(4)
Mediastinum, infiltration cellular, lymphoid	1 (20%)			1 (25%)
Mediastinum, inflammation, suppurative		1 (13%)		1 (25%)
Nasal, hemorrhage		1 (13%)		
Genital System				
Clitoral gland	(46)	(48)	(48)	(47)
Degeneration, cystic			1 (2%)	
Inflammation, chronic	1 (2%)			
Ovary	(49)	(50)	(49)	(49)
Angiectasis	2 (4%)	3 (6%)	1 (2%)	1 (2%)
Cyst	14 (29%)	16 (32%)	13 (27%)	18 (37%)
Hemorrhage	2 (4%)			
Hyperplasia, lymphoid		1 (2%)		
Inflammation, suppurative	2 (4%)	2 (4%)		2 (4%)
Thrombosis	2 (4%)	1 (2%)	1 (2%)	
Bilateral, cyst			1 (2%)	
Bilateral, inflammation, suppurative	1 (2%)			1 (2%)
Interstitial cell, hyperplasia		1 (2%)		
Oviduct	(3)	(1)		
Inflammation, suppurative	3 (100%)			
Uterus	(50)	(50)	(50)	(50)
Hemorrhage	1 (2%)			
Hyperplasia, lymphoid	1 (2%)		1 (2%)	
Inflammation, suppurative	5 (10%)	8 (16%)	6 (12%)	2 (4%)
Thrombosis				1 (2%)
Cervix, hypertrophy		1 (2%)		
Endometrium, hyperplasia, cystic	46 (92%)	44 (88%)	47 (94%)	49 (98%)

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Dermal Study of Diisopropylcarbodiimide

	Vehicle Control	10 mg/kg	20 mg/kg	40 mg/kg
Hematopoietic System				
Bone marrow	(49)	(50)	(50)	(49)
Hyperplasia	14 (29%)	5 (10%)	10 (20%)	2 (4%)
Lymph node	(11)	(13)	(10)	(10)
Hyperplasia, lymphoid			1 (10%)	
Bronchial, hyperplasia, lymphoid			1 (10%)	
Iliac, ectasia		1 (8%)	1 (10%)	3 (30%)
Iliac, hemorrhage	2 (18%)			
Iliac, hyperplasia, lymphoid	2 (18%)	2 (15%)	2 (20%)	2 (20%)
Inguinal, hyperplasia, lymphoid	1 (9%)			
Mediastinal, ectasia	1 (9%)			
Mediastinal, hemorrhage		1 (8%)		
Mediastinal, hyperplasia		1 (8%)		
Mediastinal, hyperplasia, lymphoid	1 (9%)	2 (15%)	1 (10%)	3 (30%)
Pancreatic, hemorrhage		1 (8%)		
Pancreatic, hyperplasia, lymphoid	1 (9%)	1 (8%)		1 (10%)
Renal, ectasia		1 (8%)		
Renal, hyperplasia, lymphoid	1 (9%)	1 (8%)	2 (20%)	
Lymph node, mandibular	(47)	(49)	(49)	(48)
Hemorrhage	1 (2%)			
Hyperplasia, lymphoid	6 (13%)	4 (8%)	2 (4%)	1 (2%)
Lymph node, mesenteric	(47)	(48)	(49)	(50)
Ectasia	1 (2%)	1 (2%)	5 (10%)	2 (4%)
Hematopoietic cell proliferation		1 (2%)		
Hemorrhage				1 (2%)
Hyperplasia, lymphoid	3 (6%)	6 (13%)	2 (4%)	5 (10%)
Spleen	(49)	(49)	(50)	(50)
Accessory spleen			1 (2%)	
Atrophy			1 (2%)	
Congestion	1 (2%)			
Hematopoietic cell proliferation	24 (49%)	21 (43%)	18 (36%)	13 (26%)
Hyperplasia, histiocytic	1 (2%)			
Hyperplasia, lymphoid	6 (12%)	12 (24%)	12 (24%)	6 (12%)
Capsule, inflammation, chronic, focal	1 (2%)			
Thymus	(46)	(48)	(44)	(47)
Hyperplasia, lymphoid	5 (11%)	4 (8%)	4 (9%)	1 (2%)
Integumentary System				
Mammary gland	(50)	(50)	(49)	(49)
Dilatation	1 (2%)			
Hyperplasia				1 (2%)
Skin	(50)	(50)	(50)	(50)
Ulcer	1 (2%)			
Control dermis, hyperplasia, focal				1 (2%)
Control dermis, inflammation, focal	1 (2%)		1 (2%)	1 (2%)
Control epidermis, hyperplasia, focal	1 (2%)			1 (2%)
Epidermis, hyperplasia, focal	1 (2%)			
Dermis, site of application, fibrosis				1 (2%)
Dermis, site of application, inflammation, focal	3 (6%)	2 (4%)	7 (14%)	2 (4%)
Epidermis, site of application, hyperplasia	5 (10%)	3 (6%)	7 (14%)	7 (14%)
Site of application, ulcer	2 (4%)	1 (2%)		
Subcutaneous tissue, angiectasis, focal		1 (2%)		
Subcutaneous tissue, edema	1 (2%)	2 (4%)		1 (2%)

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Dermal Study of Diisopropylcarbodiimide

	Vehicle Control	10 mg/kg	20 mg/kg	40 mg/kg
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Hyperostosis	3 (6%)	1 (2%)	1 (2%)	2 (4%)
Nervous System				
Brain	(50)	(50)	(50)	(50)
Compression, focal	2 (4%)	2 (4%)		1 (2%)
Hemorrhage, focal	1 (2%)	2 (4%)		
Infarct	1 (2%)			
Inflammation, focal		1 (2%)		
Cerebellum, hippocampus, necrosis	1 (2%)			
Cerebrum, atrophy, focal		1 (2%)		
Hippocampus, necrosis, acute		1 (2%)		
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Congestion	2 (4%)		1 (2%)	1 (2%)
Foreign body				1 (2%)
Hemorrhage		1 (2%)		
Hyperplasia, histiocytic		1 (2%)		1 (2%)
Infiltration cellular, polymorphonuclear		2 (4%)		
Mineralization, focal	1 (2%)			
Alveolar epithelium, hyperplasia, focal	1 (2%)	2 (4%)	1 (2%)	2 (4%)
Mediastinum, hyperplasia, lymphoid		2 (4%)		
Nose	(50)	(50)	(49)	(50)
Inflammation			1 (2%)	
Nasolacrimal duct, inflammation	1 (2%)		1 (2%)	
Special Senses System				
Eye	(47)	(48)	(49)	(49)
Atrophy	1 (2%)		2 (4%)	
Phthisis bulbi			1 (2%)	
Cornea, hyperplasia, squamous		1 (2%)	1 (2%)	
Cornea, inflammation, chronic		1 (2%)		
Iris, synechia		1 (2%)		
Lens, cataract		1 (2%)		
Harderian gland	(50)	(49)	(50)	(50)
Cyst				1 (2%)
Inflammation		2 (4%)		
Epithelium, hyperplasia, focal	1 (2%)	1 (2%)	1 (2%)	

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Dermal Study of Diisopropylcarbodiimide

	Vehicle Control	10 mg/kg	20 mg/kg	40 mg/kg
Urinary System				
Kidney	(49)	(49)	(50)	(49)
Congestion	1 (2%)			
Cyst	1 (2%)		4 (8%)	
Hydronephrosis			1 (2%)	1 (2%)
Hyperplasia, lymphoid	2 (4%)	2 (4%)	1 (2%)	1 (2%)
Infarct	3 (6%)	2 (4%)	1 (2%)	1 (2%)
Infiltration cellular, polymorphonuclear		1 (2%)		
Infiltration cellular, mixed cell		1 (2%)		
Inflammation	1 (2%)	1 (2%)		
Metaplasia, focal, osseous	5 (10%)	2 (4%)		1 (2%)
Nephropathy	13 (27%)	8 (16%)	11 (22%)	18 (37%)
Capsule, congestion	1 (2%)			
Papilla, necrosis	1 (2%)			
Renal tubule, accumulation, hyaline droplet	3 (6%)	1 (2%)		2 (4%)
Renal tubule, necrosis	1 (2%)			
Renal tubule, vacuolization cytoplasmic, focal	1 (2%)	1 (2%)	1 (2%)	
Urinary bladder	(50)	(50)	(49)	(50)
Angiectasis	1 (2%)			

APPENDIX E
GENETIC TOXICOLOGY

GENETIC TOXICOLOGY

SALMONELLA TYPHIMURIUM MUTAGENICITY TEST PROTOCOL

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

Each trial consisted of triplicate plates of concurrent positive and negative controls and five doses of diisopropylcarbodiimide. The high dose was limited by toxicity. Trials were generally repeated at the same or a higher S9 fraction.

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.

RAT AND MOUSE BONE MARROW MICRONUCLEUS TEST PROTOCOLS

The detailed protocols are described by Witt *et al.* (1999). Information from the 3-month dermal studies with diisopropylcarbodiimide was used to select the range of doses in these studies. Bone marrow tests were initially performed using the standard three-exposure protocol described in detail by Shelby *et al.* (1993). Male F344/N rats and B6C3F_1 mice were injected intraperitoneally (three times at 24-hour intervals) with diisopropylcarbodiimide dissolved in corn oil. Vehicle control animals were injected with corn oil only. The positive control animals received injections of cyclophosphamide. The animals were killed 24 hours after the third injection, and blood smears were prepared from bone marrow cells obtained from the femurs.

Single injection bone marrow micronucleus tests were conducted with diisopropylcarbodiimide in B6C3F_1 male mice. These studies were designed to permit the testing of higher doses than could be administered in the multiple treatment protocol described above. The positive control was again cyclophosphamide. Two different posttreatment samples were collected; peripheral blood smears were prepared 48 hours after injection and bone marrow slides were prepared 24 and 48 hours after injection.

A subchronic micronucleus test was performed in which B6C3F_1 mice were treated 5 days per week for 4 months with diisopropylcarbodiimide dissolved in ethanol; the treatment protocol was designed to match the treatment protocol employed in the 3-month dermal study. At the end of the study, bone marrow cells were obtained and slides were prepared.

Air-dried smears from all the bone marrow micronucleus tests were fixed in absolute methanol and stained with acridine orange (Tice *et al*., 1990); 2,000 PCEs were scored per animal for frequency of micronucleated cells in blood, bone marrow, or both from up to five animals per group. In addition, the percentage of PCEs among the total erythrocyte population in the bone marrow was scored for each dose group as a measure of toxicity.

The results of the bone marrow tests 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 PCEs

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

Mouse Peripheral Blood Micronucleus Test Protocol

A detailed discussion of the testing protocol was presented by Witt *et al.* (1999). At the termination of the 3-month dermal study, 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 1,000 normochromatic erythrocytes (NCEs) in up to 10 mice per dose group. In addition, the percentage of PCEs among 1,000 erythrocytes was determined for each dose group.

In the single injection study in male mice described for the bone marrow micronucleus tests, peripheral blood samples were obtained from the animals killed 48 hours after the injection, and smears were air-dried, fixed, and analyzed for micronucleated PCEs and percentage of PCEs among the total erythrocyte population.

During the 4-month dermal study, periodic blood samples (weekly through week 7, biweekly thereafter, and at the end of the study on dosing day 124) were taken from each mouse via tail snip. Samples were collected within 24 hours of the last of at least three consecutive daily treatments with diisopropylcarbodiimide. Peripheral blood slides were made for analysis of the frequency of micronuclei in 2,000 PCEs and 2,000 NCEs, and for scoring the percentage of PCEs in the total erythrocyte population in the peripheral blood in each of five animals per group.

The results of the peripheral blood tests were tabulated and the frequencies of micronucleated cells among PCEs and NCEs were analyzed as described for PCEs in the bone marrow micronucleus test protocols. Results for the 3-and 4-month studies were accepted without repeat tests, because additional test data could not be obtained.

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 judgment of the overall evidence for activity of the chemical in an assay.

RESULTS

Diisopropylcarbodiimide was not mutagenic in *S. typhimurium* strains TA97, TA98, TA100, or TA1535, with or without induced rat or hamster liver S9 activation enzymes (Table E1). Results of *in vivo* tests for chromosomal effects in mice and rats were discussed in detail by Witt *et al.* (1999) and the data are presented in Tables E2 through E6. Diisopropylcarbodiimide, administered dermally for 3 months, induced significant increases in the frequency of micronucleated NCEs in peripheral blood of male and female mice (Table E5). The percentage of PCEs in these mice was unaffected by chemical treatment. Negative results were obtained in a subsequent acute exposure bone marrow micronucleus test in male F344/N rats using an intraperitoneal injection route of chemical administration at doses that produced clear evidence of bone marrow toxicity based on decreases in percentage of PCEs (Table E2). Diisopropylcarbodiimide was then tested for induction of micronucleated PCEs in male $B6C3F_1$ mice, the same strain employed in the 3-month dermal study, and the results of this test, assaying the frequency of micronucleated PCEs in bone marrow, were negative (Table E3). The values of PCE percentages in this mouse study were unchanged with increasing dose, even though chemical-related toxicity was noted at the two highest doses tested. To permit the administration of a higher dose of diisopropylcarbodiimide in mice and to allow scoring of both blood and bone marrow erythrocytes in the same animals, single injection micronucleus studies were conducted with sampling at 24 and 48 hours posttreatment. Micronucleated erythrocytes were significantly increased in peripheral blood PCEs at 48 hours in both trials, but bone marrow smears showed increases in micronucleated PCEs that were not statistically significant at 24 or 48 hours (Table E4). As seen in the acute rat bone marrow study, the percentage of PCEs in the bone marrow of mice in Trial 1 was significantly depressed. To clarify the mixed responses in the acute and subchronic tests, a second dermal study of diisopropylcarbodiimide in male mice was performed. Analysis of the mean frequencies of micronucleated PCEs and NCEs in peripheral blood, derived from the pooling of data from interim samplings over the 4-month course of treatment, showed highly significant increases (Table E6). The frequency of micronucleated PCEs in the bone marrow of treated mice on day 124 (final day of treatment) was not significantly increased over the solvent control level. The percent PCEs were not significantly altered at any of the sample times in either bone marrow or peripheral blood in the 4-month dermal study (data not shown; Witt *et al*., 1999).

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

Strain	Dose	Revertants/Plate[b]					
		–S9		+ hamster S9		+ rat S9	
	(µg/plate)	Trial 1	Trial 2	10%	30%	10%	30%
TA100	0	120 ± 3.6	110 ± 3.3		137 ± 3.8	112 ± 5.5	152 ± 6.7
	3	118 ± 3.8	108 ± 2.4				
	10	124 ± 2.1	112 ± 1.8		137 ± 3.5	111 ± 4.0	136 ± 2.9
	33	105 ± 3.6	116 ± 1.5		129 ± 7.9	110 ± 4.3	139 ± 6.1
	100	112 ± 6.2	106 ± 0.6		118 ± 6.6	101 ± 5.0	140 ± 7.4
	333	100 ± 6.9	57 ± 6.1		122 ± 4.6	105 ± 8.0	129 ± 7.5
	1,000				113 ± 6.4	50 ± 9.5[c]	132 ± 2.4
Trial summary		Negative	Negative		Negative	Negative	Negative
Positive control[d]		870 ± 14.7	833 ± 25.0		415 ± 10.5	386 ± 7.0	366 ± 7.6
TA1535	0	9 ± 1.5	9 ± 1.7	8 ± 0.6	11 ± 2.7	7 ± 0.3	8 ± 1.2
	3	9 ± 2.0	11 ± 1.9				
	10	8 ± 1.0	10 ± 2.6	8 ± 0.6	9 ± 1.5	6 ± 0.3	7 ± 0.7
	33	9 ± 2.4	8 ± 0.3	7 ± 1.2	8 ± 1.8	11 ± 2.2	11 ± 1.5
	100	8 ± 0.3	10 ± 2.2	9 ± 0.0	8 ± 1.2	9 ± 1.5	8 ± 2.4
	333	9 ± 1.5	6 ± 1.2	7 ± 1.8	8 ± 2.3	6 ± 0.7	8 ± 0.6
	1,000			4 ± 1.2[c]	9 ± 1.2	2 ± 0.3[c]	8 ± 0.9
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		851 ± 15.6	732 ± 7.9	105 ± 5.2	198 ± 14.3	97 ± 10.3	138 ± 8.4
				+ hamster S9			
				5%	10%	10%	30%
TA97	0	105 ± 8.0	102 ± 2.5	155 ± 3.2	118 ± 10.2	147 ± 8.7	136 ± 4.3
	3	114 ± 7.0	102 ± 7.9				119 ± 9.5
	10	112 ± 8.8	105 ± 1.8		109 ± 1.3		117 ± 2.0
	33	117 ± 0.3	126 ± 7.2		121 ± 6.9		138 ± 7.9
	66			141 ± 1.0		140 ± 3.5	
	100	108 ± 4.6	111 ± 3.5	141 ± 3.3	120 ± 9.2	145 ± 8.2	125 ± 9.9
	166			149 ± 11.8		168 ± 5.2	
	333	105 ± 3.3	116 ± 10.9	148 ± 1.7	153 ± 7.3	160 ± 8.2	108 ± 6.1
	666			125 ± 16.8		123 ± 17.6	
	1,000				62 ± 2.6[c]		
Trial summary		Negative	Negative	Negative	Equivocal	Negative	Negative
Positive control		392 ± 11.9	387 ± 5.9	344 ± 17.4	393 ± 40.1	332 ± 21.0	409 ± 8.5

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

Strain	Dose	Revertants/Plate[b]					
		–S9		+ rat S9			
	(µg/plate)	Trial 1	Trial 2	5%	10%	10%	30%
TA97	0			138 ± 15.3	116 ± 7.7	136 ± 19.0	127 ± 7.9
(continued)	10				123 ± 0.0		124 ± 4.1
	33				111 ± 9.1		118 ± 8.6
	66			102 ± 2.8		128 ± 0.9	
	100			110 ± 10.7	140 ± 7.1	112 ± 12.7	135 ± 10.7
	166			131 ± 3.5		136 ± 10.7	
	333			106 ± 3.8	140 ± 4.9	138 ± 17.0	141 ± 12.5
	666			87 ± 7.1		94 ± 9.3	
	1,000				78 ± 6.1[c]		120 ± 5.8
Trial summary				Negative	Equivocal	Negative	Negative
Positive control				315 ± 22.3	330 ± 14.5	318 ± 21.3	374 ± 10.7

				+ hamster S9		+ rat S9	
				10%	30%	10%	30%
TA98	0	22 ± 2.0	10 ± 1.7	15 ± 0.3	19 ± 1.2	14 ± 1.5	23 ± 1.9
	3	18 ± 0.9	11 ± 2.0				
	10	19 ± 2.6	11 ± 0.9	17 ± 1.5	20 ± 3.1	10 ± 0.9	22 ± 2.0
	33	17 ± 1.5	10 ± 0.9	16 ± 1.5	22 ± 2.1	11 ± 2.0	22 ± 2.2
	100	17 ± 1.7	8 ± 0.6	9 ± 1.3	21 ± 2.3	14 ± 0.9	19 ± 1.5
	333	19 ± 2.9	8 ± 0.6	9 ± 0.9	23 ± 2.2	12 ± 1.5	21 ± 2.0
	1,000			4 ± 1.5[c]	22 ± 3.7	2 ± 0.9[c]	22 ± 2.4
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		374 ± 13.0	272 ± 3.9	276 ± 21.4	328 ± 21.0	168 ± 2.7	187 ± 15.1

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

TABLE E2
Induction of Micronuclei in Bone Marrow Polychromatic Erythrocytes of Male Rats Treated with Diisopropylcarbodiimide Three Times by Intraperitoneal Injection[a]

Compound	Dose (mg/kg)	Number of Rats with Erythrocytes Scored	Micronucleated PCEs/ 1,000 PCEs[b]	P Value[c]	% PCEs[b]	P Value[c]
Corn oil[d]	0	5	0.4 ± 0.19		52.1 ± 1.10	
Diisopropylcarbodiimide	3.75	5	0.2 ± 0.20	0.793	40.8 ± 3.28	0.022
	7.50	5	0.2 ± 0.20	0.793	40.9 ± 2.81	0.014
	11.25	3	1.0 ± 0.29	0.071	37.0 ± 1.32	<0.001
	15.00	2[e]	0.5 ± 0.50	—	37.5 ± 0.50	—
			P=0.088[f]		P=0.005[g]	
Cyclophosphamide[h]	25.0	5	15.1 ± 1.51	<0.001	2.3 ± 0.41	<0.001

