NTP TECHNICAL REPORT

ON THE

TOXICOLOGY AND CARCINOGENESIS

STUDIES OF CHLOROPRENE

(CAS NO. 126-99-8)

IN F344/N RATS AND B6C3F$_1$ MICE

(INHALATION STUDIES)

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

September 1998

NTP TR 467

NIH Publication No. 98-3957

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

FOREWORD

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

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

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

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

Listings of all published NTP reports and ongoing studies are available from NTP Central Data Management, NIEHS, P.O. Box 12233, MD E1-02, Research Triangle Park, NC 27709 (919-541-3419). The Abstracts and other study information for 2-year studies are also available at the NTP's World Wide Web site: http://ntp-server.niehs.nih.gov.

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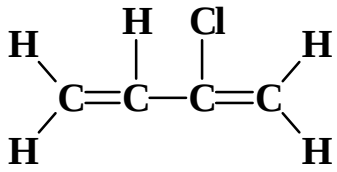
ABSTRACT



CHLOROPRENE

CAS No. 126-99-8

Chemical Formula: C_4H_5Cl Molecular Weight: 88.54

Synonyms: Chlorobutadiene; 2-chlorobuta-1,3-diene; 2-chloro-1,3-butadiene; β-chloroprene

Chloroprene is used almost exclusively in the manufacture of neoprene (polychloroprene). Chloroprene was chosen for study because it is a high-volume production chemical with limited information on its carcinogenic potential and because it is the 2-chloro analogue of 1,3-butadiene, a potent, multi-species, multi-organ carcinogen. Male and female F344/N rats and $B6C3F_1$ mice were exposed to chloroprene (greater than 96% pure) by inhalation for 16 days, 13 weeks, or 2 years. Genetic toxicology studies were conducted in *Salmonella typhimurium*, *Drosophila melanogaster*, and $B6C3F_1$ mice (bone marrow cells and peripheral blood erythrocytes).

16-DAY STUDY IN RATS

Groups of 10 male and 10 female F344/N rats were exposed to 0, 32, 80, 200, or 500 ppm chloroprene by inhalation, 6 hours per day, 5 days per week, for 16 days. Three 500 ppm males died on day 2 or 3 of the study. Mean body weight gains of 200 ppm males and females and 500 ppm females were significantly less than those of the chamber control groups. On the first day of exposure, rats exposed to 500 ppm were hypoactive and unsteady and had rapid shallow breathing. These effects were also observed to some degree in animals exposed to 200 ppm. After the second day of exposure, the effects in these groups worsened, and hemorrhage from the nose was observed.

A normocytic, normochromic, responsive anemia; thrombocytopenia; and increases in serum activities of alanine aminotransferase, glutamate dehydrogenase, and sorbitol dehydrogenase occurred on day 4 in 200 ppm females and 500 ppm males. Kidney weights of 80 and 500 ppm females were significantly greater than those of the chamber control group, as were the liver weights of 200 and 500 ppm females.

The incidences of minimal to mild olfactory epithelial degeneration of the nose in all exposed groups of males and females were significantly greater than those in the chamber control groups. The incidence of squamous metaplasia of the respiratory epithelium was significantly increased in 500 ppm males. The incidences of centrilobular to random hepatocellular necrosis in 500 ppm males and 200 ppm females were significantly greater than those in the chamber control groups.

16-DAY STUDY IN MICE

Groups of 10 male and 10 female B6C3F$_1$ mice were exposed to 0, 12, 32, 80, or 200 ppm chloroprene by inhalation, 6 hours per day, 5 days per week, for 16 days. All males and females exposed to 200 ppm died on day 2 or day 3 of the study. Mean body weight gains of males exposed to 32 or 80 ppm were significantly less than that of the chamber control group. Mice exposed to 200 ppm exhibited narcosis during exposure and were hypoactive with reduced body tone after the first day of exposure. In general, hematology and clinical chemistry parameters measured for exposed males and females were similar to those of the chamber control groups. Thymus weights of 80 ppm males and females were significantly less than those of the chamber control groups. Liver weights of 80 ppm females were significantly greater than those of the chamber control groups.

Increased incidences of multifocal random hepatocellular necrosis occurred in males and females exposed to 200 ppm. Hypertrophy of the myocardium, foci of hemorrhage, and mucosal erosion were observed in three males and three females exposed to 200 ppm. Squamous epithelial hyperplasia of the forestomach was observed in two males and two females exposed to 80 ppm. Thymic necrosis, characterized by karyorrhexis of thymic lymphocytes, was observed in all males and females in the 200 ppm groups.

13-WEEK STUDY IN RATS

Groups of 10 male and 10 female F344/N rats were exposed to chloroprene at concentrations of 0, 5, 12, 32, 80, or 200 ppm by inhalation, 6 hours per day, 5 days per week, for 13 weeks. One male exposed to 200 ppm died during the study. The final mean body weights and body weight gains of all exposed groups of males and females were similar to those of the chamber control groups. Clinical findings in 200 ppm males included red or clear discharge around the nose and eye region.

At week 13, a normocytic, normochromic, and nonresponsive anemia occurred in 200 ppm males and females. A thrombocytopenia occurred in 200 ppm males and females on day 2 and in 80 and 200 ppm females on day 22. However, at week 13, platelet counts rebounded and were minimally increased in 200 ppm males and females. On day 2, a minimal to mild increase in activated partial thromboplastin time and prothrombin time occurred in 200 ppm males and females. The 200 ppm males and females also had increased activities of serum alanine aminotransferase, glutamate dehydrogenase, and sorbitol dehydrogenase on day 22; these increases were transient, and by week 13 the serum activities of these enzymes were similar to those of the chamber controls. An alkaline phosphatase enzymeuria occurred in 200 ppm females on day 22; at week 13, an alkaline phosphatase enzymeuria occurred in 32, 80, and 200 ppm males and 200 ppm females. At week 13, a proteinuria occurred in 200 ppm males. Liver nonprotein sulfhydryl concentrations in male rats immediately following 1 day or 12 weeks of exposure to 200 ppm and in females exposed to 200 ppm for 12 weeks were significantly less than those of the chamber control groups.

Kidney weights of 200 ppm males and females and 80 ppm females were significantly greater than those of the chamber control groups. Sperm motility of 200 ppm males was significantly less than that of the controls. In neurobehavioral assessments, horizontal activity was increased in male rats exposed to 32 ppm or greater and total activity was increased in 32 and 200 ppm males.

Increased incidences of minimal to mild olfactory epithelial degeneration and respiratory metaplasia occurred in males and females exposed to 80 or 200 ppm. The incidence of olfactory epithelial degeneration in 32 ppm females was also significantly greater than that in the chamber control group. The incidence of hepatocellular necrosis in 200 ppm females was significantly greater than that in the chamber control group. Scattered chronic inflammation also occurred in the liver of male and female rats in the 200 ppm groups; the incidence in 200 ppm females was significantly greater than that in the chamber control group. The incidences of hemosiderin pigmentation were significantly increased in males and females exposed to 200 ppm.