[a] Study was performed at ILS, Inc. The detailed protocol and these data are presented by Witt *et al*. (1999). PCE=polychromatic erythrocyte
[b] Mean ± standard error
[c] Pairwise comparison with the vehicle control; dosed group values are significant at P≤0.008, positive control values are significant at P≤0.05 (ILS, 1990)
[d] Vehicle control
[e] These data were not included in the statistical evaluations due to insufficient animals in this dose group.
[f] Significance of micronucleated PCEs/1,000 PCEs tested by the one-tailed trend test; significant at P≤0.025 (ILS, 1990)
[g] Analysis of variance significant at P≤0.025
[h] Positive control

TABLE E3
Induction of Micronuclei in Bone Marrow Polychromatic Erythrocytes of Male Mice Treated with Diisopropylcarbodiimide Three Times by Intraperitoneal Injection[a]

Compound	Dose (mg/kg)	Number of Mice with Erythrocytes Scored	Micronucleated PCEs/ 1,000 PCEs[b]	P Value[c]	% PCEs[b]	P Value[c]
Corn oil[d]	0	5	3.0 ± 0.81		52.2 ± 8.57	
Diisopropylcarbodiimide	4.375	5	1.0 ± 0.45	0.999	58.3 ± 5.60	0.570
	8.75	4	2.1 ± 0.55	0.874	57.8 ± 3.51	0.575
	17.5	5	2.1 ± 0.43	0.897	59.2 ± 5.49	0.514
	35.0	3	1.3 ± 0.44	0.982	59.3 ± 4.18	0.483
			P=0.902[e]		P=0.912[f]	
Cyclophosphamide[g]	25.0	5	18.8 ± 1.90	<0.001	54.2 ± 4.31	0.842

[a] Study was performed at ILS, Inc. The detailed protocol and these data are presented by Witt *et al*. (1999). PCE=polychromatic erythrocyte
[b] Mean ± standard error
[c] Pairwise comparison with the vehicle control; dosed group values are significant at P≤0.006, positive control values are significant at P≤0.05 (ILS, 1990)
[d] Vehicle control
[e] Significance of micronucleated PCEs/1,000 PCEs tested by the one-tailed trend test; significant at P≤0.025 (ILS, 1990)
[f] Analysis of variance significant at P≤0.025
[g] Positive control

TABLE E4
Induction of Micronuclei in Polychromatic Erythrocytes of Male Mice Treated with a Single Intraperitoneal Injection of Diisopropylcarbodiimide[a]

Compound	Dose (mg/kg)	Number of Mice with Erythrocytes Scored	Micronucleated PCEs/ 1,000 PCEs[b]	P Value[c]	% PCEs[b]	P Value[c]
Trial 1						
Bone Marrow (48 hours)						
Corn oil[d]	0	5	3.0 ± 0.27		64.8 ± 1.98	
Diisopropylcarbodiimide	20	5	1.9 ± 0.29	0.942	64.0 ± 3.61	0.852
	40	5	4.3 ± 0.29	0.308	53.4 ± 6.53	0.156
	60	5	3.9 ± 0.40	0.139	43.0 ± 3.60	0.002
	80	4	4.1 ± 0.47	0.102	44.3 ± 4.76	0.016
	100	5	3.1 ± 0.19	0.449	36.5 ± 1.35	<0.001
			P=0.063[e]		P<0.001[f]	
Cyclophosphamide[g]	25	5	7.1 ± 1.74	<0.001	71.4 ± 1.85	0.041
Peripheral Blood (48 hours)						
Corn oil	0	5	2.9 ± 0.29		5.1 ± 0.58	
Diisopropylcarbodiimide	20	5	3.1 ± 0.40	0.417	6.5 ± 0.63	0.139
	40	5	4.5 ± 0.50	0.066	5.7 ± 0.77	0.540
	60	5	6.6 ± 1.91	0.001	5.3 ± 0.53	0.823
	80	4	5.1 ± 0.88	0.027	5.1 ± 0.37	0.972
	100	5	4.7 ± 0.68	0.047	5.0 ± 0.24	0.903
			P=0.007		P=0.411	
Cyclophosphamide	25	5	15.9 ± 2.36	<0.001	5.4 ± 0.40	0.702

TABLE E4
Induction of Micronuclei in Polychromatic Erythrocytes of Male Mice Treated with a Single Intraperitoneal Injection of Diisopropylcarbodiimide

Compound	Dose (mg/kg)	Number of Mice with Erythrocytes Scored	Micronucleated PCEs/ 1,000 PCEs	P Value	% PCEs	P Value[c]
Trial 2						
Bone Marrow (24 hours)						
Corn oil	0	5	0.9 ± 0.37		57.0 ± 4.10	
Diisopropylcarbodiimide	40	5	1.5 ± 0.57	0.199	55.9 ± 1.96	0.817
	60	5	1.3 ± 0.70	0.278	49.7 ± 5.76	0.336
	80	5	2.3 ± 0.46	0.044	41.9 ± 3.66	0.025
			P=0.058		P=0.069	
Cyclophosphamide	25	5	9.6 ± 2.20	<0.001	55.2 ± 1.83	0.702
Bone Marrow (48 hours)						
Corn oil	0	5	1.3 ± 0.44		58.6 ± 0.86	
Diisopropylcarbodiimide	40	5	1.2 ± 0.41	0.579	44.1 ± 4.25	0.029
	60	4	0.4 ± 0.24	0.981	45.9 ± 3.17	0.031
	80	5	0.7 ± 0.34	0.910	52.7 ± 4.79	0.292
			P=0.967		P=0.047	
Cyclophosphamide	25	5	3.2 ± 1.41	0.002	48.2 ± 3.32	0.029
Peripheral Blood (48 hours)						
Corn oil	0	5	2.9 ± 0.24		3.1 ± 0.24	
Diisopropylcarbodiimide	40	5	3.9 ± 0.80	0.112	3.1 ± 0.44	1.000
	60	4	4.8 ± 1.36	0.021	3.8 ± 0.19	0.053
	80	5	4.6 ± 0.62	0.025	3.3 ± 0.23	0.564
			P=0.016		P=0.037	
Cyclophosphamide	25	5	17.6 ± 3.44	<0.001	3.1 ± 0.45	1.000

[a] Study was performed at ILS, Inc. The detailed protocol and these data are presented by Witt *et al*. (1999). PCE=polychromatic erythrocyte
[b] Mean ± standard error
[c] Pairwise comparison with the vehicle control; dosed group values are significant at P≤0.005 for Trial 1 and P≤0.008 for Trial 2, positive control values are significant at P≤0.05 (ILS, 1990)
[d] Vehicle control
[e] Significance of micronucleated PCEs/1,000 PCEs tested by the one-tailed trend test; significant at P≤0.025 (ILS, 1990)
[f] Analysis of variance significant at P≤0.025
[g] Positive control

TABLE E5
Frequency of Micronuclei in Peripheral Blood Erythrocytes of Male and Female Mice Following Dermal Application of Diisopropylcarbodiimide for 3 Months[a]

Compound	Dose (mg/kg)	Number of Mice with Erythrocytes Scored	Micronucleated NCEs/ 1,000 NCEs[b]	P Value[c]	% PCEs[b]	P Value[c]
Male						
Ethanol[d]	0	10	2.5 ± 0.43		4.3 ± 0.13	
Diisopropylcarbodiimide	17.5	10	4.4 ± 0.54	0.016	4.2 ± 0.18	0.719
	35.0	10	5.8 ± 0.63	<0.001	4.5 ± 0.19	0.374
	70.0	10	5.8 ± 0.65	<0.001	4.6 ± 0.17	0.097
	140.0	1[e]	12.0	—	4.3	—
			P<0.001[f]		P=0.231[g]	
Female						
Ethanol	0	10	1.9 ± 0.43		4.2 ± 0.13	
Diisopropylcarbodiimide	17.5	10	4.1 ± 0.57	0.002	4.4 ± 0.21	0.601
	35.0	10	5.2 ± 0.36	<0.001	4.4 ± 0.16	0.565
	70.0	10	5.4 ± 0.31	<0.001	3.8 ± 0.19	0.074
	140.0	1[e]	4.0	—	4.7	—
			P<0.001		P=0.088	

[a] Study was performed at Microbiological Associates, Inc. The detailed protocol and these data are presented by Witt *et al.* (1999).
[b] NCE=normochromatic erythrocyte; PCE=polychromatic erythrocyte
[c] Mean ± standard error
[d] Pairwise comparison with the vehicle control; significant at P≤0.008 (ILS, 1990)
[e] Vehicle control
[f] These data were not included in the statistical evaluations due to insufficient animals in this dose group.
[g] Significance of micronucleated NCEs/1,000 NCEs tested by the one-tailed trend test; significant at P≤0.025 (ILS, 1990)
Analysis of variance, significant at P≤0.025

TABLE E6
Induction of Micronuclei in Polychromatic and Normochromatic Erythrocytes of Male Mice Following Dermal Application of Diisopropylcarbodiimide for 4 Months[a]

Compound	Dose (mg/kg)	PCEs			NCEs	
		Peripheral Blood		Bone Marrow	Peripheral Blood	
		Micronucleated PCEs/1,000 PCEs[b]	P Value[c]	Micronucleated PCEs/1,000 PCEs[d]	Micronucleated NCEs/1,000 NCEs[e]	P Value[c]
Ethanol[f]	0	3.33		1.1 ± 0.22	1.78	
Diisopropylcarbodiimide						
	17.5	4.45	0.001	0.6 ± 0.09	2.62	0.002
	35.0	4.36	0.002	0.9 ± 0.17	2.52	0.006
	70.0	5.21	<0.001	1.3 ± 0.27	2.98	<0.001
		P<0.001[g]		P=0.234	P<0.001	

[a] Study was performed at ILS, Inc. The detailed protocol and data that are summarized here are presented by Witt *et al.* (1999); five mice per group had erythrocytes scored. PCE=polychromatic erythrocyte; NCE=normochromatic erythrocyte
[b] Mean for days 4 to 124
[c] Pairwise comparison with the vehicle control; significant at P≤0.008 (ILS, 1990)
[d] Mean ± standard error on day 124
[e] Mean for days 60 to 124
[f] Solvent control
[g] Significance of micronucleated cells/1,000 cells tested by the one-tailed trend test; significant at P≤0.025 (ILS, 1990)

APPENDIX F
CLINICAL PATHOLOGY RESULTS

TABLE F1
Hematology and Clinical Chemistry Data for Rats in the 3-Month Dermal Study of Diisopropylcarbodiimide[a]

	Vehicle Control	10 mg/kg	20 mg/kg	40 mg/kg	80 mg/kg	160 mg/kg
Male						
n						
Day 3	10	10	10	10	10	10
Day 22	10	10	10	10	9	0
Week 14	10	10	10	10	0	0
Hematology						
Automated hematocrit (%)						
Day 3	39.3 ± 0.5	40.4 ± 0.6	40.1 ± 0.8	39.5 ± 0.8	40.2 ± 0.5	40.2 ± 0.3
Day 22	44.3 ± 0.5	42.8 ± 0.5	43.1 ± 0.6	43.3 ± 0.4	42.7 ± 0.5	—
Week 14	43.9 ± 0.4	43.9 ± 0.3	43.3 ± 0.2	43.0 ± 0.5	—	—
Manual hematocrit (%)						
Day 3	44.2 ± 0.5	46.2 ± 0.5	45.9 ± 0.7	45.3 ± 0.6	45.4 ± 0.5	45.7 ± 0.5
Day 22	49.1 ± 0.7	47.9 ± 0.6	48.2 ± 0.6	48.7 ± 0.4	47.7 ± 0.5	—
Week 14	47.2 ± 0.4	46.9 ± 0.3	46.4 ± 0.2	46.5 ± 0.6	—	—
Hemoglobin (g/dL)						
Day 3	14.4 ± 0.1	14.6 ± 0.1	14.6 ± 0.2	14.6 ± 0.2	14.5 ± 0.1	14.7 ± 0.1
Day 22	15.7 ± 0.2	15.3 ± 0.2	15.4 ± 0.2	15.5 ± 0.1	15.3 ± 0.2	—
Week 14	15.4 ± 0.1	15.6 ± 0.1	15.2 ± 0.1	15.2 ± 0.1	—	—
Erythrocytes (10^6/µL)						
Day 3	6.67 ± 0.10	6.76 ± 0.07	6.75 ± 0.14	6.69 ± 0.11	6.69 ± 0.08	6.77 ± 0.06
Day 22	7.59 ± 0.09	7.27 ± 0.09	7.33 ± 0.11	7.40 ± 0.08	7.26 ± 0.08	—
Week 14	8.65 ± 0.08	8.66 ± 0.09	8.51 ± 0.05	8.39 ± 0.10	—	—
Reticulocytes (10^6/µL)						
Day 3	0.22 ± 0.03	0.28 ± 0.04	0.25 ± 0.03	0.22 ± 0.03	0.25 ± 0.03	0.19 ± 0.02
Day 22	0.14 ± 0.02	0.14 ± 0.01	0.14 ± 0.01	0.13 ± 0.01	0.12 ± 0.02	—
Week 14	0.14 ± 0.01	0.13 ± 0.02	0.14 ± 0.01	0.13 ± 0.01	—	—
Nucleated erythrocytes (10^3/µL)						
Day 3	0.40 ± 0.22	0.20 ± 0.13	0.30 ± 0.15	0.70 ± 0.34	1.20 ± 0.53	0.30 ± 0.15
Day 22	0.10 ± 0.10	0.30 ± 0.15	0.30 ± 0.15	0.33 ± 0.17[b]	0.57 ± 0.20[c]	—
Week 14	0.50 ± 0.31	0.00 ± 0.00	0.30 ± 0.15	0.40 ± 0.22	—	—
Mean cell volume (fL)						
Day 3	58.9 ± 0.6	59.9 ± 0.5	59.4 ± 0.7	59.1 ± 0.4	60.2 ± 0.6	59.4 ± 0.6
Day 22	58.4 ± 0.2	58.9 ± 0.2	58.8 ± 0.3	58.6 ± 0.5	58.9 ± 0.3	—
Week 14	50.7 ± 0.1	50.7 ± 0.2	50.9 ± 0.2	51.3 ± 0.2*	—	—
Mean cell hemoglobin (pg)						
Day 3	21.6 ± 0.2	21.6 ± 0.1	21.6 ± 0.1	21.9 ± 0.1	21.8 ± 0.1	21.7 ± 0.1
Day 22	20.6 ± 0.2	21.1 ± 0.1	21.0 ± 0.2	21.0 ± 0.1	21.1 ± 0.1	—
Week 14	17.8 ± 0.1	18.0 ± 0.1	17.9 ± 0.1	18.1 ± 0.1	—	—
Mean cell hemoglobin concentration (g/dL)						
Day 3	36.8 ± 0.3	36.1 ± 0.3	36.4 ± 0.4	37.0 ± 0.3	36.2 ± 0.3	36.6 ± 0.3
Day 22	35.3 ± 0.2	35.8 ± 0.1	35.7 ± 0.2	35.9 ± 0.1	35.9 ± 0.3	—
Week 14	35.2 ± 0.1	35.5 ± 0.2	35.2 ± 0.2	35.4 ± 0.2	—	—
Platelets (10^3/µL)						
Day 3	817.7 ± 20.0	836.0 ± 24.8	796.9 ± 26.4	807.4 ± 22.7	801.4 ± 35.7	835.9 ± 31.2
Day 22	761.6 ± 19.5	755.3 ± 15.7	717.9 ± 12.0	713.7 ± 18.1	681.8 ± 19.4**	—
Week 14	637.0 ± 12.2	611.6 ± 13.8	634.4 ± 20.7	607.5 ± 13.1	—	—
Leukocytes (10^3/µL)						
Day 3	10.24 ± 0.42	9.89 ± 0.34	9.65 ± 0.49	9.34 ± 0.24	9.76 ± 0.48	11.30 ± 0.44
Day 22	9.91 ± 0.33	9.15 ± 0.46	9.60 ± 0.37	9.69 ± 0.33	8.94 ± 0.67	—
Week 14	9.44 ± 0.39	10.73 ± 0.41	9.80 ± 0.34	9.48 ± 0.85	—	—

TABLE F1
Hematology and Clinical Chemistry Data for Rats in the 3-Month Dermal Study of Diisopropylcarbodiimide

	Vehicle Control	10 mg/kg	20 mg/kg	40 mg/kg	80 mg/kg	160 mg/kg
Male						
n						
Day 3	10	10	10	10	10	10
Day 22	10	10	10	10	9	0
Week 14	10	10	10	10	0	0
Hematology (continued)						
Segmented neutrophils (10^3/μL)						
Day 3	1.06 ± 0.13	0.92 ± 0.12	1.02 ± 0.17	0.86 ± 0.17	1.09 ± 0.12	1.69 ± 0.19
Day 22	1.61 ± 0.18	1.28 ± 0.27	1.45 ± 0.11	0.94 ± 0.14**[b]	1.01 ± 0.17*[c]	—
Week 14	1.03 ± 0.08	1.25 ± 0.25	1.25 ± 0.16	1.20 ± 0.19	—	—
Bands (10^3/μL)						
Day 3	0.01 ± 0.01	0.00 ± 0.00	0.00 ± 0.00	0.01 ± 0.01	0.00 ± 0.00	0.04 ± 0.02
Day 22	0.02 ± 0.01	0.00 ± 0.00	0.03 ± 0.02	0.05 ± 0.02[b]	0.03 ± 0.02[c]	—
Week 14	0.00 ± 0.00	0.01 ± 0.01	0.01 ± 0.01	0.02 ± 0.02	—	—
Lymphocytes (10^3/μL)						
Day 3	8.99 ± 0.36	8.70 ± 0.31	8.35 ± 0.49	8.27 ± 0.20	8.51 ± 0.46	9.25 ± 0.31
Day 22	8.20 ± 0.31	7.70 ± 0.48	7.96 ± 0.39	8.61 ± 0.24[b]	8.03 ± 0.72[c]	—
Week 14	8.11 ± 0.35	9.18 ± 0.42	8.31 ± 0.24	8.01 ± 0.71	—	—
Atypical lymphocytes (10^3/μL)						
Day 3	0.00 ± 0.00	0.01 ± 0.01	0.05 ± 0.02*	0.00 ± 0.00	0.00 ± 0.00	0.03 ± 0.02
Week 14	0.02 ± 0.01	0.02 ± 0.02	0.03 ± 0.02	0.03 ± 0.02	—	—
Monocytes (10^3/μL)						
Day 3	0.19 ± 0.07	0.23 ± 0.04	0.16 ± 0.05	0.16 ± 0.05	0.12 ± 0.03	0.28 ± 0.09
Day 22	0.07 ± 0.03	0.12 ± 0.04	0.13 ± 0.03	0.21 ± 0.05*[b]	0.13 ± 0.05[c]	—
Week 14	0.23 ± 0.05	0.21 ± 0.06	0.14 ± 0.04	0.15 ± 0.03	—	—
Eosinophils (10^3/μL)						
Day 3	0.00 ± 0.00	0.04 ± 0.03	0.07 ± 0.02*	0.04 ± 0.02	0.04 ± 0.02	0.00 ± 0.00
Day 22	0.01 ± 0.01	0.05 ± 0.03	0.03 ± 0.02	0.02 ± 0.01[b]	0.02 ± 0.02[c]	—
Week 14	0.05 ± 0.02	0.06 ± 0.04	0.06 ± 0.03	0.06 ± 0.02	—	—
Clinical Chemistry						
Urea nitrogen (mg/dL)						
Day 3	20.5 ± 0.6	21.3 ± 0.5	20.1 ± 0.7	21.8 ± 0.4	20.6 ± 0.8	20.7 ± 0.6
Day 22	23.3 ± 0.5	25.0 ± 0.6	24.0 ± 0.8	23.7 ± 0.8	22.6 ± 0.7	—
Week 14	19.5 ± 0.5	20.6 ± 0.6	20.7 ± 0.4	20.1 ± 0.5	—	—
Creatinine (mg/dL)						
Day 3	0.25 ± 0.02	0.24 ± 0.02	0.25 ± 0.02	0.26 ± 0.02	0.25 ± 0.02	0.25 ± 0.02
Day 22	0.29 ± 0.01	0.30 ± 0.00	0.28 ± 0.01	0.27 ± 0.02	0.31 ± 0.01	—
Week 14	0.37 ± 0.02	0.37 ± 0.02	0.37 ± 0.02	0.34 ± 0.02	—	—
Total protein (g/dL)						
Day 3	5.6 ± 0.1	5.7 ± 0.1	5.7 ± 0.1	5.7 ± 0.1	5.7 ± 0.1	5.8 ± 0.1
Day 22	5.9 ± 0.1	5.9 ± 0.1	6.0 ± 0.1	5.9 ± 0.1	5.8 ± 0.1	—
Week 14	6.7 ± 0.1	6.5 ± 0.1	6.6 ± 0.1	6.4 ± 0.1*	—	—
Albumin (g/dL)						
Day 3	4.6 ± 0.1	4.6 ± 0.1	4.7 ± 0.1	4.6 ± 0.1	4.7 ± 0.1	4.7 ± 0.1
Day 22	4.7 ± 0.1	4.7 ± 0.1	4.8 ± 0.1	4.7 ± 0.1	4.6 ± 0.1	—
Week 14	4.9 ± 0.1	4.8 ± 0.1	4.9 ± 0.1	4.7 ± 0.0	—	—

TABLE F1
Hematology and Clinical Chemistry Data for Rats in the 3-Month Dermal Study of Diisopropylcarbodiimide

	Vehicle Control	10 mg/kg	20 mg/kg	40 mg/kg	80 mg/kg	160 mg/kg
Male (continued)						
n						
Day 3	10	10	10	10	10	10
Day 22	10	10	10	10	9	0
Week 14	10	10	10	10	0	0
Clinical chemistry (continued)						
Alanine aminotransferase (IU/L)						
Day 3	50 ± 1	51 ± 1	52 ± 2	53 ± 3	52 ± 3	64 ± 2**
Day 22	49 ± 1	50 ± 2	49 ± 2	49 ± 2	48 ± 2	—
Week 14	56 ± 1	59 ± 3	53 ± 2	54 ± 3	—	—
Alkaline phosphatase (IU/L)						
Day 3	719 ± 14	710 ± 12	723 ± 10	729 ± 20	696 ± 16	659 ± 14
Day 22	504 ± 7	481 ± 10	485 ± 11	473 ± 11*	421 ± 12**[d]	—
Week 14	272 ± 9	270 ± 4	261 ± 4	257 ± 8	—	—
Creatine kinase (IU/L)						
Day 3	357 ± 28[b]	391 ± 32	405 ± 54	477 ± 68	406 ± 62[b]	435 ± 36
Day 22	516 ± 57	569 ± 69	531 ± 55	728 ± 129	534 ± 60[d]	—
Week 14	192 ± 38	243 ± 27	267 ± 37	184 ± 32	—	—
Sorbitol dehydrogenase (IU/L)						
Day 3	20 ± 1	21 ± 1	25 ± 4	21 ± 1	23 ± 1	20 ± 1
Day 22	19 ± 1	20 ± 1	18 ± 1	18 ± 1	17 ± 2	—
Week 14	18 ± 1	17 ± 1	18 ± 1	19 ± 2	—	—
Bile acids (μmol/L)						
Day 3	29.5 ± 7.0	31.0 ± 3.5	35.2 ± 5.1	27.2 ± 3.8	25.3 ± 2.8	36.5 ± 4.5
Day 22	30.7 ± 6.3	30.5 ± 4.4	25.6 ± 5.7	44.5 ± 7.4	44.9 ± 10.5	—
Week 14	17.4 ± 2.2	13.4 ± 1.1	24.3 ± 2.7	22.5 ± 2.7	—	—
Female						
n						
Day 3	10	10	10	10	10	10
Day 22	10	10	10	10	10	0
Week 14	10	10	10	10	0	0
Hematology						
Automated hematocrit (%)						
Day 3	39.2 ± 0.4	38.7 ± 0.5	40.0 ± 0.6	39.1 ± 0.5	40.3 ± 0.4	39.7 ± 1.1
Day 22	43.1 ± 1.7	44.2 ± 0.6	46.4 ± 0.9	45.4 ± 0.5	45.7 ± 0.4	—
Week 14	44.1 ± 0.5	43.3 ± 0.4	43.6 ± 0.3	43.3 ± 0.4	—	—
Manual hematocrit (%)						
Day 3	45.2 ± 0.4	44.2 ± 0.4	45.5 ± 0.6	44.7 ± 0.3	45.5 ± 0.6	45.3 ± 1.1
Day 22	45.9 ± 1.5	47.2 ± 0.5	48.6 ± 0.6	48.1 ± 0.6	48.3 ± 0.5	—
Week 14	44.8 ± 0.3	44.1 ± 0.5	43.9 ± 0.3	43.9 ± 0.5	—	—
Hemoglobin (g/dL)						
Day 3	14.6 ± 0.1	14.5 ± 0.2	14.8 ± 0.2	14.6 ± 0.1	14.8 ± 0.1	14.7 ± 0.4
Day 22	15.2 ± 0.5	15.4 ± 0.1	16.2 ± 0.3	16.0 ± 0.2	16.0 ± 0.1	—
Week 14	15.2 ± 0.1	15.1 ± 0.1	15.1 ± 0.1	15.1 ± 0.2	—	—

TABLE F1
Hematology and Clinical Chemistry Data for Rats in the 3-Month Dermal Study of Diisopropylcarbodiimide

	Vehicle Control	10 mg/kg	20 mg/kg	40 mg/kg	80 mg/kg	160 mg/kg
Female (continued)						
n						
Day 3	10	10	10	10	10	10
Day 22	10	10	10	10	10	0
Week 14	10	10	10	10	0	0
Hematology (continued)						
Erythrocytes (10^6/μL)						
Day 3	6.64 ± 0.08	6.68 ± 0.12	6.76 ± 0.10	6.69 ± 0.10	6.88 ± 0.09	6.80 ± 0.19
Day 22	7.09 ± 0.29	7.34 ± 0.11	7.72 ± 0.16	7.60 ± 0.10	7.58 ± 0.07	—
Week 14	7.78 ± 0.09	7.65 ± 0.08	7.70 ± 0.06	7.61 ± 0.08	—	—
Reticulocytes (10^6/μL)						
Day 3	0.24 ± 0.01	0.25 ± 0.02	0.24 ± 0.02	0.27 ± 0.02	0.24 ± 0.02	0.27 ± 0.03
Day 22	0.12 ± 0.01	0.13 ± 0.01	0.12 ± 0.01	0.11 ± 0.01	0.12 ± 0.01	—
Week 14	0.12 ± 0.01	0.14 ± 0.01	0.14 ± 0.01	0.14 ± 0.01	—	—
Nucleated erythrocytes (10^3/μL)						
Day 3	0.40 ± 0.31	0.60 ± 0.27	0.80 ± 0.20	0.70 ± 0.34	1.10 ± 0.35	0.70 ± 0.21
Day 22	0.56 ± 0.18[b]	0.70 ± 0.30	0.60 ± 0.22	0.10 ± 0.10	0.20 ± 0.13	—
Week 14	1.00 ± 0.26	1.00 ± 0.37	1.70 ± 0.37	1.22 ± 0.28[b]	—	—
Mean cell volume (fL)						
Day 3	59.1 ± 0.4	58.1 ± 0.3	59.1 ± 0.4	58.4 ± 0.3	58.6 ± 0.3	58.5 ± 0.5
Day 22	60.8 ± 0.4	60.2 ± 0.2	60.1 ± 0.3	59.8 ± 0.3	60.4 ± 0.3	—
Week 14	56.7 ± 0.1	56.6 ± 0.1	56.7 ± 0.1	56.9 ± 0.1	—	—
Mean cell hemoglobin (pg)						
Day 3	21.9 ± 0.2	21.8 ± 0.1	21.9 ± 0.2	21.8 ± 0.2	21.5 ± 0.1	21.7 ± 0.1
Day 22	21.5 ± 0.2	21.0 ± 0.2	21.0 ± 0.1	21.0 ± 0.2	21.2 ± 0.1	—
Week 14	19.6 ± 0.1	19.8 ± 0.1	19.6 ± 0.1	19.9 ± 0.1	—	—
Mean cell hemoglobin concentration (g/dL)						
Day 3	37.2 ± 0.3	37.5 ± 0.2	37.0 ± 0.3	37.3 ± 0.2	36.7 ± 0.2	37.1 ± 0.2
Day 22	35.4 ± 0.3	34.9 ± 0.2	34.9 ± 0.1	35.2 ± 0.2	35.1 ± 0.2	—
Week 14	34.6 ± 0.2	34.9 ± 0.2	34.6 ± 0.2	34.9 ± 0.2	—	—
Platelets (10^3/μL)						
Day 3	776.9 ± 23.6	765.4 ± 11.6	741.1 ± 15.1	729.2 ± 23.9	772.3 ± 14.5	792.0 ± 26.1
Day 22	661.4 ± 21.0	651.4 ± 11.9	665.0 ± 9.7	616.6 ± 16.1	655.8 ± 10.3	—
Week 14	626.7 ± 23.5	634.6 ± 18.5	635.3 ± 29.1	636.2 ± 11.0	—	—
Leukocytes (10^3/μL)						
Day 3	10.06 ± 0.37	9.84 ± 0.53	9.28 ± 0.42	9.12 ± 0.49	9.45 ± 0.27	10.71 ± 0.64
Day 22	8.78 ± 0.44	9.18 ± 0.22	7.89 ± 0.37	10.20 ± 0.47	9.37 ± 0.36	—
Week 14	7.07 ± 0.56	7.39 ± 0.64	6.17 ± 0.58	7.78 ± 0.91	—	—
Segmented neutrophils (10^3/μL)						
Day 3	0.65 ± 0.09	0.89 ± 0.25	0.79 ± 0.15	0.65 ± 0.10	0.92 ± 0.13	0.97 ± 0.13
Day 22	1.04 ± 0.10[b]	1.14 ± 0.16	0.86 ± 0.20	1.05 ± 0.12	0.91 ± 0.10	—
Week 14	1.07 ± 0.20	0.99 ± 0.13	0.73 ± 0.12	1.09 ± 0.23[b]	—	—
Bands (10^3/μL)						
Day 3	0.00 ± 0.00	0.01 ± 0.01	0.00 ± 0.00	0.01 ± 0.01	0.00 ± 0.00	0.01 ± 0.01
Day 22	0.00 ± 0.00[b]	0.02 ± 0.02	0.01 ± 0.01	0.01 ± 0.01	0.01 ± 0.01	—
Week 14	0.00 ± 0.00	0.01 ± 0.01	0.00 ± 0.00	0.01 ± 0.01[b]	—	—
Lymphocytes (10^3/μL)						
Day 3	9.26 ± 0.39	8.74 ± 0.40	8.37 ± 0.36	8.38 ± 0.47	8.30 ± 0.26	9.53 ± 0.68
Day 22	7.60 ± 0.42[b]	7.77 ± 0.18	6.89 ± 0.36	8.90 ± 0.47	8.21 ± 0.31	—
Week 14	5.80 ± 0.49	6.18 ± 0.54	5.24 ± 0.55	6.39 ± 0.82[b]	—	—

TABLE F1
Hematology and Clinical Chemistry Data for Rats in the 3-Month Dermal Study of Diisopropylcarbodiimide

	Vehicle Control	10 mg/kg	20 mg/kg	40 mg/kg	80 mg/kg	160 mg/kg
Female (continued)						
n						
Day 3	10	10	10	10	10	10
Day 22	10	10	10	10	10	0
Week 14	10	10	10	10	0	0
Hematology (continued)						
Atypical lymphocytes ($10^3/\mu L$)						
Day 3	0.02 ± 0.01	0.04 ± 0.02	0.01 ± 0.01	0.01 ± 0.01	0.03 ± 0.02	0.01 ± 0.01
Day 22	0.00 ± 0.00[b]	0.00 ± 0.00	0.00 ± 0.00	0.01 ± 0.01	0.01 ± 0.01	—
Week 14	0.00 ± 0.00	0.00 ± 0.00	0.01 ± 0.01	0.01 ± 0.01[b]	—	—
Monocytes ($10^3/\mu L$)						
Day 3	0.11 ± 0.04	0.15 ± 0.04	0.09 ± 0.02	0.03 ± 0.02	0.13 ± 0.04	0.17 ± 0.05
Day 22	0.11 ± 0.03[b]	0.22 ± 0.04	0.09 ± 0.03	0.15 ± 0.03	0.11 ± 0.03	—
Week 14	0.14 ± 0.03	0.15 ± 0.03	0.12 ± 0.03	0.21 ± 0.07[b]	—	—
Eosinophils ($10^3/\mu L$)						
Day 3	0.02 ± 0.01	0.01 ± 0.01	0.02 ± 0.01	0.04 ± 0.02	0.08 ± 0.04	0.03 ± 0.02
Day 22	0.06 ± 0.01[b]	0.03 ± 0.01	0.04 ± 0.02	0.07 ± 0.03	0.12 ± 0.04	—
Week 14	0.06 ± 0.02	0.06 ± 0.03	0.07 ± 0.02	0.06 ± 0.03[b]	—	—
Clinical chemistry						
Urea nitrogen (mg/dL)						
Day 3	20.7 ± 0.7	22.0 ± 1.1	20.8 ± 0.6	21.1 ± 0.8	22.7 ± 0.6	20.4 ± 0.5
Day 22	23.1 ± 0.6	23.1 ± 0.8	25.6 ± 1.3	21.6 ± 1.0	21.0 ± 0.9	—
Week 14	23.0 ± 0.6	21.8 ± 0.4	21.9 ± 0.7	22.1 ± 0.5	—	—
Creatinine (mg/dL)						
Day 3	0.28 ± 0.01	0.29 ± 0.02	0.28 ± 0.01	0.29 ± 0.01	0.29 ± 0.01	0.31 ± 0.01
Day 22	0.27 ± 0.02	0.27 ± 0.02	0.31 ± 0.03	0.27 ± 0.02	0.27 ± 0.02	—
Week 14	0.28 ± 0.02	0.31 ± 0.01	0.33 ± 0.02	0.31 ± 0.01	—	—
Total protein (g/dL)						
Day 3	5.4 ± 0.1	5.3 ± 0.1	5.4 ± 0.0	5.3 ± 0.1	5.5 ± 0.1	5.5 ± 0.1
Day 22	5.5 ± 0.1	5.5 ± 0.1	5.5 ± 0.1	5.5 ± 0.1	5.5 ± 0.0	—
Week 14	6.3 ± 0.1	6.3 ± 0.1	6.5 ± 0.1	6.1 ± 0.1	—	—
Albumin (g/dL)						
Day 3	4.5 ± 0.1	4.4 ± 0.1	4.5 ± 0.0	4.5 ± 0.1	4.6 ± 0.1	4.5 ± 0.1
Day 22	4.4 ± 0.1	4.4 ± 0.1	4.5 ± 0.1	4.5 ± 0.1	4.5 ± 0.0	—
Week 14	4.6 ± 0.1	4.6 ± 0.1	4.8 ± 0.1	4.5 ± 0.1	—	—
Alanine aminotransferase (IU/L)						
Day 3	45 ± 1	43 ± 1	45 ± 1	47 ± 1	47 ± 2	55 ± 2**
Day 22	42 ± 2	38 ± 1	42 ± 2	42 ± 2	38 ± 1	—
Week 14	48 ± 1	48 ± 1	50 ± 2	47 ± 2	—	—
Alkaline phosphatase (IU/L)						
Day 3	610 ± 16	584 ± 16	577 ± 8	592 ± 10	589 ± 17	561 ± 8*
Day 22	375 ± 30	410 ± 10	351 ± 19	416 ± 9	369 ± 17	—
Week 14	281 ± 6	273 ± 7	290 ± 5	267 ± 6	—	—
Creatine kinase (IU/L)						
Day 3	290 ± 28	306 ± 28	289 ± 40	281 ± 27	318 ± 40	324 ± 31
Day 22	368 ± 50	282 ± 22[c]	307 ± 33[c]	328 ± 53	328 ± 48	—
Week 14	239 ± 43	212 ± 29	220 ± 36	210 ± 30	—	—

TABLE F1
Hematology and Clinical Chemistry Data for Rats in the 3-Month Dermal Study of Diisopropylcarbodiimide

	Vehicle Control	10 mg/kg	20 mg/kg	40 mg/kg	80 mg/kg	160 mg/kg
Female (continued)						
n						
Day 3	10	10	10	10	10	10
Day 22	10	10	10	10	10	0
Week 14	10	10	10	10	0	0
Clinical chemistry (continued)						
Sorbitol dehydrogenase (IU/L)						
Day 3	19 ± 1	19 ± 1	17 ± 1	18 ± 1	20 ± 1	19 ± 1
Day 22	23 ± 2	22 ± 1	26 ± 2	23 ± 1	21 ± 1	—
Week 14	20 ± 0	19 ± 0	22 ± 1	20 ± 1	—	—
Bile acids (μmol/L)						
Day 3	21.2 ± 4.6	33.3 ± 5.7	23.0 ± 2.8	32.9 ± 6.9	28.3 ± 5.5	48.3 ± 6.6**
Day 22	16.6 ± 2.5	21.3 ± 4.7	24.9 ± 4.9	19.1 ± 3.8	28.0 ± 3.7	—
Week 14	29.6 ± 4.5	25.1 ± 5.1	25.7 ± 3.1	27.5 ± 2.7	—	—

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

TABLE F2
Hematology Data for Mice in the 3-Month Dermal Study of Diisopropycarbodiimide[a]

	Vehicle Control	17.5 mg/kg	35 mg/kg	70 mg/kg	140 mg/kg
n	10	10	10	10	1
Male					
Automated hematocrit (%)	45.8 ± 0.8	44.9 ± 0.5	45.8 ± 0.7	45.0 ± 0.5	47.5
Manual hematocrit (%)	45.0 ± 0.6	44.1 ± 0.5	44.8 ± 0.5	44.1 ± 0.5	46.0
Hemoglobin (g/dL)	15.3 ± 0.2	15.2 ± 0.2	15.3 ± 0.2	15.0 ± 0.1	15.8
Erythrocytes (10^6/μL)	9.25 ± 0.18	8.98 ± 0.12	9.17 ± 0.14	9.09 ± 0.08	9.94
Reticulocytes (10^6/μL)	0.19 ± 0.02	0.18 ± 0.02	0.18 ± 0.01	0.22 ± 0.02	0.18
Nucleated erythrocytes (10^3/μL)	0.10 ± 0.10	0.10 ± 0.10	0.00 ± 0.00	0.00 ± 0.00	0.00
Mean cell volume (fL)	49.5 ± 0.3	50.1 ± 0.4	50.0 ± 0.3	49.5 ± 0.2	47.8
Mean cell hemoglobin (pg)	16.6 ± 0.2	17.0 ± 0.1	16.7 ± 0.2	16.5 ± 0.1	15.9
Mean cell hemoglobin concentration (g/dL)	33.6 ± 0.3	33.9 ± 0.2	33.4 ± 0.3	33.4 ± 0.3	33.3
Platelets (10^3/μL)	719.9 ± 30.0	756.9 ± 22.9	724.9 ± 25.4	726.9 ± 30.9	682.0
Leukocytes (10^3/μL)	4.35 ± 0.17	3.39 ± 0.33	4.26 ± 0.30	3.72 ± 0.22	5.00
Segmented neutrophils (10^3/μL)	0.42 ± 0.07	0.40 ± 0.07	0.45 ± 0.08	0.31 ± 0.04	0.50
Lymphocytes (10^3/μL)	3.90 ± 0.19	2.96 ± 0.28*	3.77 ± 0.27	3.38 ± 0.20	4.35
Monocytes (10^3/μL)	0.01 ± 0.01	0.02 ± 0.01	0.01 ± 0.00	0.01 ± 0.01	0.00
Eosinophils (10^3/μL)	0.02 ± 0.01	0.02 ± 0.01	0.04 ± 0.01	0.02 ± 0.01	0.15
Female					
Automated hematocrit (%)	47.9 ± 0.7	47.0 ± 0.6	49.0 ± 0.9	48.5 ± 0.9	49.6
Manual hematocrit (%)	46.3 ± 0.5	45.7 ± 0.5	47.0 ± 0.6	46.5 ± 0.6	48.0
Hemoglobin (g/dL)	16.0 ± 0.2	16.0 ± 0.2	16.3 ± 0.3	16.0 ± 0.2	16.6
Erythrocytes (10^6/μL)	9.74 ± 0.15	9.52 ± 0.11	9.89 ± 0.18	9.84 ± 0.17	10.22
Reticulocytes (10^6/μL)	0.14 ± 0.01	0.20 ± 0.02	0.15 ± 0.02	0.15 ± 0.02	0.08
Mean cell volume (fL)	49.2 ± 0.2	49.4 ± 0.3	49.6 ± 0.2	49.3 ± 0.2	48.5
Mean cell hemoglobin (pg)	16.5 ± 0.1	16.8 ± 0.1	16.4 ± 0.1	16.2 ± 0.1	16.2
Mean cell hemoglobin concentration (g/dL)	33.5 ± 0.2	34.0 ± 0.3	33.2 ± 0.2	33.0 ± 0.2	33.5
Platelets (10^3/μL)	520.7 ± 39.7	660.7 ± 43.0	545.8 ± 22.7	555.8 ± 33.4	742.0
Leukocytes (10^3/μL)	3.99 ± 0.27	3.74 ± 0.28	3.94 ± 0.22	3.73 ± 0.16	5.10
Segmented neutrophils (10^3/μL)	0.35 ± 0.05	0.34 ± 0.06	0.28 ± 0.04	0.37 ± 0.06	0.41
Bands (10^3/μL)	0.00 ± 0.00	0.01 ± 0.01	0.00 ± 0.00	0.01 ± 0.01	0.00
Lymphocytes (10^3/μL)	3.58 ± 0.24	3.34 ± 0.24	3.62 ± 0.19	3.33 ± 0.12	4.64
Atypical lymphocytes (10^3/μL)	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00
Monocytes (10^3/μL)	0.04 ± 0.01	0.04 ± 0.01	0.02 ± 0.01	0.02 ± 0.01	0.05
Eosinophils (10^3/μL)	0.01 ± 0.01	0.02 ± 0.01	0.02 ± 0.01	0.01 ± 0.01	0.00

* Significantly different ($P \leq 0.05$) from the vehicle control group by Dunn's test
[a] Mean ± standard error. Statistical tests were performed on unrounded data. No data available for the 280 mg/kg groups due to 100% mortality.