13-WEEK STUDY IN MICE

Groups of 10 male and 10 female B6C3F$_1$ mice were exposed to chloroprene at concentrations of 0, 5, 12, 32, or 80 ppm by inhalation, 6 hours per day, 5 days per week, for 13 weeks. All male and female mice

survived to the end of the study. The final mean body weight and body weight gain of males exposed to 80 ppm were significantly less than those of the chamber control group.

Hematocrit concentrations of females exposed to 32 or 80 ppm and erythrocyte counts of 80 ppm females were significantly less than those of the chamber control group. Platelet counts of 32 and 80 ppm females were also greater than that of the chamber control group. Increased incidences of squamous epithelial hyperplasia of the forestomach occurred in males and females exposed to 80 ppm.

2-YEAR STUDY IN RATS

Groups of 50 male and 50 female F344/N rats were exposed to chloroprene at concentrations of 0, 12.8, 32, or 80 ppm by inhalation, 6 hours per day, 5 days per week, for 2 years.

Survival, Body Weights, and Clinical Findings

Survival of males exposed to 32 or 80 ppm was significantly less than that of the chamber control group. Mean body weights of males exposed to 80 ppm were less than those of the chamber controls after week 93. Masses of the torso were observed during the study in exposed female groups, and these clinical findings correlated with mammary gland fibroadenomas observed at necropsy.

Pathology Findings

The incidences of squamous cell papilloma and squamous cell papilloma or squamous cell carcinoma (combined) of the oral cavity in male rats exposed to 32 ppm and male and female rats exposed to 80 ppm were significantly greater than those in the chamber controls and exceeded the historical control ranges.

The incidences of thyroid gland follicular cell adenoma or carcinoma (combined) in males exposed to 32 or 80 ppm were significantly greater than that in the chamber control group and exceeded the historical control range. Although the incidences of follicular cell adenoma and follicular cell adenoma or carcinoma (combined) in 80 ppm females were not significantly greater than those in the chamber controls, they did exceed the historical control range for these neoplasms.

The incidences of alveolar epithelial hyperplasia of the lung were significantly greater in all exposed groups of males and females than in the chamber control groups. The incidences of alveolar/bronchiolar carcinoma and alveolar/bronchiolar adenoma or carcinoma (combined) in 80 ppm males were slightly greater than those in the chamber control group. Although these neoplasm incidences were not significant, they exceeded the historical control range. The incidence of alveolar/bronchiolar adenoma, although not significant, was greater in 80 ppm females than in the chamber control group.

The incidences of multiple fibroadenoma of the mammary gland in all exposed groups of females were greater than that in the chamber control group. The incidences of fibroadenoma (including multiple fibroadenoma) in 32 and 80 ppm females were significantly greater than that in the chamber controls. The incidences of fibroadenoma in the chamber control group and in all exposed groups of females exceeded the historical control range.

The severity of nephropathy in exposed groups of male and female rats was slightly greater than in the chamber controls. Renal tubule adenoma and hyperplasia were observed in males and females. Additional kidney sections from male and female control and exposed rats were examined to provide a clearer indication of the potential effects of chloroprene on the kidney. The combined single- and step-section incidences of renal tubule hyperplasia in 32 and 80 ppm males and 80 ppm females and the incidences of adenoma and adenoma or carcinoma (combined) in all exposed males were significantly greater than those in the chamber controls.

A slight increase in the incidence of transitional epithelium carcinoma of the urinary bladder was observed in 80 ppm females. In addition, one 32 ppm male had a transitional epithelium carcinoma and one 80 ppm male had a transitional cell papilloma. These findings are noteworthy because no urinary bladder neoplasms have been observed in chamber control male or female F344/N rats.

In the nose, the incidences of atrophy, basal cell hyperplasia, metaplasia, and necrosis of the olfactory epithelium in 32 and 80 ppm males and females and of

atrophy and necrosis in 12.8 ppm males were significantly greater than those in the chamber control groups. The incidences of chronic inflammation were significantly increased in males exposed to 12.8 or 32 ppm and in males and females exposed to 80 ppm. The incidences of fibrosis and adenomatous hyperplasia in 80 ppm males and females were significantly greater than those in the chamber controls. Generally, lesions in the nasal cavity were mild to moderate in severity.

2-YEAR STUDY IN MICE

Groups of 50 male and 50 female B6C3F$_1$ mice were exposed to chloroprene at concentrations of 0, 12.8, 32, or 80 ppm by inhalation, 6 hours per day, 5 days per week, for 2 years.

Survival, Body Weights, and Clinical Findings

Survival of males exposed to 32 or 80 ppm and of all exposed female groups was significantly less than that of the chamber controls. The mean body weights of 80 ppm females were significantly less than those of the chamber control group after week 75. Clinical findings included masses of the head, which correlated with harderian gland adenoma and/or carcinoma in 32 ppm males and 80 ppm males and females. Dorsal and lateral torso masses of female mice correlated with mammary gland neoplasms in 32 and 80 ppm females and subcutaneous sarcomas in 12.8, 32, and 80 ppm females.

Pathology Findings

The incidences of alveolar/bronchiolar neoplasms in the lungs of all groups of exposed males and females were significantly greater than those in the chamber control groups and generally exceeded the historical control ranges. The incidences of multiple alveolar/bronchiolar adenoma and alveolar/bronchiolar carcinoma were increased in all exposed groups of males and females. The incidences of bronchiolar hyperplasia in all exposed groups of males and females were significantly greater than those in the chamber control groups.

Male mice had a pattern of nonneoplastic liver lesions along with silver-staining helical organisms within the liver consistent with infection with *Helicobacter hepaticus*. An organism compatible with *H. hepaticus* was confirmed with a polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP)-based assay. In NTP studies with *H. hepaticus*-associated hepatitis, increased incidences of hemangiosarcoma have been seen in the livers of male mice. Therefore, hemangiosarcomas of the liver were excluded from the analyses of circulatory (endothelial) neoplasms in males in this study. Even with this exclusion, the combined occurrence of hemangioma or hemangiosarcoma at other sites was significantly increased at all chloroprene exposure concentrations in males and in 32 ppm females. Incidences of neoplasms at other sites in this study of chloroprene were not considered to have been significantly impacted by the infection with *H. hepaticus* or its associated hepatitis.

The incidences of harderian gland adenoma and harderian gland adenoma or carcinoma (combined) in males exposed to 32 or 80 ppm and females exposed to 80 ppm were significantly greater than those in the chamber controls. The incidences of harderian gland adenoma or carcinoma (combined) in 32 ppm males and 80 ppm males and females exceeded the historical control ranges.

The incidences of mammary gland carcinoma and adenoacanthoma or carcinoma (combined) in 80 ppm females were significantly greater than those in the chamber control group. The incidences of mammary gland carcinoma and of adenoacanthoma in 32 and 80 ppm females exceeded the historical control ranges. Multiple mammary gland carcinomas occurred in exposed females.