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

TABLE G1
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats in the 2-Week Dermal Study of Diisopropylcarbodiimide[a]

	Vehicle Control	3 mg/animal	9 mg/animal
n	5	5	5
Male			
Necropsy body wt	207 ± 7	198 ± 5	201 ± 5
Heart			
Absolute	0.772 ± 0.022	0.736 ± 0.014	0.794 ± 0.025
Relative	0.374 ± 0.007	0.372 ± 0.004	0.395 ± 0.011
R. Kidney			
Absolute	0.997 ± 0.039	0.917 ± 0.027	0.992 ± 0.028
Relative	0.481 ± 0.004	0.463 ± 0.003	0.493 ± 0.010
Liver			
Absolute	12.316 ± 0.633	10.982 ± 0.377	12.768 ± 1.227
Relative	5.935 ± 0.125	5.545 ± 0.069	6.321 ± 0.513
Lung			
Absolute	1.276 ± 0.050	1.286 ± 0.074	1.329 ± 0.030
Relative	0.617 ± 0.015	0.652 ± 0.044	0.663 ± 0.025
R. Testis			
Absolute	1.139 ± 0.052	1.117 ± 0.021	1.123 ± 0.030
Relative	0.549 ± 0.007	0.565 ± 0.009	0.558 ± 0.001
Thymus			
Absolute	0.532 ± 0.035	0.501 ± 0.015	0.522 ± 0.010
Relative	0.256 ± 0.010	0.254 ± 0.011	0.260 ± 0.010
Female			
Necropsy body wt	131 ± 4	133 ± 4	128 ± 3
Heart			
Absolute	0.561 ± 0.012	0.571 ± 0.030	0.539 ± 0.016
Relative	0.430 ± 0.011	0.430 ± 0.009	0.423 ± 0.013
R. Kidney			
Absolute	0.645 ± 0.014	0.639 ± 0.017	0.617 ± 0.014
Relative	0.494 ± 0.013	0.483 ± 0.009	0.483 ± 0.003
Liver			
Absolute	6.613 ± 0.243	6.707 ± 0.249	6.441 ± 0.217
Relative	5.054 ± 0.117	5.060 ± 0.089	5.044 ± 0.102
Lung			
Absolute	1.075 ± 0.063	0.962 ± 0.024	0.942 ± 0.023
Relative	0.823 ± 0.047	0.730 ± 0.036	0.739 ± 0.019
Thymus			
Absolute	0.338 ± 0.007	0.369 ± 0.013	0.339 ± 0.013
Relative	0.259 ± 0.006	0.279 ± 0.011	0.267 ± 0.015

[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). No data available for the 27, 81, and 242 mg/animal groups due to 100% mortality.

TABLE G2
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats in the 3-Month Dermal Study of Diisopropylcarbodiimide[a]

	Vehicle Control	10 mg/kg	20 mg/kg	40 mg/kg
n	10	10	10	10
Male				
Necropsy body wt	323 ± 5	317 ± 10	321 ± 9	297 ± 8
Heart				
Absolute	0.468 ± 0.153	0.365 ± 0.141	0.757 ± 0.147	0.742 ± 0.189
Relative	0.144 ± 0.047	0.108 ± 0.040	0.227 ± 0.043	0.244 ± 0.061
R. Kidney				
Absolute	1.211 ± 0.023	1.117 ± 0.117	1.256 ± 0.042	1.176 ± 0.032
Relative	0.375 ± 0.005	0.347 ± 0.035	0.391 ± 0.006	0.396 ± 0.005
Liver				
Absolute	12.362 ± 0.257	12.307 ± 0.479	12.518 ± 0.438	11.410 ± 0.322
Relative	3.825 ± 0.058	3.875 ± 0.045	3.888 ± 0.034	3.845 ± 0.056
Lung				
Absolute	1.650 ± 0.069	1.705 ± 0.083	1.698 ± 0.111	1.593 ± 0.069
Relative	0.511 ± 0.020	0.546 ± 0.041	0.526 ± 0.025	0.537 ± 0.020
R. Testis				
Absolute	1.453 ± 0.018	1.414 ± 0.035	1.429 ± 0.027	1.412 ± 0.023
Relative	0.450 ± 0.007	0.449 ± 0.014	0.446 ± 0.007	0.478 ± 0.012
Thymus				
Absolute	0.032 ± 0.005	0.070 ± 0.036	0.037 ± 0.004	0.043 ± 0.007
Relative	0.010 ± 0.002	0.022 ± 0.011	0.012 ± 0.001	0.015 ± 0.003
Female				
Necropsy body wt	193 ± 3	193 ± 4	191 ± 3	180 ± 3**
Heart				
Absolute	0.734 ± 0.018	0.729 ± 0.015	0.733 ± 0.013	0.720 ± 0.013
Relative	0.380 ± 0.008	0.378 ± 0.007	0.383 ± 0.004	0.400 ± 0.007
R. Kidney				
Absolute	0.794 ± 0.034	0.764 ± 0.021	0.794 ± 0.016	0.761 ± 0.032
Relative	0.410 ± 0.013	0.396 ± 0.008	0.415 ± 0.008	0.422 ± 0.015
Liver				
Absolute	6.978 ± 0.135	6.916 ± 0.212	6.986 ± 0.143	6.233 ± 0.186*
Relative	3.614 ± 0.047	3.579 ± 0.074	3.653 ± 0.055	3.458 ± 0.059
Lung				
Absolute	1.311 ± 0.054	1.316 ± 0.045	1.307 ± 0.028	1.327 ± 0.040
Relative	0.679 ± 0.024	0.683 ± 0.026	0.684 ± 0.016	0.739 ± 0.023
Thymus				
Absolute	0.248 ± 0.008	0.277 ± 0.016	0.243 ± 0.019	0.241 ± 0.014
Relative	0.129 ± 0.005	0.144 ± 0.008	0.127 ± 0.009	0.134 ± 0.007

* Significantly different ($P \leq 0.05$) from the vehicle control group by Dunnett's test
** Significantly different ($P \leq 0.01$) from the vehicle control group by Williams' test
[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). No data available for the 80 and 160 mg/kg groups due to 100% mortality.

TABLE G3
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 2-Week Dermal Study of Diisopropylcarbodiimide[a]

	Vehicle Control	1 mg/animal	3 mg/animal
n	5	5	5
Male			
Necropsy body wt	25.3 ± 0.8	25.7 ± 1.0	25.3 ± 0.8
Heart			
Absolute	0.128 ± 0.005	0.129 ± 0.003	0.128 ± 0.003
Relative	0.507 ± 0.016	0.504 ± 0.015	0.509 ± 0.013
R. Kidney			
Absolute	0.263 ± 0.010	0.269 ± 0.011	0.255 ± 0.008
Relative	1.036 ± 0.023	1.050 ± 0.039	1.010 ± 0.010
Liver			
Absolute	1.439 ± 0.053	1.439 ± 0.063	1.454 ± 0.049
Relative	5.677 ± 0.070	5.608 ± 0.172	5.763 ± 0.189
Lung			
Absolute	0.199 ± 0.008	0.178 ± 0.002*	0.180 ± 0.006
Relative	0.790 ± 0.044	0.695 ± 0.020	0.712 ± 0.026
R. Testis			
Absolute	0.102 ± 0.004	0.107 ± 0.003	0.106 ± 0.004
Relative	0.404 ± 0.007	0.417 ± 0.014	0.419 ± 0.007
Thymus			
Absolute	0.057 ± 0.005	0.055 ± 0.004	0.062 ± 0.006
Relative	0.224 ± 0.020	0.215 ± 0.013	0.244 ± 0.021
Female			
Necropsy body wt	22.8 ± 0.6	22.3 ± 0.4	22.9 ± 0.3
Heart			
Absolute	0.128 ± 0.005	0.125 ± 0.003	0.129 ± 0.003
Relative	0.561 ± 0.018	0.561 ± 0.006	0.564 ± 0.006
R. Kidney			
Absolute	0.202 ± 0.010	0.198 ± 0.009	0.206 ± 0.009
Relative	0.887 ± 0.032	0.888 ± 0.033	0.900 ± 0.032
Liver			
Absolute	1.321 ± 0.066	1.326 ± 0.028	1.379 ± 0.034
Relative	5.782 ± 0.157	5.937 ± 0.115	6.026 ± 0.104
Lung			
Absolute	0.190 ± 0.018	0.182 ± 0.009	0.183 ± 0.008
Relative	0.828 ± 0.056	0.815 ± 0.036	0.799 ± 0.034
Thymus			
Absolute	0.073 ± 0.006	0.071 ± 0.006	0.076 ± 0.010
Relative	0.319 ± 0.022	0.318 ± 0.030	0.334 ± 0.046

* Significantly different ($P \leq 0.05$) from the vehicle control group by Dunnett's test

[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). No data available for the 9, 27, and 81 mg/animal groups due to 100% mortality.

TABLE G4
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 3-Month Dermal Study of Diisopropylcarbodiimide[a]

	Vehicle Control	17.5 mg/kg	35 mg/kg	70 mg/kg	140 mg/kg
n	10	10	10	10	1
Male					
Necropsy body wt	33.6 ± 1.0	32.5 ± 0.6	32.7 ± 0.7	31.8 ± 0.6	22.9
Heart					
Absolute	0.153 ± 0.005	0.152 ± 0.004	0.155 ± 0.005	0.155 ± 0.003	0.167
Relative	0.458 ± 0.016	0.470 ± 0.014	0.475 ± 0.015	0.490 ± 0.013	0.729
R. Kidney					
Absolute	0.303 ± 0.006	0.329 ± 0.007*	0.328 ± 0.006*	0.307 ± 0.006	0.256
Relative	0.905 ± 0.016	1.016 ± 0.027**	1.007 ± 0.025**	0.966 ± 0.013	1.118
Liver					
Absolute	1.621 ± 0.052	1.643 ± 0.036	1.669 ± 0.035	1.576 ± 0.021	1.188
Relative	4.828 ± 0.059	5.065 ± 0.090	5.112 ± 0.082*	4.961 ± 0.074	5.188
Lung					
Absolute	0.260 ± 0.015	0.269 ± 0.013	0.270 ± 0.019	0.246 ± 0.007	0.023
Relative	0.780 ± 0.051	0.831 ± 0.037	0.825 ± 0.053	0.778 ± 0.036	0.100
R. Testis					
Absolute	0.123 ± 0.004	0.120 ± 0.003	0.121 ± 0.001	0.121 ± 0.003	0.097
Relative	0.369 ± 0.013	0.369 ± 0.007	0.371 ± 0.007	0.381 ± 0.005	0.424
Thymus					
Absolute	0.039 ± 0.004	0.047 ± 0.007	0.049 ± 0.004	0.036 ± 0.002	0.026
Relative	0.116 ± 0.011	0.145 ± 0.020	0.151 ± 0.013	0.112 ± 0.007	0.114
Female					
Necropsy body wt	28.1 ± 0.6	28.3 ± 0.7	27.9 ± 0.8	28.7 ± 0.8	21.5
Heart					
Absolute	0.154 ± 0.007	0.148 ± 0.006	0.145 ± 0.008	0.160 ± 0.005	0.130
Relative	0.549 ± 0.032	0.525 ± 0.026	0.521 ± 0.028	0.558 ± 0.017	0.605
R. Kidney					
Absolute	0.225 ± 0.008	0.227 ± 0.004	0.240 ± 0.013	0.243 ± 0.007	0.181
Relative	0.800 ± 0.022	0.805 ± 0.015	0.865 ± 0.048	0.851 ± 0.029	0.842
Liver					
Absolute	1.500 ± 0.055	1.510 ± 0.033	1.470 ± 0.070	1.592 ± 0.051	1.036
Relative	5.335 ± 0.141	5.367 ± 0.157	5.272 ± 0.198	5.556 ± 0.139	4.819
Lung					
Absolute	0.344 ± 0.014	0.328 ± 0.018	0.350 ± 0.014	0.365 ± 0.014	0.220
Relative	1.223 ± 0.042	1.164 ± 0.061	1.262 ± 0.061	1.285 ± 0.070	1.023
Thymus					
Absolute	0.066 ± 0.008	0.054 ± 0.005	0.053 ± 0.004	0.054 ± 0.002	0.041
Relative	0.235 ± 0.028	0.191 ± 0.016	0.188 ± 0.008	0.190 ± 0.010	0.191

* Significantly different ($P \leq 0.05$) from the vehicle control group by 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). No data available for the 280 mg/kg groups due to 100% mortality.

APPENDIX H
REPRODUCTIVE TISSUE EVALUATIONS AND ESTROUS CYCLE CHARACTERIZATION

TABLE H1
Summary of Reproductive Tissue Evaluations for Male Rats in the 3-Month Dermal Study of Diisopropylcarbodiimide[a]

	Vehicle Control	10 mg/kg	20 mg/kg	40 mg/kg
n	10	10	10	10
Weights (g)				
Necropsy body wt	323 ± 5	317 ± 10	321 ± 9	297 ± 8
L. Cauda epididymis	0.1561 ± 0.0033	0.1512 ± 0.0052	0.1563 ± 0.0055	0.1423 ± 0.0042
L. Epididymis	0.4719 ± 0.0095	0.4608 ± 0.0089	0.4800 ± 0.0068	0.4399 ± 0.0137
L. Testis	1.4921 ± 0.0171	1.4864 ± 0.0237	1.4992 ± 0.0330	1.4405 ± 0.0240
Spermatid measurements				
Spermatid heads (10^7/g testis)	8.91 ± 0.48	8.48 ± 0.24	9.10 ± 0.27	9.01 ± 0.17
Spermatid heads (10^7/testis)	13.31 ± 0.75	12.59 ± 0.35	13.64 ± 0.50	12.98 ± 0.37
Spermatid count (mean/10^{-4} mL suspension)	66.55 ± 3.75	62.93 ± 1.73	68.18 ± 2.48	64.90 ± 1.84
Epididymal spermatozoal measurements				
Motility (%)	86.44 ± 0.59	87.19 ± 0.79	77.37 ± 8.67	87.57 ± 0.97
Concentration (10^6/g cauda epididymal tissue)	418 ± 27	595 ± 128	430 ± 43	461 ± 42

[a] Data are presented as mean ± standard error. Differences from the vehicle control group are not significant by Dunnett's test (body and tissue weights) or Dunn's test (spermatid and epididymal spermatozoal measurements).

TABLE H2
Estrous Cycle Characterization for Female Rats in the 3-Month Dermal Study of Diisopropylcarbodiimide[a]

	Vehicle Control	10 mg/kg	20 mg/kg	40 mg/kg
n	10	10	10	10
Necropsy body wt (g)	193 ± 3	193 ± 4	191 ± 3	180 ± 3**
Estrous cycle length (days)	5.06 ± 0.06[b]	4.94 ± 0.06[c]	5.00 ± 0.00[b]	5.00 ± 0.00[b]
Estrous stages (% of cycle)				
Diestrus	46.7	53.3	54.2	55.8
Proestrus	17.5	15.8	18.3	13.3
Estrus	20.0	20.0	16.7	18.3
Metestrus	15.8	10.0	10.8	11.7
Uncertain diagnoses	0.0	0.8	0.0	0.8

** Significantly different ($P \leq 0.01$) from the vehicle control group by Williams' test
[a] Necropsy body weight and estrous cycle length data are presented as mean ± standard error. Differences from the vehicle control group for estrous cycle length are not significant by Dunn's test. By multivariate analysis of variance, dosed females do not differ significantly from the vehicle control females in the relative length of time spent in the estrous stages.
[b] Estrous cycle was longer than 12 days or unclear in 1 of 10 animals.
[c] Estrous cycle was longer than 12 days or unclear in 2 of 10 animals.

TABLE H3
Summary of Reproductive Tissue Evaluations for Male Mice in the 3-Month Dermal Study of Diisopropylcarbodiimide[a]

	Vehicle Control	17.5 mg/kg	35 mg/kg	70 mg/kg
n	10	10	10	10
Weights (g)				
Necropsy body wt	33.6 ± 1.0	32.5 ± 0.6	32.7 ± 0.7	31.8 ± 0.6
L. Cauda epididymis	0.0170 ± 0.0008	0.0174 ± 0.0006	0.0175 ± 0.0007	0.0176 ± 0.0004
L. Epididymis	0.0494 ± 0.0011	0.0530 ± 0.0015	0.0493 ± 0.0013	0.0476 ± 0.0016
L. Testis	0.1219 ± 0.0087	0.1144 ± 0.0029	0.1110 ± 0.0024	0.1164 ± 0.0024
Spermatid measurements				
Spermatid heads (10^7/g testis)	16.80 ± 0.85	15.67 ± 0.34	17.51 ± 0.63	16.86 ± 0.43
Spermatid heads (10^7/testis)	1.99 ± 0.06	1.79 ± 0.04*	1.94 ± 0.06	1.96 ± 0.04
Spermatid count (mean/10^{-4} mL suspension)	62.23 ± 1.93	55.88 ± 1.27*	60.55 ± 2.01	61.13 ± 1.31
Epididymal spermatozoal measurements				
Motility (%)	79.91 ± 1.86	66.73 ± 11.16	83.83 ± 1.44	81.53 ± 1.44
Concentration (10^6/g cauda epididymal tissue)	872 ± 162	729 ± 86	807 ± 85	729 ± 91

* Significantly different ($P \leq 0.05$) from the vehicle control group by Dunn's test
[a] Data are presented as mean ± standard error. Differences from the vehicle control group are not significant by Dunnett's test (body and tissue weights) or Dunn's test (spermatid heads/g testis and epididymal spermatozoal measurements).

TABLE H4
Estrous Cycle Characterization for Female Mice in the 3-Month Dermal Study of Diisopropylcarbodiimide[a]

	Vehicle Control	17.5 mg/kg	35 mg/kg	70 mg/kg
n	10	10	10	10
Necropsy body wt (g)	28.1 ± 0.6	28.3 ± 0.7	27.9 ± 0.7	28.7 ± 0.8
Estrous cycle length (days)	4.15 ± 0.08	4.28 ± 0.15[b]	4.45 ± 0.19	4.80 ± 0.39
Estrous stages (% of cycle)				
Diestrus	25.8	29.2	24.2	28.3
Proestrus	24.2	17.5	28.3	25.8
Estrus	27.5	30.0	25.0	23.3
Metestrus	22.5	22.5	22.5	22.5
Uncertain diagnoses	0.0	0.8	0.0	0.0

[a] Necropsy body weight and estrous cycle length data are presented as mean ± standard error. Differences from the vehicle control group are not significant by Dunnett's test (body weight) or Dunn's test (estrous cycle length). By multivariate analysis of variance, dosed females do not differ significantly from the vehicle control females in the relative length of time spent in the estrous stages.
[b] Estrous cycle was longer than 12 days or unclear in 1 of 10 animals.

APPENDIX I
CHEMICAL CHARACTERIZATION AND DOSE FORMULATION STUDIES

CHEMICAL CHARACTERIZATION AND DOSE FORMULATION STUDIES

PROCUREMENT AND CHARACTERIZATION

Diisopropylcarbodiimide

Diisopropylcarbodiimide was obtained from Aldrich Chemical Company (Milwaukee, WI) in three lots. Lot 01207BG was used during the 2-week and 3-month studies; lot 13016JS was used during the 2-year studies. One additional lot (09330DR) was used solely for dose formulation stability studies and was not used in the animal studies. Identity and purity analyses were conducted by the analytical chemistry laboratory at Midwest Research Institute (Kansas City, MO) and by the study laboratories at Microbiological Associates, Inc. (Bethesda, MD; 2-week and 3-month studies), and Southern Research Institute (Birmingham, AL; 2-year studies); physical properties, moisture content, and stability of the bulk diisopropylcarbodiimide were determined by the analytical chemistry laboratory. Reports on analyses performed in support of the diisopropylcarbodiimide studies are on file at the National Institute of Environmental Health Sciences.

Lot 01207BG, a colorless liquid, was identified as diisopropylcarbodiimide by the study laboratory using infrared (IR) spectroscopy. Lot 13016JS was identified as diisopropylcarbodiimide by the study laboratory using IR and proton nuclear magnetic resonance (NMR) spectroscopy and by the analytical chemistry laboratory using IR, proton NMR, and ultraviolet/visible spectroscopy and gas chromatography (GC)/mass spectrometry by system A (Table I1). All spectra were consistent with the structure of diisopropylcarbodiimide and with literature references (*Aldrich* 1981, 1985, 1993. Representative IR and proton NMR spectra are presented in Figures I1 and I2).

The purity of lot 01207BG was determined by the study laboratory using GC system B. The purity of lot 13016JS was determined by the study laboratory using GC system C and by the analytical chemistry laboratory using thin layer chromatography (TLC) and GC system D. The moisture content of lot 13016JS was determined by the analytical chemistry laboratory using Karl Fischer titration; the boiling point and relative density of this lot were also measured by the analytical chemistry laboratory.

For lot 01207BG, GC by system B indicated a major peak and five impurity peaks with areas ranging from 0.05% to 0.27% of the total peak area. Fourteen minor impurities were present in the sample chromatograms. The overall purity of lot 01207BG was determined to be 99.35%.

For lot 13016JS, the boiling point (147.2° C) and relative density (0.813 at 25° C) were consistent with the literature values for diisopropylcarbodiimide (*Aldrich*, 1985). Karl Fischer titration indicated 0.06% water in the bulk chemical. TLC detected a major, a minor, and two trace spots. GC by system C indicated a relative purity of 102% when compared to a frozen reference sample from the analytical chemistry laboratory and a mean purity of 99.6% when calculated on an area percent. GC by system D indicated a major peak and five impurity peaks with a combined area of approximately 0.5% of the total peak area; the purity of the test article was determined to be approximately 99.5%. The overall purity of lot 13016JS was determined to be greater than 99%.

The analytical chemistry laboratory conducted accelerated stability studies of lot 13016JS with samples stored for 2 weeks in amber vials with Teflon®-lined septa at approximately 5°, 25°, and 60° C compared to frozen samples from the same lot stored at –20° C. Analysis using GC system E indicated that the test article was stable when protected from light at temperatures up to approximately 60° C for at least 2 weeks. To ensure stability, the bulk chemical was stored at room temperature under nitrogen, protected from light as recommended by the manufacturer. Stability was monitored by the study laboratories during the 3-month and 2-year studies using GC systems B and C, respectively; no degradation of the bulk chemical was detected.

Anhydrous Ethanol

Anhydrous ethanol was obtained in two lots (09115LU and 09309PI) from Aldrich Chemical Company for use during the 2-year studies. Identity and purity analyses of both lots were conducted by the study laboratory. The chemical, a clear liquid, was identified as ethanol using IR spectroscopy; the sample spectra were a good match for the reference spectrum of ethanol (*Aldrich,* 1985). The purity of each lot was determined using GC by system F. No impurities were detected that exceeded a relative concentration of 0.1% in either lot.

To ensure stability, the bulk chemical was stored at room temperature. Purity reanalyses were performed by the study laboratory at approximately 6-month intervals during the 2-year study; no degradation of the ethanol was detected.

Preparation and Analysis of Dose Formulations

Except for the 242 mg (rats) and 81 mg (mice) dose formulations, which were used neat in the 2-week studies, the dose formulations were prepared by mixing diisopropylcarbodiimide and anhydrous ethanol to give the required concentrations; formulations were prepared once for the 2-week studies and weekly, biweekly, or monthly for the 3-month and 2-year studies (Table I2). The dose formulations were stored at room temperature (2-week and 3-month studies) or refrigerated (2-year studies) for up to 28 days.

Because the dose formulations were the neat test article or true solutions of the test article in ethanol, homogeneity studies were not performed. A stability study of a 10 mg/mL dose formulation of lot 01207BG was conducted by the study laboratory using GC by system G; stability was confirmed for at least 28 days for the dose formulation stored at ambient temperature in sealed containers. In a subsequent 35-day dose formulation stability study of lot 09330DR (not used in the animal studies), the analytical chemistry laboratory utilized GC by system H to determine that a 2 mg/mL dose formulation was stable for at least 21 days when stored refrigerated in sealed glass containers and for up to 3 hours when exposed to light at ambient temperature. The study laboratory conducted a stability study of 5.0 and 20.0 mg/mL dose formulations of lot 13016JS and determined that the formulations were stable for at least 35 days when stored refrigerated in sealed glass containers.

Periodic analyses of the dose formulations of diisopropylcarbodiimide were conducted by the study laboratories using GC by systems G (2-week and 3-month studies) and C (2-year studies). During the 2-week studies, the dose formulations were analyzed once; all five dose formulations for rats and mice were within 10% of the target concentrations (Table I3). Animal room samples of these dose formulations were also analyzed; all five of the animal room samples for rats and mice were within 10% of the target concentrations. Dose formulations were analyzed at the beginning, midpoint, and end of the 3-month studies; animal room samples of these dose formulations were also analyzed (Table I4). Of the dose formulations analyzed, all 14 for rats and 13 for mice were within 10% of the target concentrations; all 12 and 13 of the animal room samples for rats and mice, respectively, were within 10% of the target concentrations. During the 2-year studies, the dose formulations were generally analyzed every 8 to 12 weeks; animal room samples of these dose formulations were also analyzed (Table I5). All 33 of the dose formulations analyzed and used for rats and mice were within 10% of the target concentrations. Of the animal room samples analyzed, 11 of 12 for rats and 10 of 12 for mice were within 10% of the target concentrations.

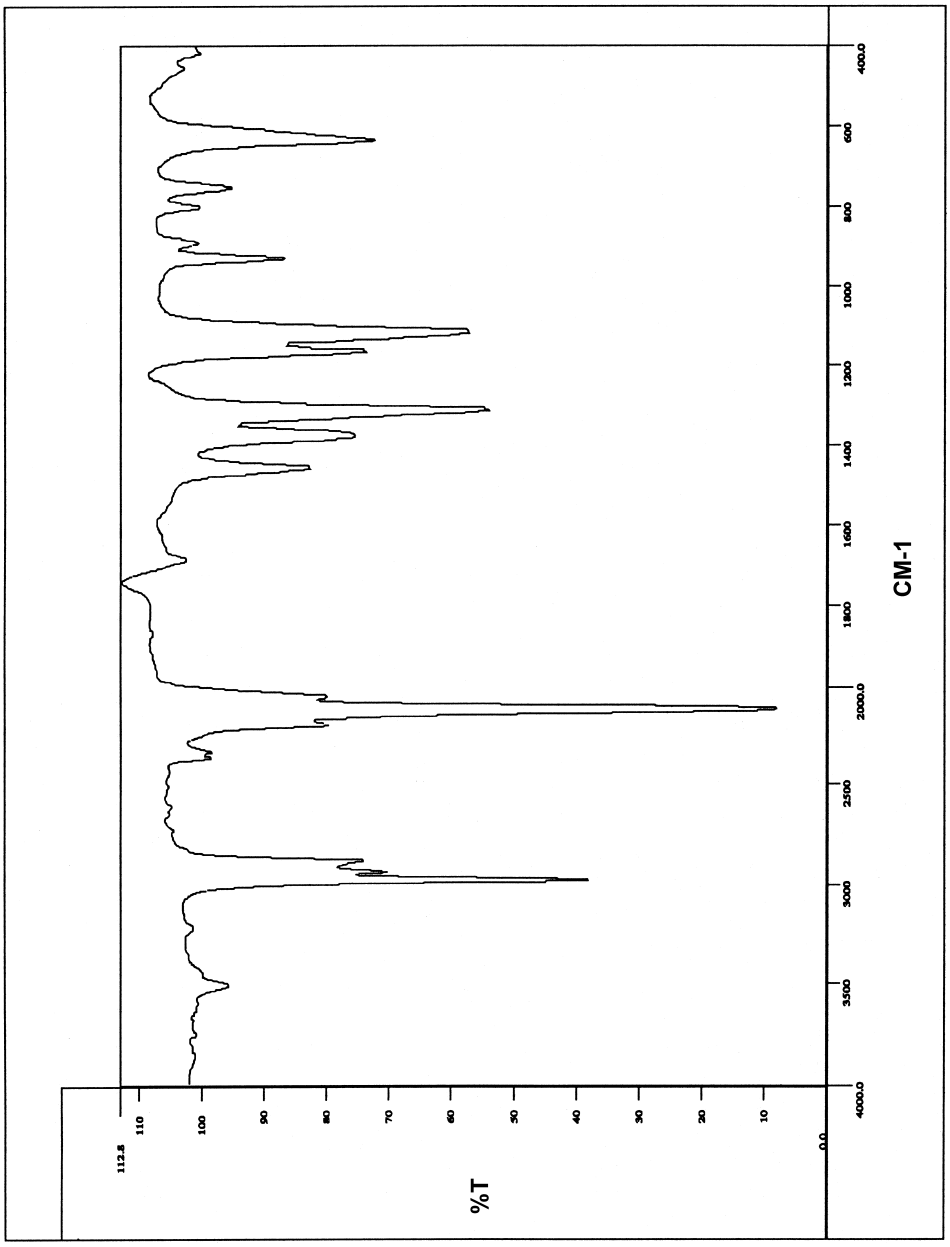


FIGURE I1
Infrared Absorption Spectrum of Diisopropylcarbodiimide

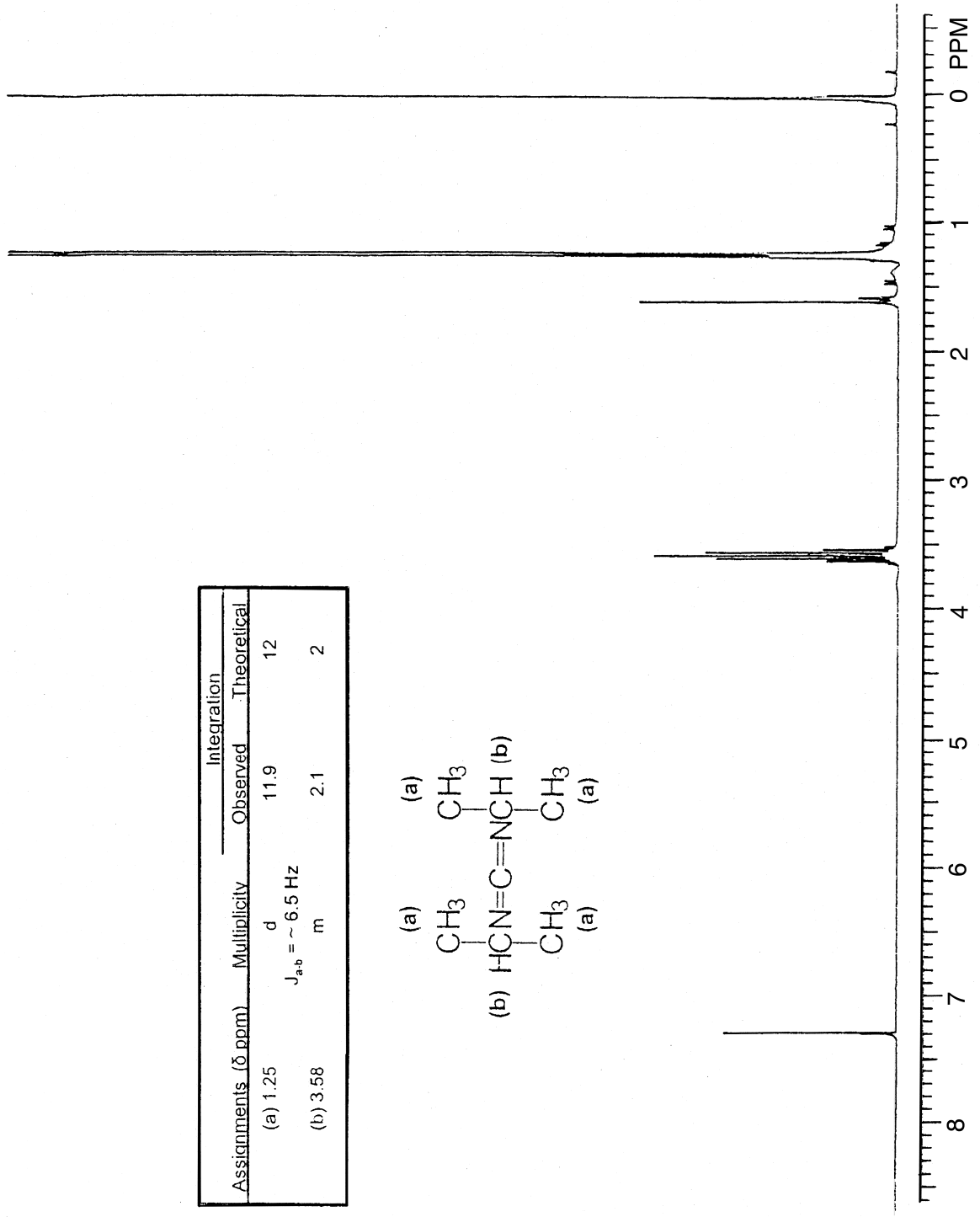


FIGURE I2
Proton Nuclear Magnetic Resonance Spectrum of Diisopropylcarbodiimide

TABLE I1
Gas Chromatography Systems Used in the Dermal Studies of Diisopropylcarbodiimide[a]

Detection System	Column	Carrier Gas	Oven Temperature Program
System A			
Mass spectrometer	DB-5, 30 m × 0.25 mm, 0.25 µm (J&W Scientific, Folsom, CA)	Helium 40 cm^3/second	50° C, held for 5 minutes, then 10° C/minute to 250° C, held for 3 minutes
System B			
Flame ionization	HP-1, 5 m × 0.53 mm, (Hewlett-Packard, Palo Alto, CA)	Helium	35° C, then 10° C/minute to 185° C, held for 5 minutes
System C			
Flame ionization	DB-5, 30 m × 0.53 mm, 1.5 µm (J&W Scientific)	Helium at 8 mL/minute	50° C, then 10° C/minute to 250° C
System D			
Flame ionization	Rtx-5, 30 m × 0.53 mm, 1.0 µm (Restek, Bellefonte, PA)	Helium at 10 mL/minute	50° C, held for 5 minutes, then 10° C/minute to 250° C, held for 3 minutes
System E			
Flame ionization	Rtx-5, 30 m × 0.53 mm, 1.0 µm (Restek)	Helium at 10 mL/minute	70° C isothermal
System F			
Flame ionization	SPB-1, 30 m × 0.53 mm, 1.0 µm (Supelco, Inc., Bellefonte, PA)	Helium at 8 mL/minute	40° C, held for 4 minutes, then 10° C/minute to 220° C
System G			
Flame ionization	J&W DB-1, 30 m × 0.53 mm, 3 µm (J&W Scientific)	Nitrogen at 17.5 mL/minute	115° C isothermal
System H			
Flame ionization	DB-5, 30 m × 0.53 mm, 1.5 µm (J&W Scientific)	Helium at 10 mL/minute	50° C, held for 6 minutes, then 15° C/minute to 250° C, held for 3 minutes

[a] Gas chromatographs manufactured by Thermo Electron Corp. (Finnigan), San Jose, CA (A), Hewlett-Packard, Palo Alto, CA (B, C, F, G), Varian, Palo Alto, CA (systems D, E, H); mass spectrometer was manufactured by Finnigan.

TABLE I2
Preparation and Storage of Dose Formulations in the Dermal Studies of Diisopropylcarbodiimide

2-Week Studies	3-Month Studies	2-Year Studies
Preparation		
The highest dose of diisopropylcarbodiimide was administered as the neat liquid. The next highest dose concentration was prepared by diluting a weighed amount of the test chemical in anhydrous ethanol; aliquots of this solution were diluted with additional anhydrous ethanol to obtain formulations of the three lower concentrations. Dose formulations were prepared once.	The most concentrated dose formulation for each species was prepared by diluting a weighed amount of the test chemical in anhydrous ethanol; aliquots of these solutions were diluted with additional anhydrous ethanol to obtain formulations of the four lower concentrations. Dose formulations for the rat study were prepared weekly for 4 weeks and at 2-week intervals thereafter; for the mouse study, dose formulations were prepared at 2-week intervals throughout.	A weighed amount of the test chemical was diluted with anhydrous ethanol to obtain each desired concentration for the dose formulations. Dose formulations were prepared biweekly until June 26, 2000, and monthly thereafter.
Chemical Lot Number		
01207BG	01207BG	13016JS
Maximum Storage Time		
28 days	28 days	28 days
Storage Conditions		
Stored at room temperature	Stored at room temperature	Refrigerated at approximately 5° C
Study Laboratory		
Microbiological Associates, Inc. (Bethesda, MD)	Microbiological Associates, Inc. (Bethesda, MD)	Southern Research Institute (Birmingham, AL)

TABLE I3
Results of Analyses of Dose Formulations Administered to Rats and Mice in the 2-Week Dermal Studies of Diisopropylcarbodiimide

Date Prepared	Date Analyzed	Target Concentration (mg/mL)	Determined Concentration[a] (mg/mL)	Difference from Target (%)
May 31, 1994	June 1, 1994	10	10.2	+2
		30	29.2	–3
		90	86.1	–4
		269	256	–5
		806	764	–5
	June 27, 1994[b]	10	9.95	–1
		30	29.3	–2
		90	88.9	–1
		269	248	–8
		806	800	–1
	June 27, 1994[c]	10	10.2	+2
		30	29.1	–3
		90	89.7	0
		269	266	–1
		806	794	–1

[a] Results of duplicate analyses. For rats, dosing volume was 0.3 mL/animal: 10 mg/mL=3 mg/animal; 30 mg/mL=9 mg/animal; 90 mg/mL=27 mg/animal; 269=81 mg/animal; 806 mg/mL=242 mg/animal (the neat test article was used as this dose formulation); for mice, dosing volume was 0.1 mg/animal: 10 mg/mL=1 mg/animal; 30 mg/mL=3 mg/animal; 90 mg/mL=9 mg/animal; 269 mg/mL=27 mg/animal; 806 mg/mL=81 mg/animal (the neat test article was used as this dose formulation).
[b] Animal room samples for rats
[c] Animal room samples for mice

TABLE I4
Results of Analyses of Dose Formulations Administered to Rats and Mice in the 3-Month Dermal Studies of Diisopropylcarbodiimide

Date Prepared	Date Analyzed	Target Concentration (mg/mL)	Determined Concentration[a] (mg/mL)	Difference from Target (%)
Rats				
August 31, 1994	August 31, 1994	20	19.3	–4
		40	37.1	–7
		80	76.9	–4
		160	153	–4
		320	313	–2
	September 21, 1994[b]	20	19.9	–1
		40	38.2	–5
		80	76.4	–5
		160	151	–6
		320	308	–4
October 5, 1994	October 5, 1994	20	19.2	–4
		40	38.6	–4
		80	78.1	–2
		160	156	–3
		320	315	–2
	October 26, 1994[b]	20	19.5	–3
		40	38.8	–3
		80	78.0	–3
		160	148	–8
November 16, 1994	November 16,1994	20	21.0	+5
		40	40.2	+1
		80	79.1	–1
		160	159	–1
	December 12, 1994[b]	20	21.3	+7
		40	40.1	0
		80	78.1	–2
Mice				
August 31, 1994	August 31, 1994	8.75	8.99	+3
		17.5	18.0	+3
		35	33.7	–4
		70	68.0	–3
		140	139	–1
	September 21, 1994[b]	8.75	9.65	+10
		17.5	18.8	+7
		35	34.8	–1
		70	68.6	–2
		140	135	–4

TABLE I4
Results of Analyses of Dose Formulations Administered to Rats and Mice in the 3-Month Dermal Studies of Diisopropylcarbodiimide

Date Prepared	Date Analyzed	Target Concentration (mg/mL)	Determined Concentration (mg/mL)	Difference from Target (%)
Mice (continued)				
October 12, 1994	October 13, 1994	8.75	9.38	+7
		17.5	17.8	+2
		35	35.0	0
		70	69.4	–1
	November 2, 1994[b]	8.75	9.00	+3
		17.5	17.7	+1
		35	34.3	–2
		70	67.4	–4
November 28, 1994	November 28, 1994	8.75	8.81	+1
		17.5	16.9	–3
		35	34.7	–1
		70	69.9	0
	December 12, 1994[b]	8.75	9.09	+4
		17.5	17.5	0
		35	35.4	+1
		70	68.8	–2

[a] Results of duplicate analyses. For rats, dosing volume=0.5 mL/kg; 20 mg/mL=10 mg/kg, 40 mg/mL=20 mg/kg, 80 mg/mL=40 mg/kg, 160 mg/mL=80 mg/kg, 320 mg/mL=160 mg/kg. For mice, dosing volume=2 mL/kg; 8.75 mg/mL=17.5 mg/kg, 17.5 mg/mL=35 mg/kg, 35 mg/mL=70 mg/kg, 70 mg/mL=140 mg/kg, 140 mg/mL=280 mg/kg