The incidences of hepatocellular carcinoma in all exposed female groups and hepatocellular adenoma or carcinoma (combined) in 32 and 80 ppm females were significantly greater than those in the chamber controls; in the 80 ppm group, the incidence exceeded the historical control ranges for carcinoma and adenoma or carcinoma (combined). The incidence of eosinophilic foci in 80 ppm females was also significantly greater than that in the chamber controls.

The incidences of sarcoma of the skin were significantly greater in all exposed groups of females than in the chamber controls. The incidences of sarcoma of the mesentery were also increased in all exposed groups of females.

The incidence of squamous cell papilloma in 80 ppm females was greater than that in the chamber controls; the difference was not significant, but the incidence exceeded the historical control range. Males also showed a positive trend in the incidence of squamous cell papilloma of the forestomach. In males and females exposed to 80 ppm, the incidences of hyperplasia of the forestomach epithelium were significantly greater than those in the chamber controls.

Carcinomas of the Zymbal's gland were seen in three 80 ppm females, and two carcinomas metastasized to the lung. Zymbal's gland carcinomas have not been reported in control female mice in the NTP historical database.

The incidence of renal tubule adenoma in 80 ppm males was greater than that in the chamber controls. Though this difference was not significant, the incidence of this rare neoplasm exceeded the historical control range. The incidences of renal tubule hyperplasia in males exposed to 32 or 80 ppm were significantly greater than that in the chamber controls. Additional sections of kidney were examined from control and exposed males to verify these findings. The combined single- and step-section incidence of renal tubule adenoma in 80 ppm males and the combined incidences of renal tubule hyperplasia in all groups of exposed male mice were greater than those in the chamber controls.

The incidences of olfactory epithelial atrophy, adenomatous hyperplasia, and metaplasia in 80 ppm males and females were significantly greater than those in the chamber controls. The incidences of hematopoietic proliferation of the spleen in 32 and 80 ppm males and in all groups of exposed females were significantly greater than those in the chamber controls.

GENETIC TOXICOLOGY

Chloroprene was not mutagenic in any of the tests performed by the NTP. No induction of mutations was noted in any of four strains of *S. typhimurium* in the presence or the absence of S9 metabolic activation enzymes, and no induction of sex-linked recessive lethal mutations was observed in germ cells of male *D. melanogaster* treated with chloroprene via feeding or injection. In male mice exposed to chloroprene by inhalation for 12 days over a 16-day period, no induction of chromosomal aberrations, sister chromatid exchanges, or micronucleated erythrocytes in bone marrow or peripheral blood occurred. Results of a second micronucleus assay in male and female mice after 13 weeks of exposure to chloroprene via inhalation were also negative.

CONCLUSIONS

Under the conditions of these 2-year inhalation studies, there was *clear evidence of carcinogenic activity** of chloroprene in male F344/N rats based on increased incidences of neoplasms of the oral cavity; increased incidences of neoplasms of the thyroid gland, lung, and kidney were also attributed to chloroprene exposure. There was *clear evidence of carcinogenic activity* of chloroprene in female F344/N rats based on increased incidences of neoplasms of the oral cavity; increased incidences of neoplasms of the thyroid gland, mammary gland, and kidney were also attributed to exposure to chloroprene. Low incidences of urinary bladder neoplasms in male and female rats and lung neoplasms in female rats may also have been related to exposure to chloroprene.

There was *clear evidence of carcinogenic activity* of chloroprene in male B6C3F$_1$ mice based on increased incidences of neoplasms of the lung, circulatory system (hemangiomas and hemangiosarcomas), and harderian gland; increased incidences of neoplasms of the forestomach and kidney were also attributed to exposure to chloroprene. There was *clear evidence of carcinogenic activity* of chloroprene in female B6C3F$_1$ mice based on increased incidences of neoplasms of the lung, circulatory system (hemangiomas and hemangiosarcomas), harderian gland, mammary gland, liver, skin, and mesentery; increased incidences of neoplasms of the forestomach and Zymbal's gland were also attributed to exposure to chloroprene.

Exposure of male and female rats to chloroprene was associated with increased incidences of alveolar epithelial hyperplasia in the lung; nephropathy; and several nonneoplastic effects in the nose including olfactory epithelial atrophy, fibrosis, adenomatous hyperplasia, basal cell hyperplasia, chronic inflammation, respiratory metaplasia, and necrosis. Exposure of male and female mice to chloroprene was associated with increased incidences of bronchiolar hyperplasia and histiocytic cell infiltration in the lung; epithelial hyperplasia in the forestomach; renal

tubule hyperplasia (males only); several effects in the nose including olfactory epithelial atrophy, respiratory metaplasia, and adenomatous hyperplasia; and hematopoietic cell proliferation in the spleen.

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* Explanation of Levels of Evidence of Carcinogenic Activity is on page 14. A summary of the Technical Reports Review Subcommittee comments and the public discussion on this Technical Report appears on page 16.

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

	Male F344/N Rats	Female F344/N Rats	Male $B6C3F_1$ Mice	Female $B6C3F_1$ Mice
Exposure concentrations	0, 12.8, 32, or 80 ppm by inhalation	0, 12.8, 32, or 80 ppm by inhalation	0, 12.8, 32, or 80 ppm by inhalation	0, 12.8, 32, or 80 ppm by inhalation
Body weights	80 ppm group less than chamber control group	Exposed groups similar to chamber control group	Exposed groups similar to chamber control group	80 ppm group less than chamber control group
Survival rates	13/50, 9/50, 5/50, 4/50	29/49, 28/50, 26/50, 21/50	27/50, 27/50, 14/50, 13/50	35/50, 16/50, 1/50, 3/50
Nonneoplastic effects	Lung: alveolar epthelial hyperplasia (5/50, 16/50, 14/49, 25/50) Kidney: severity of nephropathy (2.8, 3.0, 3.1, 3.5) Nose (olfactory epithelium): atrophy (3/50, 12/50, 46/49, 48/49); fibrosis (0/50, 0/50, 0/49, 47/49); adenomatous hyperplasia (2/50, 0/50, 1/49, 42/49); basal cell hyperplasia (0/50, 0/50, 38/49, 46/49); chronic inflammation (0/50, 5/50, 9/49, 49/49); metaplasia (6/50, 5/50, 45/49, 48/49); necrosis (0/50, 11/50, 26/49, 19/49)	Lung: alveolar epithelial hyperplasia (6/49, 22/50, 22/50, 34/50) Kidney: severity of nephropathy (1.9, 2.0, 2.0, 2.2) Nose (olfactory epithelium): atrophy (0/49, 1/50, 40/50, 50/50); fibrosis (0/49, 0/50, 0/50, 49/50); adenomatous hyperplasia (0/49, 0/50, 0/50, 27/50); basal cell hyperplasia (0/49, 0/50, 17/50, 49/50); chronic inflammation (0/49, 0/50, 2/50, 33/50); metaplasia (0/49, 1/50, 35/50, 50/50); necrosis (0/49, 0/50, 8/50, 12/50)	Lung: bronchiolar hyperplasia (0/50, 10/50, 18/50, 23/50); histiocytic cell infiltration (7/50, 8/50, 11/50, 22/50) Forestomach: epithelial hyperplasia (4/50, 6/48, 7/49, 29/50) Kidney: renal tubule hyperplasia (0/50, 4/49, 5/50, 5/50) Nose (olfactory epithelium): atrophy (7/50, 8/48, 7/50, 49/50); metaplasia (6/50, 5/48, 5/50, 49/50); adenomatous hyperplasia (3/50, 2/48, 2/50, 48/50) Spleen: hematopoietic cell proliferation (26/50, 22/49, 35/50, 31/50)	Lung: bronchiolar hyperplasia (0/50, 15/49, 12/50, 30/50); histiocytic cell infiltration (1/50, 14/49, 18/50, 23/50) Forestomach: epithelial hyperplasia (4/50, 3/49, 8/49, 27/50) Nose (olfactory epithelium): atrophy (6/50, 5/49, 4/49, 47/50); metaplasia (2/50, 3/49, 1/49, 44/50); adenomatous hyperplasia (2/50, 3/49, 0/49, 44/50) Spleen: hematopoietic cell proliferation (13/50, 25/49, 42/49, 39/50)