[b] Animal room samples

TABLE I5
Results of Analyses of Dose Formulations Administered to Rats and Mice in the 2-Year Dermal Studies of Diisopropylcarbodiimide

Date Prepared	Date Analyzed	Target Concentration (mg/mL)	Determined Concentration[a] (mg/mL)	Difference from Target (%)
Rats				
April 17, 2000	April 18, 2000	20	20.0	0
		40	40.1	0
		80	80.3	0
	May 10-11, 2000[b]	20	20.5	+3
		40	41.7	+4
		80	84.8	+6
May 1, 2000	May 2-3, 2000	20	19.7	–2
		40	39.7	–1
		80	80.3	0
June 26, 2000	June 29-30, 2000	20	20.2	+1
		40	40.1	0
		80	80.9	+1
September 18, 2000	September 19-20, 2000	20	20.1	+1
		40	41.1	+3
		80	80.6	+1
December 11, 2000	December 12-13, 2000	20	20.3	+2
		40	40.9	+2
		80	81.6	+2
	January 16-17, 2001[b]	20	21.4	+7
		40	42.1	+5
		80	85.1	+6
March 5, 2001	March 6-7, 2001	20	18.7	–7
		40	39.0	–3
		80	77.7	–3
April 30, 2001	May 1-2, 2001	20	20.1	+1
		40	40.0	0
		80	79.9	0
July 23, 2001	July 24-25, 2001	20	20.0	0
		40	40.0	0
		80	80.0	0
	August 27-28, 2001[b]	20	21.1	+6
		40	42.6	+7
		80	100.0	+25
September 17, 2001	September 18-19, 2001	20	19.8	–1
		40	40.5	+1
		80	78.5	–2
December 10, 2001	December 11-12, 2001	20	21.2	+6
		40	42.3	+6
		80	86.5	+8

TABLE I5
Results of Analyses of Dose Formulations Administered to Rats and Mice in the 2-Year Dermal Studies of Diisopropylcarbodiimide

Date Prepared	Date Analyzed	Target Concentration (mg/mL)	Determined Concentration (mg/mL)	Difference from Target (%)
Rats (continued)				
February 6, 2002	February 6-7, 2002	20	19.9	–1
		40	39.0	–3
		80	79.4	–1
	March 11-12, 2002[b]	20	19.1	–5
		40	38.8	–3
		80	74.4	–7
Mice				
May 1, 2000	May 2-3, 2000	5	5.26	+5
		10	9.69	–3
		20	19.8	–1
	May 25, 2000[b]	5	5.74	+15
		10	10.8	+8
		20	21.9	+10
June 26, 2000	June 29-30, 2000	5	5.10	+2
		10	10.1	+1
		20	20.1	+1
September 18, 2000	September 19-20, 2000	5	5.03	+1
		10	10.1	+1
		20	20.4	+2
December 11, 2000	December 12-13, 2000	5	4.99	0
		10	10.1	+1
		20	20.2	+1
	January 16-17, 2001[b]	5	5.36	+7
		10	10.7	+7
		20	21.3	+7
March 5, 2001	March 6-7, 2001	5	4.74	–5
		10	9.69	–3
		20	19.4	–3
April 30, 2001	May 1-2, 2001	5	4.99	0
		10	10.0	0
		20	20.2	+1
July 23, 2001	July 24-25, 2001	5	4.97	–1
		10	10.0	0
		20	19.9	–1
	August 27-28, 2001[b]	5	5.43	+9
		10	11.0	+10
		20	22.1	+11

TABLE I5
Results of Analyses of Dose Formulations Administered to Rats and Mice in the 2-Year Dermal Studies of Diisopropylcarbodiimide

Date Prepared	Date Analyzed	Target Concentration (mg/mL)	Determined Concentration (mg/mL)	Difference from Target (%)
Mice (continued)				
September 17, 2001	September 18-19, 2001	5	5.85[c]	+17
		10	9.81	–2
		20	19.9	–1
September 19, 2001	September 19, 2001	5	4.96	–1
December 10, 2001	December 11-12, 2001	5	0.976[c]	–80
		10	4.83[c]	–52
		20	18.3[c]	–9
December 13, 2001	December 13, 2001	5	5.37	+7
		10	10.8	+8
		20	21.7	+9
February 6, 2002	February 6-7, 2002	5	4.95[d]	–1
		10	9.96[d]	0
		20	19.6[d]	–2
	March 11-12, 2002[b]	5	5.14	+3
		10	10.6	+6
		20	20.2	+1
April 29, 2002	April 30-May 1, 2002	5	4.90	–2
		10	9.89	–1
		20	20.0	0

[a] Results of duplicate analyses. For rats, dosing volume=0.5 mL/kg; 20 mg/mL=10 mg/kg, 40 mg/mL=20 mg/kg, 80 mg/mL=40 mg/kg. For mice, dosing volume=2 mL/kg; 5 mg/mL=10 mg/kg, 10 mg/mL=20 mg/kg, 20 mg/mL=40 mg/kg
[b] Animal room samples
[c] Remixed; not used in study
[d] Results of remix

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

TABLE J1
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 J2
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 J3
Nutrient Composition of NTP-2000 Rat and Mouse Ration

Nutrient	Mean ± Standard Deviation	Range	Number of Samples
Protein (% by weight)	14.1 ± 0.65	13.2 – 15.7	24
Crude fat (% by weight)	8.1 ± 0.30	7.6 – 8.6	24
Crude fiber (% by weight)	9.1 ± 0.56	8.0 – 10.5	24
Ash (% by weight)	5.2 ± 0.27	4.8 – 5.8	24
Amino Acids (% of total diet)			
Arginine	0.748 ± 0.053	0.670 – 0.850	12
Cystine	0.223 ± 0.027	0.150 – 0.250	12
Glycine	0.702 ± 0.043	0.620 – 0.750	12
Histidine	0.343 ± 0.023	0.310 – 0.390	12
Isoleucine	0.534 ± 0.041	0.430 – 0.590	12
Leucine	1.078 ± 0.059	0.960 – 1.140	12
Lysine	0.729 ± 0.065	0.620 – 0.830	12
Methionine	0.396 ± 0.053	0.260 – 0.460	12
Phenylalanine	0.611 ± 0.038	0.540 – 0.660	12
Threonine	0.492 ± 0.045	0.430 – 0.590	12
Tryptophan	0.129 ± 0.016	0.110 – 0.160	12
Tyrosine	0.378 ± 0.054	0.280 – 0.460	12
Valine	0.658 ± 0.049	0.550 – 0.710	12
Essential Fatty Acids (% of total diet)			
Linoleic	3.89 ± 0.278	3.49 – 4.54	12
Linolenic	0.30 ± 0.038	0.21 – 0.35	12
Vitamins			
Vitamin A (IU/kg)	4,629 ± 767	3,060 – 6,090	24
Vitamin D (IU/kg)	1,000[a]		
α-Tocopherol (ppm)	84.3 ± 17.06	52.0 – 110.0	12
Thiamine (ppm)[b]	7.0 ± 0.79	6.0 – 8.7	25
Riboflavin (ppm)	6.4 ± 2.11	4.20 – 11.20	12
Niacin (ppm)	78.6 ± 10.86	66.4 – 98.2	12
Pantothenic acid (ppm)	23.1 ± 3.61	17.4 – 29.1	12
Pyridoxine (ppm)[b]	8.88 ± 2.05	6.4 – 12.4	12
Folic acid (ppm)	1.84 ± 0.56	1.26 – 3.27	12
Biotin (ppm)	0.337 ± 0.13	0.225 – 0.704	12
Vitamin B_{12} (ppb)	64.8 ± 50.9	18.3 – 174.0	12
Choline (ppm)[b]	3,094 ± 292	2,700 – 3,790	12
Minerals			
Calcium (%)	1.041 ± 0.045	0.964 – 1.140	24
Phosphorus (%)	0.605 ± 0.036	0.552 – 0.701	24
Potassium (%)	0.668 ± 0.023	0.627 – 0.694	12
Chloride (%)	0.368 ± 0.033	0.300 – 0.423	12
Sodium (%)	0.189 ± 0.016	0.160 – 0.212	12
Magnesium (%)	0.200 ± 0.009	0.185 – 0.217	12
Sulfur (%)	0.176 ± 0.026	0.116 – 0.209	12
Iron (ppm)	177 ± 46.2	135 – 311	12
Manganese (ppm)	53.4 ± 6.42	42.1 – 63.1	12
Zinc (ppm)	52.5 ± 6.95	43.3 – 66.0	12
Copper (ppm)	6.64 ± 1.283	5.08 – 9.92	12
Iodine (ppm)	0.535 ± 0.242	0.233 – 0.972	12
Chromium (ppm)	0.545 ± 0.125	0.330 – 0.751	12
Cobalt (ppm)	0.23 ± 0.041	0.20 – 0.30	12

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

TABLE J4
Contaminant Levels in NTP-2000 Rat and Mouse Ration[a]

	Mean ± Standard Deviation[b]	Range	Number of Samples
Contaminants			
Arsenic (ppm)	0.21 ± 0.022	0.16 – 0.25	24
Cadmium (ppm)	0.04 ± 0.005	0.04 – 0.06	24
Lead (ppm)	0.09 ± 0.097	0.05 – 0.54	24
Mercury (ppm)	<0.02		24
Selenium (ppm)	0.23 ± 0.055	0.14 – 0.36	24
Aflatoxins (ppb)	<5.00		24
Nitrate nitrogen (ppm)[c]	12.0 ± 3.55	6.85 – 21.1	24
Nitrite nitrogen (ppm)[c]	<0.61		24
BHA (ppm)[d]	<1.0		24
BHT (ppm)[d]	<1.0		24
Aerobic plate count (CFU/g)	14 ± 13	10 – 70	24
Coliform (MPN/g)	2.9 ± 1.2	0.0 – 3.6	24
Escherichia coli (MPN/g)	<10		24
Salmonella (MPN/g)	Negative		24
Total nitrosoamines (ppb)[e]	4.7 ± 1.14	3.1 – 7.5	24
N-Nitrosodimethylamine (ppb)[e]	2.2 ± 0.54	1.2 – 3.2	24
N-Nitrosopyrrolidine (ppb)[e]	2.4 ± 1.18	1.0 – 5.1	24
Pesticides (ppm)			
α-BHC	<0.01		24
β-BHC	<0.02		24
γ-BHC	<0.01		24
δ-BHC	<0.01		24
Heptachlor	<0.01		24
Aldrin	<0.01		24
Heptachlor epoxide	<0.01		24
DDE	<0.01		24
DDD	<0.01		24
DDT	<0.01		24
HCB	<0.01		24
Mirex	<0.01		24
Methoxychlor	<0.05		24
Dieldrin	<0.01		24
Endrin	<0.01		24
Telodrin	<0.01		24
Chlordane	<0.05		24
Toxaphene	<0.10		24
Estimated PCBs	<0.20		24
Ronnel	<0.01		24
Ethion	<0.02		24
Trithion	<0.05		24
Diazinon	<0.10		24
Methyl chlorpyrifos	0.149 ± 0.094	0.020 – 0.418	24
Methyl parathion	<0.02		24
Ethyl parathion	<0.02		24
Malathion	0.173 ± 0.136	0.020 – 0.557	24
Endosulfan I	<0.01		24
Endosulfan II	<0.01		24
Endosulfan sulfate	<0.03		24

[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 K
SENTINEL ANIMAL

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 five male and five female control rats and five male and five female sentinel mice at the end of the 3-month study. For the 2-year studies, serum samples were collected from five male and five female sentinel rats and mice at 6, 12, and 18 months and five 40 mg/kg males and females at study termination. Blood from each animal was collected and allowed to clot, and the serum was separated. The samples were processed appropriately and sent to Microbiological Associates, Inc. (Rockville, MD), or BioReliance Corp. (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	
PVM (pneumonia virus of mice)	Study termination
RCV/SDA	
(rat coronavirus/sialodacryoadenitis virus)	Study termination
Sendai	Study termination
Immunofluorescence Assay	
Sendai	Study termination
Hemagglutination Inhibition	
H-1 (Toolan's H-1 Virus)	Study termination
KRV (Kilham rat virus)	Study termination
2-Year Study	
ELISA	
Mycoplasma arthritidis	Study termination
Mycoplasma pulmonis	Study termination
PVM	6, 12, and 18 months, study termination
RCV/SDA	6, 12, and 18 months, study termination
Sendai	6, 12, and 18 months, study termination
Immunofluorescence Assay	
Parvovirus	6, 12, and 18 months, study termination

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
PVM	Study termination
Reovirus 3	Study termination
Sendai	Study termination
Immunofluorescence Assay	
GDV II	Study termination
Reovirus 3	Study termination
Hemagglutination Inhibition	
K (papovavirus)	Study termination
MVM (minute virus of mice)	Study termination
Polyoma virus	Study termination

2-Year Study

ELISA	
Ectromelia virus	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-FL	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	
EDIM	12 months
GDVII	6 months
LCM	Study termination
Mouse adenoma virus-FL	Study termination
MCMV (mouse cytomegalovirus)	Study termination
Parvovirus	6, 12, and 18 months, study termination

RESULTS

All serology tests were negative.

APPENDIX L
ABSORPTION, DISTRIBUTION, METABOLISM, AND EXCRETION

ABSORPTION, DISTRIBUTION, METABOLISM, AND EXCRETION

INTRODUCTION

Because toxicity testing has shown diisopropylcarbodiimide to be very toxic (Microbiological Associates, 1995), the objectives of these studies were to determine the absorption and rates and routes of excretion of radiolabeled compounds following dermal exposure to [^{14}C]-diisopropylcarbodiimide and to determine the rates and routes of excretion of radiolabeled compounds and the time course of radioactivity in blood following intravenous injection of [^{14}C]-diisopropylcarbodiimide.

MATERIALS AND METHODS

Young adult male Fischer 344/N rats and B6C3F$_1$ mice were obtained from Charles River Laboratories (Raleigh, NC). Animals were quarantined for at least 1 week prior to being used in a study. Animals used for excreta collection were acclimated to metabolism chambers 1 day prior to dosing. Animals were fed certified Purina Rodent Chow (#5002; Ralston Purina Co., St. Louis, MO) and furnished tap water *ad libitum*. Prior to study initiation, animals were housed in polycarbonate cages. Contact bedding was Sani-Chips® (P.J. Murphy Forest Products Corp., Montville, NJ). During metabolism studies, animals were housed individually in all-glass, Roth-type metabolism chambers which provided for separate collection of urine and feces. Air circulation was 100% fresh filtered air with 10 to 15 air changes per hour and no interchange of air between rooms. Room temperature was maintained at 64° to 79° F, and relative humidity ranged from 30% to 70%. Light/darkness was cycled at 12-hour intervals. Each dose group contained at least three study animals.

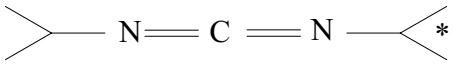
Anesthesia was used to avoid undue pain or distress. Rats were anesthetized with an intramuscular injection of ketamine:xylazine (7:1, approximately 60 mg/kg or to effect). Mice were anesthetized with an intraperitoneal injection of sodium pentobarbital (60 mg/kg or to effect). Anesthetized rats were euthanized by cutting the diaphragm after final blood collection or by CO_2 asphyxiation at the end of the study. Anesthetized mice were euthanized by cervical dislocation, cutting the diaphragm, or CO_2 asphyxiation after final blood collection.

For dermal studies in rats, nonocclusive protective appliances were prepared from charcoal-impregnated filters. A circular template with an inner diameter of approximately 7 cm and an outer diameter of approximately 8 cm was transferred to a charcoal filter. A gathering stitch was sewn at the inner diameter mark with a second row of tighter stitches applied at the outer diameter mark. When drawn together, the inner gathering stitches formed a blister-shaped appliance with a flat edge that was used to glue the appliance onto the rat's back using Duro® Quick Gel®. A ring of Teflon® tubing was used to reinforce the inside top of the appliance, and keep the appliance off the dose application site. A metal protective shield was also placed over the appliance and attached to the animal using Duro® Quick Gel® and an Elastoplast® adhesive bandage.

For dermal studies in mice, the protective appliance was a wire mesh tissue capsule (Shandon-Lipshaw, Philadelphia, PA) covered by a charcoal-impregnated filter (3M® Company, St. Paul, MN). A metal protective shield was also placed over the capsule and attached to the animal using Duro® Quick Gel® and an Elastoplast® adhesive bandage.

Approximately 24 hours prior to dermal dose administration, animals were anesthetized and the fur on their backs was removed with a No. 40 animal clipper (Oster® Professional Products). The clipped area was washed with soapy water, rinsed with water, and dried. The clipped area was examined for nicks or breaks in the skin. Any animals with broken skin in the clipped area were excluded. For rats, a dose site of approximately 12 cm^2 was inscribed within the clipped area using a permanent felt-tip marker. For mice, a dose site of approximately 3 cm^2 was inscribed. A protective appliance, previously described, was attached to the back of each animal.

Nonradiolabeled diisopropylcarbodiimide (purity 99%), lot EN08119EN, was obtained from Aldrich Chemical Company (Milwaukee, WI). The identity of the nonradiolabeled diisopropylcarbodiimide was confirmed by nuclear magnetic resonance spectroscopy (NMR) and gas chromatography/mass spectrometry. Diisopropylcarbodiimide, labeled with ^{14}C in the 2-propyl position (20 mCi/mmol, 10 mCi), was received from Wizard Laboratories, Inc. (West Sacramento, CA), at a stated radiochemical purity of 98.7% (by thin layer chromatography).



* Position of ^{14}C

Structure of [^{14}C]-Diisopropylcarbodiimide

The radiochemical purity of [^{14}C]-diisopropylcarbodiimide was initially estimated at Research Triangle Institute (Research Triangle Park, NC) by high performance liquid chromatography (HPLC). The HPLC system consisted of a Waters model 510 pump (Waters, Inc., Milford, MA), a Rheodyne model 7125 injector, a Supelcogel TPR-100 column (150 × 4.6 mm; Supelco, Inc., Bellefonte, PA), and a ß-Ram radioactivity detector equipped with a 100-µL solid glass scintillator flow cell. The mobile phase was acetonitrile at a flow rate of 0.75 mL/minute (Method 1).

The chromatographic resolution of [^{14}C]-diisopropylcarbodiimide and [^{14}C]-diisopropylurea, a known metabolite of diisopropylcarbodiimide, was achieved with an HPLC system using an Alltech Alltima™ cyano column (250 × 4.6 mm ID, 5 µm, 100 Å; Alltech, Deerfield, IL) and a mobile phase consisting of hexanes:ethanol (95:5, v:v) at a flow rate of 0.75 mL/minute (Method 2). This method was used to determine the radiochemical purity of [^{14}C]-diisopropylcarbodiimide. Unlabeled 1,3-diisopropylurea was prepared from diisopropylcarbodiimide by acid hydrolysis. Approximately 2 mL of diisopropylcarbodiimide was mixed with approximately 20 mL of 0.1 M HCl. A white precipitate formed almost immediately. The mixture was filtered, and the solid diisopropylurea precipitate was rinsed with distilled water. The diisopropylurea was dried and then analyzed by GC/MS and NMR to confirm its identity.

To determine the stability of diisopropylcarbodiimide in whole blood from rats, a solution of [^{14}C]-diisopropylcarbodiimide in propylene glycol was added to 1-mL samples of blood at 37° C. After mixing and incubating for approximately 1, 5, 10, or 30 minutes, 1 mL of hexanes was added to each sample. The samples were vortexed and centrifuged for 12 minutes at approximately 1,500 × g. Weighed aliquots of the hexanes extracts and pellets (after solubilization) were analyzed by liquid scintillation spectrometry and the total radioactivity extracted from blood was calculated. The extracts were then analyzed by HPLC using Method 2.

The concentration of ^{14}C in each dose formulation was determined prior to, during, and after dosing the animals. The radiochemical purity of each dose formulation was determined on the day of dosing by analysis of discrete fractions of HPLC column effluent using liquid scintillation counting (LSC).

The dose administered to each animal was based on its body weight on the day of dosing. Dermal dose formulations for rats and mice contained sufficient quantities of radiolabeled and nonradiolabeled diisopropylcarbodiimide (as appropriate) dissolved in hexanes to deliver doses of 4 to 41 mg/kg (approximately 0.07 to 0.9 mg/cm^2) to rats, and 7 to 82 mg/kg (approximately 0.06 to 0.8 mg/cm^2) to mice.

After use of the dosing apparatus, the needle was wiped with a Kimwipe® and the empty dosing apparatus was reweighed. The needle wipe was analyzed by LSC. The dermal dose per rat or mouse (in µCi) was calculated as the difference in the weight of the syringe/needle dosing apparatus filled (S_B) and empty (S_A) multiplied by the

concentration of ^{14}C in the dosing formulation (A_D) minus the ^{14}C contained in the needle wipe after dosing (NW) as shown:

$$\mu Ci/rat \text{ or mouse} = (S_B - S_A)\, A_D - NW$$

Intravenous dose formulations for mice contained sufficient quantities of radiolabeled and nonradiolabeled diisopropylcarbodiimide (as appropriate) dissolved in propylene glycol to deliver a dose of approximately 8 mg/kg to mice in a dose volume of 1.3 mL/kg. The dose formulation was prepared on the day of dose administration and administered into one of the lateral tail veins. The intravenous dose (in µCi) was calculated using the formula described above for the dermal studies in rats and mice.

In order to determine the efficiency of recovery from the charcoal filter, a solution of [^{14}C]-diisopropylcarbodiimide in hexanes (approximately 25 µL), equivalent to a dermal dose formulation, was applied directly onto three pieces of charcoal-impregnated filter similar in size to the appliance covers used for the dermal experiments in mice. After approximately 20 minutes, each filter was cut into four pieces, oxidized, and analyzed by LSC.

In order to estimate efficiency of collection of [^{14}C]-diisopropylcarbodiimide above the dermal application site, a volatilization experiment was conducted using a charcoal-impregnated filter as the primary trapping medium. A solution of [^{14}C]-diisopropylcarbodiimide in hexanes (approximately 50 µL) was applied to the internal base of a 20-mL glass scintillation vial (Vial A) fitted with a Teflon® septum cap. Vial A was purged continuously with nitrogen through the septum, and the base of the scintillation vial was heated in a dry-bath incubator at approximately 32° C. The outlet tube of Vial A was packed with charcoal-impregnated filter material that led to another scintillation vial (Vial B) also fitted with a Teflon® septum cap. Vial B contained a solution of 0.1 M HCl (approximately 3 mL) and was vented into an exhaust hood. The charcoal-impregnated filter material was oxidized using a Packard Model 306C oxidizer (Perkin Elmer Life Sciences, Inc., Meriden, CT). $^{14}CO_2$ was trapped using Carbo-sorb® and analyzed by LSC using Permafluor® (Perkin Elmer Life Sciences, Inc.) as a scintillant. Samples, including the contents of Vials A and B, were assayed directly for total radioactivity by liquid scintillation counting.

Urine and feces were collected separately into containers cooled with dry ice. Urine was collected in this manner at 8, 24, 48, and 72 hours for the excretion studies. The urine collection containers were rinsed with methanol and then water at 8, 24, and 48 hours. The methanol rinses were analyzed separately. At sacrifice, urine was collected directly from the bladder and added to the 72-hour urine collection. Feces were collected at 24, 48, and 72 hours. Urine and feces collections were stored in the dark at approximately –20° C until analyzed. After the animals were removed from the cages for sacrifice, the cages were rinsed well with water. An additional cage rinse using hexanes was also performed in an effort to recover volatilized radiolabel. All rinses were analyzed for radioactivity.

Radiolabeled volatile organics and $^{14}CO_2$ were collected by passing air through the metabolism chamber (flow=approximately 200 to 550 mL/minute) through two cold traps, each containing approximately 60 mL of ethanol and then through a series of two traps, each containing approximately 500 mL of 1 N NaOH. The first cold trap was maintained at approximately 4° C using a water/ice bath, the second maintained at approximately –60° C using an isopropanol/dry ice bath. For the studies, the traps were analyzed at 0 hours and analyzed and changed at 8, 24, 48, and 72 hours after dosing. The radiolabeled volatile organics were also collected by passing air from the metabolism chamber through a charcoal sorbent tube. The charcoal trap was located between the cryogenic and $^{14}CO_2$ traps and was changed with the other traps at 4, 8, 24, 48, and 72 hours.

A skin wash procedure was performed after 6 hours of dermal exposure to [^{14}C]-diisopropylcarbodiimide. The rats were anesthetized and the metal protective shield was removed and swiped for radioactivity. The charcoal filter was removed from the dose site, cut into approximately 20 to 25 pieces for rats and 10 to 12 pieces for mice,

placed into Combustocones® (Perkin Elmer Life Sciences, Inc.) in scintillation vials, and rapidly oxidized. For all the above-mentioned studies, the dose site, still attached to the animal, was thoroughly washed with gauzes soaked with hexanes, soapy water, and water. The gauzes and oxidized charcoal filters were analyzed by LSC. Afterwards, clean gauze was placed over the dose application site and wrapped with an Elastoplast® adhesive bandage for the duration of the study. At the termination of the dermal study in rats, animals were anesthetized and the Elastoplast® adhesive bandage was removed from the skin and extracted with acetone. The skin gauze was cut into approximately 8 to 10 pieces and divided into separate 20-mL scintillation vials each containing 2 mL of ethanol. The dose site was then removed by blunt dissection, and care was taken not to remove any muscle or adipose from under the skin. The excised skin was placed into a Nalgene® bottle containing approximately 75 mL of 2 N ethanolic NaOH.

At the termination of the 72-hour study, each animal was anesthetized, and its metal appliance shield was removed and stored in a plastic bag. The polyester/cotton fabric cover was removed from the foam appliance and placed into an amber bottle along with the Elastoplast® adhesive bandage and both were stored at approximately –20° C. The charcoal filter was removed from the appliance, cut into ten pieces, placed into Combustocones® in scintillation vials, and stored at approximately –20° C until oxidized. The appliance was then removed and cut into 8 pieces and divided into separate 20-mL scintillation vials each containing approximately 2 mL of ethanol. The dose application site and surrounding skin were carefully excised by blunt dissection. Care was taken not to remove any muscle or adipose from under the skin. The excised skin was attached to a glass and rinsed well with hexanes and the rinse collected. The dose site was then thoroughly washed with gauzes soaked with either hexanes or soapy water and the rinses were separately collected. The washed skin was placed into a Nalgene bottle containing approximately 75 mL of 2 N ethanolic NaOH. The rinses, dose application site wash gauzes, and the appliance pieces were analyzed by LSC.

Blood collections (approximately 300 µL) were taken in some studies at 0, 0.02, 0.07, 0.13, 0.33, 1, 2, 8, 24, and 48 hours postdosing. Blood samples were collected into heparinized, disposable 1-mL glass syringes (GlasPak™, Becton Dickinson & Co, Franklin Lakes, NJ). For tissue distribution studies, kidney, liver, lung, spleen, heart, testes, bladder, brain, and samples of adipose, muscle, and skin were excised from the animals and assayed for radioactivity. Carcasses were digested in 2 N ethanolic NaOH (500 mL for rats and approximately 75 mL for mice).

All samples collected during the studies were assayed for total radioactivity either directly (after dissolution in scintillation cocktail) or following digestion in an organic tissue solubilizer or 2 N ethanolic NaOH. Darkened samples were neutralized and bleached (using organic perchloric acid/hydrogen peroxide) prior to LSC. After addition of the scintillation cocktail, samples containing bases were allowed to sit in the dark for approximately 6 hours to minimize nonspecific chemiluminescence before being assayed. All samples were assayed for ^{14}C in a Packard liquid scintillation counter (Perkin Elmer Life Sciences, Inc.). The scintillation spectrometer was checked monthly for counting efficiency and was calibrated for quench correction using the external standard method. Approximately 12 mL of scintillation cocktail were added to duplicate aliquots of urine (approximately 0.1 to 0.6 g), methanol rinse (approximately 0.1 to 0.6 g), cage rinse (approximately 0.4 to 2.0 g) and hexanes cage rinse (approximately 0.5 to 1.0 g). Approximately 12 mL of scintillation cocktail were added to scintillation vials containing the samples of skin wash gauze and skin gauze cover. The samples were analyzed directly for total radioactivity. Duplicate aliquots (approximately 0.1 g) of the skin wash and hexanes skin rinse were also analyzed for radioactivity. Approximately 12 mL of scintillation cocktail was added to scintillation vials containing the rinse aliquots.

Duplicate aliquots (0.5 to 2.0 g) of the breath trap contents were weighed into scintillation vials containing approximately 12 mL of scintillation cocktail and samples were assayed for total radioactivity. Duplicate aliquots of the charcoal tube contents were oxidized and assayed for total radioactivity. Feces were homogenized with an approximately equal mass of water. The weight of the feces homogenate was determined, and weighed aliquots (0.05 to 0.2 g) were solubilized in 2 mL of Soluene®-350 (Perkin Elmer Life Sciences, Inc.). After digestion,

approximately 12 mL of scintillation cocktail were added and the samples were analyzed for total radioactivity. Duplicate aliquots (approximately 0.05 g) of blood were weighed into scintillation vials containing 2 mL of Soluene®-350. The samples were neutralized and decolorized by treatment with perchloric acid/hydrogen peroxide and assayed for radioactivity. Tissue samples (approximately 0.01 to 0.9 g) were digested in 2 mL of Soluene®-350 using a mechanical shaker. Small tissues and organs, and aliquots of large tissues (i.e., skin, adipose) were analyzed in their entirety. For rats, if large organs (i.e., liver) were homogenized, weighed aliquots of the homogenate were analyzed. Colored tissues were neutralized and decolorized with perchloric acid/hydrogen peroxide, and assayed for radioactivity. Residual radioactivity present in the carcass and dose application site was recovered by digesting the tissues in 2 N ethanolic sodium hydroxide. To hasten digestion, the carcass and dose application site collections were shaken for approximately 96 hours. After complete digestion, aliquots (approximately 0.2 to 0.7 g) were analyzed for total radioactivity. The amount of radiolabel reported for the residual carcass was calculated by subtracting the measured amounts of radiolabel in the large tissues (adipose, muscle, skin, and blood) from the measured amount in the total carcass digest.

RESULTS

With baseline resolution, the radiochemical purity of [^{14}C]-diisopropylcarbodiimide was found to be approximately 94%, with an impurity of approximately 3% detected at the retention time for [^{14}C]-diisopropylurea. The identity of a synthetic standard of 1,3-diisopropylurea was confirmed by both mass spectrometry and ^{1}[H]-NMR spectroscopy.

When rat blood was spiked with [^{14}C]-diisopropylcarbodiimide in propylene glycol and extracted almost immediately, approximately 70% of the radiolabel was extracted by hexanes. Following 30 minutes of incubation, only approximately 15% of the radiolabeled dose was extracted. When the hexanes extracts were analyzed by HPLC, approximately 90% of the radiolabel extracted after incubation for up to 10 minutes was [^{14}C]-diisopropylcarbodiimide. By 30 minutes, only 73% of the extracted radiolabel (which represented approximately 15% of the total radiolabel) eluted as [^{14}C]-diisopropylcarbodiimide.

Charcoal-impregnated cellulose filters retained approximately 90.6% of the applied radioactivity after 20 minutes of storage at room temperature. When the experiment was repeated with additional time points and storage of the filters in sealed scintillation vials, the charcoal-impregnated filters retained approximately 97.6%, 96.4%, 97.3%, 95.5%, and 95.9%, respectively, of the applied radioactivity when analyzed 0, 3, 24, 48, and 72 hours after dosing.

Dermal Studies

Rats

As shown in Tables L1 and L2, approximately 1.4% and 0.5% of the administered radioactivity was excreted in urine for Study A1 (4.1 mg/kg) and Study A2 (3.9 mg/kg), respectively, and less than 0.2% was excreted in feces through 72 hours following dose application for both studies. Less than 2% of the radioactivity was measured as volatile organics or $^{14}CO_2$ for Study A1, while approximately 0.5% of the dose was measured as volatile organics for Study A2. For Study B, a minimal fraction of the 40.9 mg/kg dose (approximately 1% of the total) was excreted in urine, feces, and breath over the same time interval (Table L3).

As shown in Table L4, total dermal absorption of the radiolabeled doses was approximately 7% and 2% for Studies A1 and A2, respectively. Approximately 1% and 0.6% of the radiolabeled doses remained in the dose application site skin for studies A1 and A2, respectively. Less than 0.5% was found in the residual carcass for both studies. For Study B, approximately 0.1% of the radiolabeled dose remained in the dose application site skin as well as in the carcass; total dermal absorption of the radiolabeled dose was approximately 1%.

In Study A1, the average total recovery of the radiolabeled dose was approximately 72% and included approximately 65% of the dose that was unabsorbed. When this study was repeated (Study A2), the average total recovery was approximately 86% and included approximately 84% of the dose that was unabsorbed. For Study B,

the average total recovery was approximately 97% of the radiolabeled dose and included approximately 96% of the dose that was unabsorbed.

Table L5 shows the concentration of diisopropylcarbodiimide-derived radiolabeled material in the tissues 72 hours following each dermal exposure. For each study, only a negligible percentage of the dose was found in the assayed tissues and the residual carcass. None of the tissues collected for Study A1 were found to have appreciable tissue:blood ratios (values >10). For Studies A2 and B, the tissue:blood ratios could not be determined since the calculated disintegrations per minute for blood were not significantly different from background samples.

Mice

In Study E, mice received an average dermal dose of 6.9 mg/kg (approximately 0.06 mg/cm^2 and approximately 26.6 µCi/animal). During the exposure, the dose application site was protected by a charcoal-covered wire tissue capsule appliance that was put in place after the dose was applied. Approximately 0.7% of the administered radioactivity was excreted in the urine, and approximately 0.4% was excreted in the feces through 72 hours following dose application (Table L6). Less than 1% of the radioactivity was trapped as volatile organics and $^{14}CO_2$. Results presented in Table L7 show that an average of only 6.5% of the administered dose was recovered in 72 hours following dose application. Less than 0.2% of the radiolabeled dose remained in the dose application site skin and the residual carcass. Approximately 2% of the dose was absorbed during the 72-hour exposure. Table L8 shows the concentrations of diisopropylcarbodiimide-derived radiolabel in the tissues 72 hours following dose application. Only a negligible percentage of the dose was found in the tissues and residual carcass; however, an elevated tissue:blood ratio (>10) was observed for skin.

Intravenous Studies

In Study G, mice received an average intravenous dose of 7.6 mg/kg (2.01 µCi/animal). As shown in Table L9, approximately 37% of the administered dose was excreted in urine, and approximately 11% was excreted in feces through 48 hours following dose administration. An average of 29% of the radioactivity was exhaled as $^{14}CO_2$, and approximately 8% was exhaled as volatile organics. Approximately 84% of the radiolabeled dose was recovered after 48 hours.

Table L10 shows the concentrations of diisopropylcarbodiimide-derived radiolabel in the tissues 48 hours following dosing. Only a negligible percentage of the dose was found in selected tissues and the residual carcass. None of the assayed tissues were found to have appreciable tissue:blood ratios.

In Study H, mice received an average intravenous bolus dose of 7.8 mg/kg (1.02 µCi/animal). As shown in Table L11, 7.6% of the injected dose was measured in blood 1 minute after dosing. Considerable animal-to-animal variation was observed in the concentration of radioactivity in blood during the first hour. Thereafter, the average radioactivity measured in blood steadily decreased to less than 0.3% of the injected dose at 48 hours after dosing.

DISCUSSION

The radiochemical purity of [^{14}C]-diisopropylcarbodiimide was found to be sufficiently high (approximately 94% with an impurity of approximately 3%) to enable disposition studies. In earlier studies, sublimation of the test chemical complicated dermal studies with a similar carbodiimide, dicyclohexylcarbodiimide. Hence, an *in vitro* volatilization experiment was performed with [^{14}C]-diisopropylcarbodiimide to determine whether volatilization would complicate dermal studies involving this test chemical as well. The *in vitro* experiment demonstrated that the use of a trapping material to recover volatized dose would be required for acceptable mass balance in dermal studies.

An experiment to test charcoal as a potential dermal appliance trap for volatilized [^{14}C]-diisopropylcarbodiimide demonstrated that the volatilized radiolabel could be recovered from a charcoal-impregnated filter by combustion with subsequent analysis by LSC. This experiment was run for approximately 20 minutes without a freeze-thaw cycle for the samples, and did not address the continued stability of [^{14}C]-diisopropylcarbodiimide-related compounds in charcoal beyond approximately 20 minutes. Subsequently, an experiment was conducted to determine the effect of a freeze-thaw cycle on the stability of diisopropylcarbodiimide-related compounds trapped on activated charcoal. This experiment confirmed that an acceptable percentage of radiolabeled doses could be recovered from a charcoal-impregnated filter by combustion with subsequent analysis by LSC if the samples were oxidized and analyzed within 72 hours of dose administration.

Blister-type appliances constructed form charcoal-impregnated cellulose were developed for use in recovering volatilized dermal doses of diisopropylcarbodiimide. Prior to use of the charcoal protective appliances in any in-life studies, the appliances were tested to determine the optimal dosing procedure that would ensure adequate recovery of radiolabeled doses, uniform dosing across the dose application site area, and minimal contamination of the appliance or surrounding skin with the applied dose.

Because the covering of the dose site was opaque, it was not possible to actually view the dose as it was being applied to the skin. To simulate the results of dose application, a mock dose formulation containing food coloring in ethanol was applied through the charcoal appliance using several techniques. After removal of the appliance, the food coloring aided in visualizing where the dose had accumulated. By use of specially constructed appliances that contained Teflon®-sheeted windows, actual dose administration was observed to verify delivery of the dose over the entire dose application area. In summary, these experiments led to the development of a nonocclusive dermal appliance that was subsequently used with success to improve recoveries of radiolabeled doses in mass balance studies involving [^{14}C]-diisopropylcarbodiimide.

In addition to its volatility, [^{14}C]-diisopropylcarbodiimide is also extremely reactive; it reacts rapidly in blood to form products that are not extracted by nonpolar organic solvents. In an *in vitro* experiment, after 30 minutes of incubation, only 15% of administered radiolabel was extracted from blood with hexanes. Of this 15%, approximately 73% was identified as diisopropylcarbodiimide by HPLC analysis. It was postulated that it was still possible to measure diisopropylcarbodiimide after 30 minutes only because of the small size of the blood sample; likely, the blood component(s) that reacted with diisopropylcarbodiimide was of limited supply. In systemic circulation, this would not be the case, so it would be unlikely that parent diisopropylcarbodiimide could be measured in blood in an in-life experiment.

Dermal studies were conducted in rats at doses of approximately 4 and 41 mg/kg to determine the dermal absorption of diisopropylcarbodiimide, the rates and routes of excretion, and the terminal body burden. The dose application site was protected by a foam appliance covered with a charcoal-impregnated filter to help trap volatilized diisopropylcarbodiimide. Diffusion of diisopropylcarbodiimide into the foam led to the conclusion that the appliance was not suitable for adequate recovery of the radiolabeled dose, and prompted the use of a nonocclusive blister-type charcoal-impregnated appliance. The high radiochemical dose and the volatility of diisopropylcarbodiimide led to high levels of radioactivity in the dose-site appliances. Due to these high levels of radiolabel, the appliances had to be reanalyzed. The low recovery of radiolabeled doses was most likely due to desorption of ^{14}C from the charcoal filter and possibly the foam appliance prior to analysis. Therefore, the exposure time was limited to 6 hours to minimize desorption time, and the charcoal appliances were combusted within a few hours of removal from the animals. These changes resulted in improved recovery of the radiolabeled doses. The average total recoveries were approximately 72%, 86%, and 97% of the radiolabeled doses and included approximately 65%, 84%, and 96% of the doses that were unabsorbed, respectively.

In rats, only small percentages of the radiolabeled doses were absorbed (approximately 6.6%, 1.9%, and 1.1%) and excreted (approximately 5.1%, 1.0%, and 1.0%). None of the assayed tissues were found to have substantially elevated tissue:blood ratios, and no target organs were identified. The majority of each dose appeared to have been

volatilized from the dose application site and was not available for absorption. The tissue:blood ratio could not be determined for two of the three dermal studies in rats because the measured radioactivity in blood was not significantly different from that of background.

A similar study was performed in mice at a dermal dose of 6.9 mg/kg, again to determine the dermal absorption of diisopropylcarbodiimide, the rates and routes of excretion, and the terminal body burden. During the study, the dose application site was not occluded, but was protected by a metal tissue capsule covered with a charcoal-impregnated filter to trap volatilized diisopropylcarbodiimide. The appliance was attached to the animal after the dose was applied. Only a small percentage of the radiolabeled dose was absorbed (approximately 2.3%) and excreted (approximately 2.2%) during the 72-hour study. Almost none of the dose remained in the dose application site skin or the residual carcass, including the selected tissues, suggesting that the applied dermal dose rapidly volatilized from the dose application site. The average total recovery was only approximately 7% of the radiolabeled dose and included approximately 4% of the dose that was unabsorbed. A possible explanation for the low recovery is that the dose volatilized from the dose application site prior to being covered with the charcoal-covered appliance.