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

	Male F344/N Rats	Female F344/N Rats	Male $B6C3F_1$ Mice	Female $B6C3F_1$ Mice
Neoplastic effects	Oral cavity: squamous cell papilloma (0/50, 2/50, 4/50, 10/50); squamous cell papilloma or squamous cell carcinoma (0/50, 2/50, 5/50, 12/50) Thyroid gland: follicular cell adenoma or carcinoma (0/50, 2/50, 4/49, 5/50) Lung: alveolar/ bronchiolar carcinoma (0/50, 2/50, 1/49, 4/50); alveolar/bronchiolar adenoma or carcinoma (2/50, 2/50, 4/49, 6/50) Kidney: renal tubule adenoma (extended evaluation - 1/50, 6/50, 6/50, 7/50; standard and extended evaluations combined - 1/50, 7/50, 6/50, 8/50); renal tubule adenoma or carcinoma (extended evaluation - 1/50, 7/50, 6/50, 7/50; standard and extended evaluations combined - 1/50, 8/50, 6/50, 8/50)	Oral cavity: squamous cell papilloma (1/49, 2/50, 2/50, 7/50); squamous cell papilloma or squamous cell carcinoma (1/49, 3/50, 5/50, 11/50) Thyroid gland: follicular cell adenoma or carcinoma (1/49, 1/50, 1/50, 5/50) Mammary gland: fibroadenoma (24/49, 32/50, 36/50, 36/50) Kidney: renal tubule adenoma or carcinoma (standard and extended evaluations combined - 0/49, 0/50, 0/50, 4/50)	Lung: alveolar/ bronchiolar adenoma (8/50, 18/50, 22/50, 28/50); alveolar/ bronchiolar carcinoma (6/50, 12/50, 23/50, 28/50); alveolar/ bronchiolar adenoma or carcinoma (13/50, 28/50, 36/50, 43/50) Circulatory system: hemangiosarcoma (3/50, 13/50, 22/50, 19/50); hemangiosarcoma (excludes liver) (1/50, 11/50, 16/50, 15/50); hemangioma or hemangiosarcoma (3/50, 14/50, 23/50, 21/50); hemangioma or hemangiosarcoma (excludes liver) (1/50, 12/50, 18/50, 17/50) Harderian gland: adenoma (2/50, 5/50, 8/50, 10/50); adenoma or carcinoma (2/50, 5/50, 10/50, 12/50) Forestomach: squamous cell papilloma (1/50, 0/50, 2/50, 4/50) Kidney: renal tubule adenoma (extended evaluation 0/50, 1/49, 2/50, 6/50); standard and extended evaluations combined - 0/50, 2/49, 3/50, 9/50)	Lung: alveolar/ bronchiolar adenoma (2/50, 16/49, 29/50, 26/50) alveolar/ bronchiolar carcinoma (2/50, 14/49, 16/50, 28/50); alveolar/ bronchiolar adenoma or carcinoma (4/50, 28/49, 34/50, 42/50) Circulatory system: hemangioma (0/50, 0/50, 2/50, 3/50); hemangiosarcoma (4/50, 6/50, 17/50, 5/50); hemangioma or hemangiosarcoma (4/50, 6/50, 18/50, 8/50) Harderian gland: adenoma (1/50, 3/50, 3/50, 8/50); adenoma or carcinoma (2/50, 5/50, 3/50, 9/50) Mammary gland: carcinoma (3/50, 4/50, 7/50, 12/50) Liver: hepatocellular carcinoma (4/50, 11/49, 14/50, 19/50); hepatocellular adenoma or carcinoma (20/50, 26/49, 20/50, 30/50) Skin: sarcoma (0/50, 11/50, 11/50, 18/50) Mesentery: sarcoma (0/50, 4/50, 8/50, 3/50) Forestomach: squamous cell papilloma or squamous cell carcinoma (1/50, 0/50, 0/50, 4/50) Zymbal's gland: carcinoma (0/50, 0/50, 0/50, 3/50)

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

	Male F344/N Rats	Female F344/N Rats	Male $B6C3F_1$ Mice	Female $B6C3F_1$ Mice
Uncertain findings	Urinary bladder: transitional epithelium carcinoma (0/50, 0/50, 1/50, 0/49); transitional epithelium papilloma (0/50, 0/50, 0/50, 1/49)	Urinary bladder: transitional epithelium carcinoma (0/49, 0/50, 0/50, 2/50) Lung: alveolar/ bronchiolar adenoma (1/49, 0/50, 0/50, 3/50)	None	None
Levels of evidence of carcinogenic activity	Clear evidence	Clear evidence	Clear evidence	Clear evidence
Genetic toxicology				
Salmonella typhimurium gene mutation:			Negative with and without S9 in strains TA98, TA100, TA1535, and TA1537	
Sex-linked recessive lethal mutations				
Drosophila melanogaster:			Negative	
Sister chromatid exchanges				
Mouse bone marrow cells *in vivo*:			Negative in male mice	
Chromosomal aberrations				
Mouse bone marrow cells *in vivo*:			Negative in male mice	
Micronucleated erythrocytes				
Mouse peripheral blood *in vivo* (12 exposures):			Negative in male mice	
Mouse peripheral blood *in vivo* (13-week exposure):			Negative in male and female mice	

EXPLANATION OF LEVELS OF EVIDENCE OF CARCINOGENIC ACTIVITY

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

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

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

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

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

NATIONAL TOXICOLOGY PROGRAM BOARD OF SCIENTIFIC COUNSELORS
TECHNICAL REPORTS REVIEW SUBCOMMITTEE

The members of the Technical Reports Review Subcommittee who evaluated the draft NTP Technical Report on chloroprene on 11 December 1996 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 11 December 1996, the draft Technical Report on the toxicity and carcinogenesis studies of chloroprene 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.L. Melnick, NIEHS, introduced the toxicology and carcinogenesis studies of chloroprene by discussing the uses of the chemical and rationale for study, describing the experimental design, reporting on survival and body weight effects, and reporting on compound-related neoplastic and nonneoplastic lesions in rats and mice. The proposed conclusions for the 2-year studies were *clear evidence of carcinogenic activity* in male and female F344/N rats and B6C3F_1 mice.

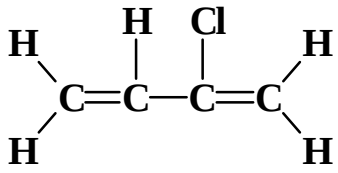
Dr. Ward, a principal reviewer, agreed with the proposed conclusions. He commented that there were many nonneoplastic lesions in the nasal cavity of rats and mice but no nasal neoplasms. He stated that the Discussion section should indicate that many toxic and reparative nasal lesions did not lead to neoplasms, in regard to a current theory/hypothesis that chronic lesions may lead to cancer. Dr. Ward said it was important to know whether the hyperplasias in many organs were focal or diffuse. Dr. Melnick said most of the hyperplasias were focal and this would be emphasized in the text. Because so many tissues were involved, Dr. Ward suggested an additional summary table for comparison to 1,3-butadiene, which might list target organs of toxicity and carcinogenesis. Dr. Melnick agreed.

Dr. Goldsworthy, the second principal reviewer, agreed with the proposed conclusions. He noted the significant changes in survival and body weights that occurred during the study. Dr. Goldsworthy thought the differing decreases in body weights between exposure concentrations might call into question the numbers derived from the dose-response curves. Additionally, he asked for clarification of the impact of *Helicobacter* infection on the interpretation of hepatocellular neoplasms and liver hemangiomas in male mice (see Appendix O).

Dr. Russo, the third principal reviewer, agreed with the proposed conclusions.

Dr. Goldsworthy moved that the Technical Report on chloroprene be accepted with the revisions discussed and with the conclusions as written for male and female rats and mice, *clear evidence of carcinogenic activity*. Dr. Russo seconded the motion, which was accepted unanimously with nine votes.

INTRODUCTION



CHLOROPRENE

CAS No. 126-99-8

Chemical Formula: C_4H_5Cl Molecular Weight: 88.54

Synonyms: Chlorobutadiene; 2-chlorobuta-1,3-diene; 2-chloro-1,3-butadiene; β-chloroprene

CHEMICAL AND PHYSICAL PROPERTIES

Chloroprene is a pungent-smelling, ether-like, colorless, flammable liquid with a boiling point of 59.4° C, a specific gravity of 0.9583 at 20° C, and a vapor pressure of 188 mm Hg at 20° C. It is soluble in ether, acetone, benzene, and most organic solvents and is slightly soluble in water. Chloroprene has a flash point of –20° C and an explosive limit of 4% to 20% in air and is therefore highly flammable (IARC, 1979; *Patty's*, 1981; *Hawley's*, 1987). Chloroprene is highly reactive, forming peroxides and spontaneously polymerizing at room temperature and in the presence of oxygen (Stewart, 1971).

PRODUCTION, USE, AND HUMAN EXPOSURE

Chloroprene is produced by the addition of hydrochloric acid to dimerized acetylene or by the chlorination of 1,3-butadiene (IARC, 1979; *Hawley's*, 1987). Large volumes of chloroprene are produced for industrial use; cumulative annual production in Japan, Western Europe, and the United States in 1989 was approximately 880 million pounds (Weissermel and Arpe, 1990).

Chloroprene is used almost exclusively as an intermediate in the production of polychloroprene elastomer (neoprene). Polychloroprene is used in automotive rubber goods, wire and cable coatings, construction applications, fabric coatings, cements, sealants, and adhesives (IARC, 1979; ACGIH, 1985; *Hawley's*, 1987). The United States Food and Drug Administration permits the use of polychloroprene as a component of coatings and in rubber articles intended for use in contact with food (CFR 21 §§ 175.105, 175.300, 177.2600). Polychloroprene may contain up to 0.5% free chloroprene (ACGIH, 1986).

The main sources of environmental releases of chloroprene are probably the effluent and emmissions from facilities that produce chloroprene or polychloroprene elastomers. Volatilization is the predominant mechanism of removal of chloroprene from water. Chloroprene's fate in the atmosphere may follow one of two paths: reaction with photochemically generated hydroxyl radicals or reaction with ozone (ACGIH, 1985). Reaction of chloroprene with hydroxyl radicals or ozone may form formaldehyde, 1-chloroacrolein, glyoxal, chloroglyoxal, and chlorohydroxy acids or other aldehydes.

The most probable route of human exposure to chloroprene is inhalation by workers employed in the manufacture of chloroprene or polychloroprene. Human exposure may also occur through ingestion or by contact with the skin or eye (IARC, 1979). In 1977 an estimated 2,500 to 3,000 workers were exposed to chloroprene during its manufacture and polymerization; potential concentrations were as high as 6,760 ppm in some polymerization areas (Infante *et al.*, 1977). The National Occupational Exposure Survey estimated that from 1981 through 1983, approximately 17,700 workers were occupationally exposed to chloroprene (NIOSH, 1990a). Chloroprene is an irritant to the eyes, skin, and mucous membranes of the respiratory tract and may also cause temporary hair loss. Chloroprene may also affect the central nervous system, liver, kidneys, myocardium, and digestive system (*Patty's*, 1981; Sittig, 1985; ACGIH, 1986). In 1980, based on results from rodent studies, the American Conference of Governmental Industrial Hygienists lowered the recommended threshold limit value for chloroprene in the work environment from 25 ppm to 10 ppm (36 mg/m^3) (ACGIH, 1996). The Occupational Safety and Health Administration has set the occupational exposure standard for chloroprene at 25 ppm, based largely on results of 4-week inhalation toxicity studies in rats and hamsters (Clary *et al.*, 1978). NIOSH recommends a 15-minute ceiling value of 1 ppm (3.6 mg/m^3) (NIOSH, 1990b).

ABSORPTION, DISTRIBUTION, METABOLISM, AND EXCRETION

Chloroprene may be absorbed from the skin, lungs, and gastrointestinal tract (ACGIH, 1985). The wide distribution of chloroprene or its metabolites in the body is evidenced by the numerous target sites of acute or subchronic exposure: liver, lungs, spleen, central nervous system, kidneys, epicardium, testes, and bone marrow (ACGIH, 1985).

There have been no conclusive studies on the metabolic fate of chloroprene. It has been suggested that chloroprene metabolism may follow a pathway similar to that of vinyl chloride, with 2-chloro-1,2-epoxybutene-3 and 2-chloro-3,4-epoxybutene-1 formed as intermediates. These epoxide intermediates may then be detoxified by glutathione conjugation (Haley, 1978). This hypothesis is supported by the work of Summer and Greim (1980), who observed rapid depletion of hepatic glutathione and elevated excretion of urinary thioethers in rats administered 200 mg/kg chloroprene in olive oil by gavage. The epoxide intermediate may also be detoxified by epoxide hydrolase (Plugge and Jaeger, 1979).