Two dermal studies were conducted in mice with doses of approximately 80 mg/kg to determine the dermal absorption versus volatility of diisopropylcarbodiimide after a 6-hour exposure. For both studies, the dose application site was protected by a blister-type nonocclusive charcoal-impregnated appliance. The dose was administered through the appliance to minimize the volatilization loss of diisopropylcarbodiimide during dosing. An appliance with an outer diameter of 6 cm (ungathered) was attached to the backs of the mice prior to dosing. This appliance did not create a proper seal on the animal and resulted in a recovery of 82.5%. A smaller appliance was fashioned with an outer diameter of 5 cm, and the recovery was successfully increased to 91.2%. For these two dermal studies in mice, similar to the results from the dermal studies in rats, only small percentages of the radiolabeled doses were absorbed (approximately 0.1% and 0.5%, respectively) and excreted (approximately 0.02% and 0.01%, respectively). Once again, the majority of the dose was recovered in the charcoal-impregnated appliances. In the first study, approximately 82.4% of the dose was not absorbed, of which 82.3% was contained in the charcoal appliance; in the second study, approximately 90.7% of the dose was unabsorbed and 90.5% was contained in the appliance. The majority of the dose rapidly volatilized from the dose application site and was not available for absorption.

Following a 7.6 mg/kg intravenous dose to mice, approximately 37% of the administered dose was excreted in urine, and approximately 11% was excreted in feces within 48 hours after dosing. Approximately 29% of the radioactivity was exhaled as $^{14}CO_2$, and approximately 8% was exhaled as volatile organics. Only a small percentage of the dose was found in the analyzed tissues (approximately 7%) and the residual carcass (approximately 1.7%). None of the assayed tissues were found to have elevated tissue:blood ratios of radiolabel and approximately 84% of the radiolabeled dose was recovered after 48 hours.

An intravenous injection study was conducted in mice using a dose of 7.8 mg/kg to determine the time course of radioactivity in blood. At each time point, three to four animals were sacrificed and aliquots of blood were analyzed (serial blood sampling from the same animal was not possible). At 1 minute postdosing, only approximately 7.6% of the administered radiolabel was measured in circulatory blood. This was the highest measured percentage of any time point, but a steady trend did not follow. For the first hour, the animal-to-animal variation in the amount of circulating radiolabel was high. After 1 hour, the percentage of the dose measured in blood steadily decreased at each subsequent time point until less than 0.3% of the dose remained in blood at 48 hours after dosing. The amount of radiolabel recovered in blood suggests that diisopropylcarbodiimide may chemically react at or near the site of injection and not be entirely systemically available. In addition, the identity of the radiolabeled compounds measured in blood is uncertain. It is probable that the radioactivity is not associated with [^{14}C]-diisopropylcarbodiimide, but rather radiolabeled metabolites or reaction products in blood. The formation of reaction products or metabolites may contribute to the variability observed during the first postdosing hour.

REFERENCE

Microbiological Associates (1995). Final Report of the Fourteen-Day and Thirteen-Week Prechronic Dermal Toxicity Studies of Diisopropylcarbodiimide (DIC) in Fischer 344 Rats and B6C3F$_1$ Mice (Contract No. N01-ES-15319) (April 19, 1995). Microbiological Associates, Inc., Bethesda, MD.

TABLE L1
Cumulative Excretion of Radioactivity by Male F344/N Rats After a Single Dermal Application of 4.1 mg/kg [^{14}C]-Diisopropylcarbodiimide: Study A1[a]

End of Collection Period (hours)	Urine	Feces	Volatile Organics Trapped by Ethanol	Volatile Organics Trapped by Charcoal	Exhaled CO_2	Total
4	—[b]	—	1.2 ± 0.5	0.004 ± 0.003	0.24 ± 0.01	1.4 ± 0.5
8	0.31 ± 0.07	—	1.3 ± 0.5	0.006 ± 0.004	0.45 ± 0.03	2.0 ± 0.6
24	0.8 ± 0.1	0.11 ± 0.03	1.5 ± 0.5	0.006 ± 0.004	1.0 ± 0.1	3.3 ± 0.8
48	1.1 ± 0.1	0.16 ± 0.04	1.5 ± 0.5	0.006 ± 0.004	1.5 ± 0.2	4.3 ± 0.8
72	1.4 ± 0.2[c]	0.19 ± 0.04	1.6 ± 0.5	0.006 ± 0.004	1.9 ± 0.3	5.1 ± 0.9

[a] Data are presented as cumulative percentage of the dose (mean ± standard deviation) for four rats.
[b] No collection was scheduled for this time interval
[c] Cage rinse is included

TABLE L2
Cumulative Excretion of Radioactivity by Male F344/N Rats After a Single Dermal Application of 3.9 mg/kg [^{14}C]-Diisopropylcarbodiimide: Study A2[a]

End of Collection Period (hours)	Urine	Feces	Volatile Organics Trapped by Ethanol	Total
8	0.11 ± 0.02	—[b]	0.4 ± 0.2	0.5 ± 0.2
24	0.31 ± 0.06	0.037 ± 0.009	0.5 ± 0.2	0.8 ± 0.2
48	0.40 ± 0.07	0.08 ± 0.01	0.5 ± 0.2	1.0 ± 0.3
72	0.46 ± 0.07[c]	0.09 ± 0.02	0.5 ± 0.2	1.0 ± 0.3

[a] Data are presented as cumulative percentage of the dose (mean ± standard deviation) for four rats.
[b] No collection was scheduled for this time interval
[c] Cage rinse is included

TABLE L3
Cumulative Excretion of Radioactivity by Male F344/N Rats After a Single Dermal Application of 40.9 mg/kg [^{14}C]-Diisopropylcarbodiimide: Study B[a]

End of Collection Period (hours)	Urine[b]	Feces[c]	Volatile Organics Trapped by Ethanol	Exhaled CO_2[d]	Total
8	0.03 ± 0.03	—[e]	0.7 ± 0.2	0.15	0.8 ± 0.3
24	0.07 ± 0.08	0.010	0.7 ± 0.2	0.15	0.9 ± 0.3
48	0.10 ± 0.11	0.010	0.8 ± 0.2	0.15	0.9 ± 0.4
72	0.11 ± 0.12	0.010	0.8 ± 0.2	0.15	1.0 ± 0.4

[a] Data are presented as cumulative percentage of the dose (mean ± standard deviation) for four rats.
[b] Urine at 8, 24, and 48 hours included the methanol rinse for that time interval. The cage rinse was not included in the 72-hour collection because the value was not significantly different from background.
[c] n=1
[d] n=2
[e] No collection was scheduled for this time interval

TABLE L4
Distribution of Radioactivity in Male F344/N Rats 72 Hours After a Single Dermal Application of [^{14}C]-Diisopropylcarbodiimide[a]

	Study A1 4.1 mg/kg	Study A2 3.9 mg/kg	Study B 40.9 mg/kg
Absorbed Dose			
Urine	1.4 ± 0.2[b]	0.5 ± 0.1[c]	0.1 ± 0.1[d]
Feces	0.19 ± 0.04	0.09 ± 0.02	0.01[e]
Exhaled CO_2	1.9 ± 0.3	—[f]	0.2[g]
Volatile Organics Trapped by Ethanol	1.6 ± 0.5	0.5 ± 0.2	0.8 ± 0.2
Volatile Organics Trapped by Charcoal	0.006 ± 0.004	—	—
Application Site Skin	1.2 ± 0.2	0.6 ± 0.3	0.1 ± 0.1
Residual Carcass[h]	0.3 ± 0.2	0.2 ± 0.1	0.1[g]
Collected Tissues	0.068 ± 0.007	0.022 ± 0.001	0.001 ± 0.002
Total Absorbed Dose	6.6 ± 0.8	1.9 ± 0.6	1.1 ± 0.5
Total Unabsorbed Dose (appliance, skinwash, etc.)	65.4 ± 3.0	84.1 ± 0.9[i]	95.5 ± 3.2[i]
Total Dose Recovered	72.0 ± 3.8	86.0 ± 0.7	96.6 ± 2.7

[a] Data are presented as percentage (mean ± standard deviation) for four rats.
[b] Water cage rinse and methanol rinse included
[c] Water cage rinse included
[d] Hexanes cage rinse and methanol rinse included. The water cage rinse was not included because the value was not significantly different from background.
[e] n=1
[f] Not applicable
[g] n=2
[h] Dose recovered in the residual carcass less the dose measured in skin, muscle, adipose, and blood.
[i] Oxidized charcoal cover within the unabsorbed analysis was corrected for the oxidizer efficiency.

TABLE L5
Tissue Distribution of Radiolabel in Male F344/N Rats 72 Hours After a Single Dermal Application of [^{14}C]-Diisopropylcarbodiimide

Tissue	Diisopropylcarbodiimide Equivalents in Tissue (ng-Eq/g)	Tissue:Blood Ratio	Dose in Total Tissue (%)[a]
Study A1: 4.1 mg/kg[b]			
Adipose	20.3 ± 2.2	1.40 ± 0.16	0.031 ± 0.004
Bladder	34.8 ± 7.2	2.40 ± 0.51	0.00029 ± 0.00006
Blood	14.5 ± 0.9	—[d]	0.0164 ± 0.0007
Brain	16.3 ± 1.1	1.12 ± 0.04	0.0030 ± 0.0002
Heart	24.7 ± 2.9	1.70 ± 0.18	0.0019 ± 0.0001
Kidney	61.1 ± 7.6	4.20 ± 0.41	0.011 ± 0.001
Liver	48.7 ± 9.1	3.33 ± 0.50	0.045 ± 0.006
Lung	27.2 ± 4.2	1.88 ± 0.34	0.0025 ± 0.0005
Muscle	13.4 ± 0.7	0.92 ± 0.09	0.14 ± 0.01
Skin[c]	65.4 ± 17.3	4.48 ± 1.00	0.24 ± 0.06
Spleen	26.3 ± 2.9	1.81 ± 0.18	0.0013 ± 0.0001
Testes	13.1 ± 0.7	0.90 ± 0.03	0.0037 ± 0.0002
Study A2: 3.9 mg/kg[b]			
Adipose	11.1 ± 3.2	NA	0.019 ± 0.005
Bladder	NA	NA	NA
Blood	NA	NA	NA
Brain	3.8 ± 0.4	NA	0.00077 ± 0.00006
Heart	6.3 ± 2.2	NA	0.0005 ± 0.0001
Kidney	17.7 ± 1.7	NA	0.0038 ± 0.0003
Liver	16.1 ± 0.6	NA	0.0156 ± 0.0008
Lung	5.7 ± 1.4	NA	0.0006 ± 0.0002
Muscle[e]	3.9	NA	0.05
Skin[c]	25.9 ± 18.5	NA	0.11 ± 0.07
Spleen[f]	8.0	NA	0.0004
Testes	2.6 ± 0.8	NA	0.0008 ± 0.0002
Study B: 40.9 mg/kg[g]			
Adipose	88	NA	0.014
Bladder	NA	NA	NA
Blood	NA	NA	NA
Brain	24.7	NA	0.0005
Heart	42.9	NA	0.0004
Kidney	154.2	NA	0.003
Liver	NA	NA	NA
Lung	47.9	NA	0.0004
Muscle		NA	
Skin[c,e]	86.6	NA	0.03
Spleen	NA	NA	NA
Testes	22.2	NA	0.0006

NA=Not applicable. Disintegrations per minute values for aliquots were not significantly different from background; tissue: blood ratios cannot be calculated when concentrations in blood are indistinguishable from background.

[a] Percent dose was calculated using the following values for the mass of total tissue, expressed as percent of body weight: adipose, 7.0%; blood, 5.2%; muscle, 48.0%; and skin, 17.0%.

[b] Data are presented as mean ± standard deviation for four rats.

[c] Excludes application site skin

[d] Unity

[e] n=2

[f] n=3

[g] Data values represent individual rats

TABLE L6
Cumulative Excretion of Radioactivity by Male B6C3F$_1$ Mice After a Single Dermal Application of 6.9 mg/kg [^{14}C]-Diisopropylcarbodiimide: Study E[a]

End of Collection Period (hours)	Urine[b]	Feces	Volatile Organics Trapped by Ethanol	Volatile Organics Trapped by Charcoal	Exhaled CO_2	Total
4	—[c]	—	0.16 ± 0.10	0.004 ± 0.002	0.7 ± 0.1	0.9 ± 0.2
8	0.3 ± 0.3	—	0.2 ± 0.1	0.005 ± 0.001	0.7 ± 0.1	1.2 ± 0.3
24	0.5 ± 0.3	0.2 ± 0.2	0.3 ± 0.1	0.005 ± 0.001	0.8 ± 0.1	1.8 ± 0.3
48	0.6 ± 0.3	0.3 ± 0.2	0.3 ± 0.1	0.005 ± 0.001	0.8 ± 0.1	2.0 ± 0.3
72	0.7 ± 0.4	0.4 ± 0.2	0.3 ± 0.1	0.005 ± 0.001	0.8 ± 0.1	2.2 ± 0.3

[a] Data are presented as cumulative percentage of the dose (mean ± standard deviation) for four mice.
[b] Included methanol rinse at 8, 24, and 48 hours; cage rinse included at 72 hours
[c] No collection was scheduled for this time interval

TABLE L7
Distribution of Radioactivity in Male B6C3F$_1$ Mice 6 or 72 Hours After a Single Dermal Application of [^{14}C]-Diisopropylcarbodiimide: Study E[a]

	6.9 mg/kg[b]
Absorbed Dose	
Urine[c]	0.7 ± 0.4
Feces	0.4 ± 0.2
Exhaled CO_2	0.8 ± 0.1
Volatile Organics Trapped by Ethanol	0.3 ± 0.1
Volatile Organics Trapped by Charcoal	0.005 ± 0.001
Application Site Skin	0.13 ± 0.03
Residual Carcass[d]	0.01 ± 0.01
Collected Tissues	0.014 ± 0.001
Total Absorbed Dose	2.3 ± 0.4
Unabsorbed Dose	
Charcoal Cover	1.7 ± 0.5
Skin Wash	0.8 ± 0.5
Appliance/Elastoplast® Extract	1.6 ± 0.3
Instrument Swipe	0.01 ± 0.01
Hexanes Cage Rinse	0.01 ± 0.00
Total Unabsorbed Dose	4.1 ± 0.6
Total Dose Recovered	6.5 ± 0.6

NA=Not applicable. Value was not significantly different from background and the absorbed dose could not be calculated.
[a] Data are presented as percentages
[b] Data are presented as mean ± standard deviation for four mice; study duration was 72 hours
[c] Urine included cage rinse and methanol rinse.
[d] Dose recovered in the residual carcass less the dose measured in skin, muscle, adipose, and blood.

TABLE L8
Tissue Distribution of Radiolabel in Male B6C3F$_1$ Mice 72 Hours After a Single Dermal Application of 6.9 mg/kg [^{14}C]-Diisopropylcarbodiimide: Study E[a]

Tissue	Diisopropylcarbodiimide Equivalents in Tissue (ng-Eq/g)	Tissue:Blood Ratio	Dose in Total Tissue (%)[b]
Adipose	21.0 ± 17.1	7.76 ± 7.01	0.03 ± 0.02
Bladder	11.8 ± 3.6	4.19 ± 1.65	0.00020 ± 0.00007
Blood	2.91 ± 0.62	—[d]	0.0031 ± 0.0006
Brain	5.63 ± 0.40	1.98 ± 0.30	0.0014 ± 0.0001
Heart	7.52 ± 0.73	2.63 ± 0.28	0.00060 ± 0.00009
Kidney	13.3 ± 2.0	4.64 ± 0.55	0.0033 ± 0.0005
Liver	9.63 ± 1.48	3.37 ± 0.61	0.0071 ± 0.0007
Lung	5.49 ± 0.21	1.94 ± 0.31	0.00051 ± 0.00004
Muscle	4.46 ± 0.59	1.56 ± 0.27	0.028 ± 0.003
Skin[c]	31.4 ± 13.7	11.6 ± 6.0	0.06 ± 0.03
Spleen	4.67 ± 0.32	1.66 ± 0.37	0.00018 ± 0.00001
Testes	3.49 ± 0.59	1.23 ± 0.29	0.00040 ± 0.00005

[a] Data are presented as mean ± standard deviation for four mice.
[b] Percent dose was calculated using the following values for the mass of total tissue, expressed as percent of body weight: adipose, 9.6%; blood, 7.6%; muscle, 45.2%; and skin, 14.4%.
[c] Excludes application site skin
[d] Unity

TABLE L9
Cumulative Excretion of Radioactivity by Male B6C3F$_1$ Mice After a Single Intravenous Injection of 7.6 mg/kg [^{14}C]-Diisopropylcarbodiimide: Study G[a]

End of Collection Period (hours)	Urine	Feces	Volatile Organics	Exhaled CO_2	Total
4	—[b]	—	6.68 ± 1.66	7.87 ± 2.63	14.6 ± 4.10
8	3.09 ± 6.89[c]	—	7.50 ± 1.59	24.9 ± 1.76	35.0 ± 7.71
24	26.1 ± 7.79	6.26 ± 3.55	7.78 ± 1.63	28.0 ± 1.43	69.0 ± 6.20
48	36.8 ± 8.05[d]	10.6 ± 5.59	7.92 ± 1.62	29.2 ± 1.44	84.4 ± 3.58

[a] Data are presented as cumulative percentage of the dose (mean ± standard deviation) for six mice.
[b] No collection was scheduled for this time interval
[c] n=5
[d] Cage rinse is included

TABLE L10
Tissue Distribution of Radiolabel in Male B6C3F$_1$ Mice 48 Hours After a Single Intravenous Injection of 7.6 mg/kg [^{14}C]-Diisopropylcarbodiimide: Study G[a]

Tissue	Diisopropylcarbodiimide Equivalents in Tissue (ng-Eq/g)	Tissue:Blood Ratio	Dose in Total Tissue (%)[b]
Adipose	1,770 ± 692	8.18 ± 3.73	2.36 ± 0.895
Bladder	486 ± 60.5	2.21 ± 0.378	0.00810 ± 0.00165
Blood	222 ± 19.9	—[c]	0.235 ± 0.0264
Brain	581 ± 221	2.60 ± 0.868	0.142 ± 0.0484
Heart	1,140 ± 536	5.10 ± 2.18	0.0965 ± 0.0758
Kidney	2,040 ± 280	9.28 ± 1.85	0.458 ± 0.0718
Liver	508 ± 46.9	2.28 ± 0.0691	0.411 ± 0.0581
Lung	456 ± 86.9	2.05 ± 0.309	0.0445 ± 0.0187
Muscle	415 ± 125	1.87 ± 0.577	2.62 ± 0.849
Skin	448 ± 122	2.04 ± 0.635	0.899 ± 0.262
Spleen	371 ± 19.7	1.68 ± 0.158	0.0160 ± 0.00315
Testes	223 ± 30.7	1.00 ± 0.149	0.0245 ± 0.00425

[a] Data are presented as mean ± standard deviation for six mice.
[b] Percent dose was calculated using the following values for the mass of total tissue, expressed as percent of body weight: adipose, 9.6%; blood, 7.6%; muscle, 45.2%; and skin, 14.4%
[c] Unity

TABLE L11
Concentrations of Radiolabel in Blood of Male B6C3F$_1$ Mice After a Single Intravenous Injection of 7.8 mg/kg [^{14}C]-Diisopropylcarbodiimide: Study H[a]

Time Period After Dosing	Diisopropylcarbodiimide Equivalents in Blood (ng-Eq/g Blood)				
	Set 1	Set 2	Set 3	Set 4	Mean[b]
1 minute	6,920	8,710	8,060	—	7,900 ± 906[d]
4 minutes	2,850	601	140	823	1,100 ± 1,200
8 minutes	3,780	5,110	—[c]	4,590	4,490 ± 672[d]
20 minutes	3,900	1,230	4,430	3,580	3,290 ± 1,410
1 hour	10,300	5,640	2,000	NA	5,970 ± 4,150[d]
2 hours	4,230	4,610	4,780	4,820	4,610 ± 265
8 hours	638	615	523	755	633 ± 95.4
24 hours	418	314	314	302	337 ± 54.3
48 hours	198	203	230	—	210 ± 17.0[d]
	% of Dose in Blood				
1 minute	6.64	8.35	7.87	—	7.62 ± 0.883[d]
4 minutes	2.84	0.617	0.131	0.820	1.10 ± 1.19
8 minutes	3.69	5.00	—	4.48	4.39 ± 0.657[d]
20 minutes	3.74	1.20	4.03	3.63	3.15 ± 1.31
1 hour	10.0	4.97	1.95	NA	5.65 ± 4.08[d]
2 hours	4.05	4.55	4.67	4.56	4.46 ± 0.275
8 hours	0.611	0.624	0.501	0.762	0.624 ± 0.107
24 hours	0.404	0.310	0.313	0.268	0.324 ± 0.0575
48 hours	0.192	0.194	0.226	—	0.204 ± 0.0194[d]

NA=Not applicable; value was not significantly different from background, therefore value could not be calculated.
[a] Each timepoint involved a different mouse.
[b] Data are presented as mean ± standard deviation for four mice.
[c] No data available due to dosing error.
[d] n=3

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ISSN 2378-8925