TOXICITY

Experimental Animals

The oral LD_{50} for chloroprene is 251 mg/kg body weight in rats and 260 mg/kg in mice (Asmagulian and Badalian, 1971). In rats, the approximate LC_{50} of chloroprene for a 4-hour inhalation exposure is 2,280 ppm (Clary *et al.*, 1978). A study by von Oettingen *et al.* (1936) reported a minimum lethal dose of 2.5 mg/L (700 ppm) in cats administered chloroprene by inhalation for 8 hours; death occurred 1 to 3 hours after exposure ended. The International Technical Information Institute (1981) lists 8-hour inhalation LC_{100} values of 165 ppm for rats, 825 ppm for mice, 355 ppm for cats, and 1,064 ppm for rabbits and a subcutaneous injection LC_{LO} value of 1,450 mg chloroprene/kg body weight for mice.

The brain, kidney, liver, lung, heart, and testis have been identified as target organs of chloroprene toxicity. Plugge and Jaeger (1979) observed liver injury, evidenced by increased serum sorbitol dehydrogenase activity, in male Sprague-Dawley rats exposed to 225 or 300 ppm chloroprene by inhalation for 4 hours and necropsied 24 hours after exposure ended. Liver nonprotein sulfhydryl concentrations were increased in fasted rats exposed to 100, 150, 225, or 300 ppm, and serum lactate dehydrogenase activity was increased in rats exposed to 300 ppm. Lung nonprotein sulfhydryl concentrations were decreased in the 100 and 300 ppm groups; no other evidence of lung injury was observed.

In 4-week inhalation studies (6 hours per day, 5 days per week) conducted by Clary *et al.* (1978), signs of toxicity were observed in male and female Wistar rats and Syrian golden hamsters exposed to 40, 160, or 625 ppm chloroprene, and chemical-related deaths occurred in both species in the 160 and 625 ppm groups. In the 625 ppm groups of each species, signs of toxicity included eye irritation, restlessness, lethargy, nasal discharge, orange urine, hair loss, and reduced body weight gains. Body weights of rats were

less in all exposed groups than in the controls. Hematology and urinalysis parameters were not affected significantly by exposure to chloroprene. Chloroprene exposure produced significant changes in kidney, liver, and lung weights of male and female rats and hamsters. Gross examination of animals that died during exposure revealed that livers were dark and swollen and lungs were grayish with hemorrhagic areas; livers of several rats and hamsters in the 625 ppm groups that survived until the end of the studies were also dark and swollen. Microscopic examination revealed slight to severe centrilobular degeneration and necrosis in the livers in 10 of 10 male rats and 8 of 10 female rats exposed to 625 ppm and in two of the three male rats exposed to 160 ppm that died before the end of the study. The mucous membrane of the nasal cavity of exposed hamsters was irritated, and the lungs of rats that died early exhibited small hemorrhages and perivascular edema. Renal tubule epithelial degeneration was also observed in exposed rats.

Nyström (1948) tested the effect of inhalation of 1,400 ppm chloroprene (5 mg/L air) for 6 hours on renal function in a group of five milk-fed rats. By the fourth day after exposure, urea nitrogen clearance was reduced, with values returning to normal by the fourteenth day of exposure. Jaeger *et al*. (1975a,b) found that fasted adult male Holtzman rats were markedly more sensitive to chloroprene hepatotoxicity than were exposed rats fed *ad libitum*. Additionally, rats were more sensitive to chloroprene exposure at night, when glutathione concentrations were low (Jaeger *et al.*, 1975a).

Inhalation of 0.56 or 3 mg chloroprene/m^3 (0.16 or 0.8 ppm chloroprene) by rats for 6 months was reported to result in damage to the cerebral cortex, Ammon's horn, corpora quadrigemina, optic thalamus, and pons and to produce hyperemia of the brain, cell shriveling, pyknotic nuclei, karyolysis, and decomposition of cytoplasm (Mnatsakanyan, 1965).

In toxicity studies reviewed by Haley (1978), dogs exposed to 8 to 20 mL/L (7.7 to 19.2 mg/m^3) chloroprene by inhalation developed jaundice. Chronic inhalation of chloroprene by dogs produced decreased blood glucose concentration, increased blood pyruvate concentration, excitation, mydriasis, convulsions, muscle atonia, hemoptysis, and narcosis and death from pulmonary edema. Changes in higher nervous activity, the cells of the cerebral cortex, and brain vasculature, as well as decreases in serum cholinesterase activity, have been observed following chronic inhalation exposure of dogs to chloroprene.

Thirteen-week inhalation toxicology studies were conducted in male and female F344/N rats and $B6C3F_1$ mice at exposure concentrations of 0, 5, 12, 32, and 80 ppm (6 hours per day, 5 days per week; Melnick *et al.*, 1996a). A 200 ppm exposure group was also included for rats only. In rats, exposure to 80 or 200 ppm chloroprene caused degeneration and metaplasia of the olfactory epithelium, while anemia, hepatocellular necrosis, and reduced sperm motility were seen only in the 200 ppm group. In mice, exposure to 80 ppm chloroprene caused a marginal decrease in body weight gain in males and epithelial hyperplasia of the forestomach in males and females. The complete results of these studies are presented in this Technical Report.

Humans

Symptoms of acute exposure to high concentrations of chloroprene in air include central nervous system depression; injury to the lung, liver, and kidney; skin and mucous membrane irritation; and respiratory difficulties (Nyström, 1948; Irish, 1963). Contact with chloroprene and its polymers may also produce hair loss and dermatitis (Schwartz, 1945; Nyström, 1948; Ritter and Carter, 1948; Volkova, 1971). Chloroprene exposure (0.3 to 0.48 mg/L; 83 to 133 ppm) was reported to induce diuresis and increased 17-ketosteroid concentrations in Soviet children (Mnatsakanyan, 1966). Arevshatyan (1972) also reported periodontal changes in workers exposed to chloroprene.

Reports of chronic exposure to chloroprene cite effects on blood morphology and the cardiovascular system and on liver, lung, kidney, and nervous function, as well as corneal conjunctivitis and focal necrosis, nausea, indigestion, and loss of appetite (ITII, 1981). Studies by Volkova (1976) and Bagdinov (1973) cited in Sanotskii (1976) reported decreased erythrocyte, leukocyte, and thrombocyte counts in workers at a chloroprene production facility. There was a particularly sharp decrease in thrombocyte counts of women who had worked at the facility from 1 to 5 years. In addition, hemoglobin concentrations were often reduced below the normal range. Cardiovascular effects included tachycardia, reduced arterial pressure,

and muffled heart sounds. Liver effects include hepatomegaly, toxic hepatitis, and decreased liver function (Orlova and Solovyova, 1962; Bagdinov, 1973; Volkova, 1976; NIOSH, unpublished). Gooch and Hawn (1981) found no clinically significant hematologic or biochemical alterations in workers exposed to chloroprene at a DuPont chemical facility.

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

Experimental Animals

Soviet researchers have reported that chloroprene is embryotoxic and teratogenic at concentrations below 1 ppm (IARC, 1979). Sal'nikova (1968) and Sal'nikova and Fomenko (1973) exposed pregnant rats and mice to chloroprene concentrations between 15 ppb and 4.1 ppm by inhalation; concentrations of 36 ppb and greater were reported to be embryotoxic. Maternal exposure to chloroprene was also linked to decreased pup survival prior to weaning and low pup body weights at weaning. In a review of the Soviet literature, Sanotskii (1976) reported that male white rats exposed to 1.7 mg/m^3 (0.5 ppm) chloroprene for 4.5 months had decreased numbers of normal sperm, decreased sperm motility, and increased numbers of dead sperm. Sanotskii (1976) also reported an increase in the number of seminiferous tubules with desquamating epithelium in male C57BL/6 mice exposed to 0.32 mg/m^3 (0.09 ppm) for 2 months and increased dominant lethal mutations in germ cells of male and female C57BL/6 mice exposed to 3.5 mg/m^3 (1 ppm) for 2 months. Exposure of pregnant white rats to 4 mg/m^3 (1.1 ppm) produced decreased fetal body weights and increased fetal death.

Other reports do not support or agree with the Soviet findings. Culik *et al.* (1978) observed slight increases in resorptions and fetal body lengths in litters of ChR-CD rats exposed to 10 ppm and in fetal body weights and lengths in litters of dams exposed to 25 ppm chloroprene by inhalation, 4 hours per day, from gestation days 3 to 20; however, these authors observed no other reproductive or developmental effects in a series of teratology, embryotoxicity, and reproductive toxicity studies at exposures up to 25 ppm chloroprene. Exposure of pregnant New Zealand white rabbits to 10, 40, or 175 ppm chloroprene vapor, 6 hours per day, 7 days per week, on gestation days 6 through 28 produced no observable toxic effects to the dam or the offspring (Mast *et al.*, 1994).

Humans

Chloroprene exposure has been reported to affect male reproductive function; however, many of these reports cite the same Russian study, Fomenko (1974). Sanotskii's (1976) review of this study stated that examination of chloroprene workers revealed functional disturbances in spermatogenesis after 6 to 10 years of work in chloroprene production and morphological abnormalities of sperm after 11 or more years. Cases of spontaneous abortion in the wives of chloroprene workers occurred more than three times as often as in the control group. Sanotskii (1976) also cited reports of congenital abnormalities in the children of women working in a chloroprene factory and cases of pregnancies "taking an unfavorable course" in women working with chloroprene latex. However, the methods used to gather data in these studies have been questioned (ACGIH, 1985).

CARCINOGENICITY

Experimental Animals

Chloroprene is the 2-chloro analogue of 1,3-butadiene, a chemical which was shown by NTP to be a potent multi-organ carcinogen in mice exposed by inhalation (Huff *et al.*, 1985; Melnick *et al.*, 1990a; NTP, 1993). Qinan *et al*. (1989) exposed Kunming albino mice to 0, 2.9, 19, or 189 mg chloroprene/m^3 by inhalation (0, 0.8, 5.3, or 53 ppm, respectively), 4 hours per day, 6 days per week, for 7 months. All surviving mice were killed at the end of the eighth month of the study. Compared to controls, exposed mice developed a significantly greater number of lung tumors (1.3%, 8.1%, 9.4%, and 19.7% in the respective groups). Tumor multiplicity was significantly increased in the 189 mg/m^3 group. Most of these tumors were papilloadenomas, although a few were adenomas.

The USEPA summarized a study by Zil'fian and Fichidzhyan (1972), who investigated the effect of chloroprene administration in 60 mixed-breed white mice. Groups of 30 mice received either 0.1 mg/g peach oil subcutaneously or transplanted Crocker murine sarcoma cells in suspension in 0.1 mg/g peach oil. In the latter group, chloroprene administration was

found to increase neoplasm growth. This effect was attributed to an immunosuppressive activity of chloroprene.

Menezes *et al*. (1979) transplanted chloroprene-treated (1, 10, or 100 mg/mL for 42 days) and untreated cultured hamster lung cells subcutaneously into newly born hamsters and intraocularly into adult hamsters. Untreated cells did not produce neoplasms; however, cells treated with 1 mg chloroprene/mL produced fibrosarcomas within 14 weeks. Sills *et al*. (1993) found that several types of neoplasms from chloroprene-treated B6C3F_1 mice were positive for the protein product of the mutated p53 tumor suppressor gene.

Zil'fian *et al*. (1975) found no induction of neoplasms in mice receiving skin applications of chloroprene or in rats dosed subcutaneously or by intragastric gavage. Ponomarkov and Tomatis (1980) dosed female DB IV rats with 100 mg chloroprene/kg in olive oil by gavage on gestation day 17 and dosed their offspring with 50 mg/kg by stomach tube for their life span after weaning. Although exposed rats had higher incidences of subcutaneous fibroma, chloroprene administration did not affect overall neoplasm incidences.

Humans

In a study of the relationship between industrial chemical exposure and lung cancer risk, Khachatrian (1972a) found that workers were 2.67 times less likely to develop lung cancer if they had not worked with chloroprene-related chemicals. Khachatrian (1972b) also found a correlation between the incidence of skin cancer and degree of exposure to chloroprene; an inverse relationship was found between degree of exposure and age at diagnosis of skin cancer. Khachatrian's (1972a,b) methodology has been criticized (IARC, 1979). Pell (1978) reported increased incidences of digestive, lymphatic, and hematopoietic cancer in chloroprene workers at two DuPont plants. Pell (1978) did not distinguish between chloroprene manufacturing and polychloroprene manufacturing or attempt to control for confounding variables such as prior occupational exposure to other chemicals.

Herbert (1976) reported a case of liver angiosarcoma in a man who had worked for 15 years with liquid polychloroprene (which may contain up to 5,000 ppm chloroprene) or with finished polychloroprene. Concentrations between 0.14 and 0.2 ppm were measured in the air at the man's place of work. The individual had no prior exposure to any chemicals linked to this particular neoplasm (e.g., vinyl chloride). Although information on the carcinogenicity of chloroprene is limited, this singular occurrence was considered a potential health concern due to the rarity of liver angiosarcoma in the general population and the structural similarity between chloroprene and vinyl chloride (Infante *et al.*, 1977). In both case control and cohort studies in China of workers exposed to chloroprene, Shouqi *et al*. (1989) found a significant correlation between cancer deaths and exposure to chloroprene. Maintenance mechanics had the highest risk of cancer. Standardized mortality ratios for liver, lung, and lymphatic cancers were significantly elevated in this group.

GENETIC TOXICITY

Results of mutagenicity tests with chloroprene appear to indicate little mutagenic activity, but the inconsistency among laboratories in the weakly positive responses noted in some tests complicate an assessment of the overall genetic toxicity profile of chloroprene. Chloroprene was reported to be mutagenic, with and without metabolic activation with induced liver S9 enzymes, to *Salmonella typhimurium* strains TA100 (Bartsch *et al.*, 1975) and TA1530 (Bartsch *et al.*, 1979); in these investigations, the level of mutagenic activity was enhanced by the addition of S9. In contrast, Zeiger *et al*. (1987) found no evidence of mutagenic activity for chloroprene in four strains of *S. typhimurium*, including strain TA100. More recently, Westphal *et al*. (1994), using a modified preincubation protocol to control for the volatility of chloroprene, reported no mutagenic activity for freshly distilled chloroprene (highly pure) in strain TA100; however, an S9-independent mutagenic response that correlated directly with the age of older aliquots of chloroprene was observed with and without volatility control. Westphal *et al*. (1994) attributed the increasing mutagenicity of aged chloroprene samples to the accumulation of several decomposition products in the chloroprene distillate, notably cyclic chloroprene dimers, which were identified by gas chromatography/mass spectrometry. Like Bartsch *et al*. (1975, 1979), Westphal *et al*. (1994) found that S9 enhanced the mutagenic response of *S. typhimurium* strain TA100 to aged chloroprene. In eukaryotic test systems,

chloroprene was not mutagenic in cultured V79 Chinese hamster cells (Drevon and Kuroki, 1979). It gave conflicting responses in *Drosophila* sex-linked recessive lethal assays; Vogel (1979) reported weakly positive results in a feeding study conducted within a sealed desiccator, and, more recently, Foureman *et al*. (1994) reported no significant increase in sex-linked recessive lethal mutations in germ cells of male flies exposed to chloroprene through feeding or injection. Foureman *et al*. (1994) also provided a thorough discussion of the possible reasons for the discordant results obtained between the two laboratories in this assay, including differences in chloroprene purity, *Drosophila* strain tested, statistical methods of data analysis, and sample size.

In mammalian systems *in vivo*, chloroprene, administered by inhalation at concentrations from 0.036 to 0.97 ppm for 2 months, was reported to induce dominant lethal mutations in germ cells of male rats and mice and chromosomal aberrations in bone marrow cells of C57BL/6 mice (Sanotskii, 1976). A more recent study of the *in vivo* mutagenic activity of chloroprene showed no effects on the frequencies of sister chromatid exchanges, chromosomal aberrations, or micronucleated erythrocytes in bone marrow or peripheral blood of $B6C3F_1$ mice exposed for 12 days to chloroprene at concentrations of 12, 32, or 80 ppm (Tice *et al.*, 1988). Results of a second micronucleus assay in male and female mice after 90 days of exposure to chloroprene (5 to 80 ppm) by inhalation were also negative. The differences in bone marrow chromosomal effects between these studies and those of Sanotskii (1976) may have been the result of strain-related differences in chloroprene tissue distribution and detoxification processes or of variations in experimental protocols, including the age of the chloroprene.

STUDY RATIONALE

Chloroprene was chosen for study by the National Toxicology Program because it is a high-volume production chemical and because information on its carcinogenic potential in experimental animals and humans was limited. In addition, chloroprene is the 2-chloro analogue of 1,3-butadiene, a potent multi-organ carcinogen in rats and mice, which has consistently been associated with increased risk of lymphatic and hematopoietic cancers in occupationally exposed workers. Thus, the results of the current studies allow assessment of the effects of the chlorine substitution on the carcinogenicity of 1,3-butadiene. Inhalation was chosen as the route of exposure because it is the most likely route of human exposure.

MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF CHLOROPRENE

Chloroprene was obtained for the 16-day and 13-week studies from Denka Chemical Company (Houston, TX) in five lots. Chloroprene for the 2-year studies was supplied by Mobay Synthetic Corporation (Houston, TX) in 12 lots. Identity, purity, and stability studies of lot 12103-4-1, from the first shipment of chloroprene to the study laboratory, were performed by the analytical chemistry laboratory, Midwest Research Institute (Kansas City, MO) (Appendix K). Reports on the analyses conducted by the analytical chemistry laboratory and performed in support of the chloroprene studies are on file at the National Institute of Environmental Health Sciences. Subsequent purity and identity analyses of chloroprene lots were performed by the study laboratory.

The chemical, a clear colorless liquid, was identified as chloroprene by infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopy and by boiling point and density. The purity of lot 12103-4-1 was determined by elemental analysis, Karl Fischer water analysis, approximation of *t*-butylcatechol, thin-layer chromatography, and gas chromatography. Peroxide concentration was analyzed for lot 12103-4-1. Elemental analyses for carbon, hydrogen, and chlorine agreed with the theoretical values for chloroprene. Karl Fischer water analysis indicated less than 0.01% water. Approximation of *t*-butylcatechol inhibitor indicated 40 to 50 ppm. Thin-layer chromatography indicated one major spot. Thin-layer chromatography of a second sample left at room temperature overnight revealed another spot in addition to the major spot. Gas chromatography by one system indicated four impurities with a cumulative peak area of 0.96% relative to the major peak; gas chromatography by a second system indicated six impurities with a total area of 3.30% relative to the major peak area. Gas chromatography/mass spectrometry identified six impurities: chlorobutene, chlorobutadiene, toluene, and three chloroprene dimers. Five additional impurity peaks with areas less than 0.1% were also observed. Titration for peroxide indicated 1.96 ± 0.06 mEq peroxide per kilogram of sample. The overall purity was determined to be approximately 96%.

The remaining lots were identified by the study laboratory as chloroprene by infrared spectroscopy. Purity of the remaining lots was determined by the laboratory using gas chromatography; all lots exceeded the 96% purity minimum required by the study design.

Chloroprene received for the 16-day and 13-week studies was fortified at the study laboratory with 0.1% each of the stabilizers phenothiazine and *t*-butylcatechol. Chloroprene received for the 2-year studies was procured with 0.1% of each stabilizer added by the producer.

Stability was monitored by the study laboratory throughout the studies by gas chromatography using flame ionization detection and titration for peroxides. The concentrations of the stabilizers phenothiazine and *t*-butylcatechol were also determined with gas chromatography. No degradation of the bulk chemical was detected; all lots used during the studies had less than 1 mEq peroxide per kilogram. The stabilizer concentrations were acceptable. To ensure stability, the bulk chemical was stored under a nitrogen headspace in the original containers at approximately 20° C.

VAPOR GENERATION AND EXPOSURE SYSTEM

The vapor generation system consisted of an evaporation flask in a hot-water bath (72° C, 16-day studies; 66° C, 13-week and 2-year studies) and a temperature-controlled, cooled condenser column. The chloroprene vapor was pumped at a steady rate from a dry-ice-chilled reservoir into the rotating flask (16-day studies) or held covered under a positive nitrogen headspace (13-week and 2-year studies). A calibrated flow of nitrogen was metered into the base of the cooled condenser column, which was attached to the flask, and carried vapor rising from the flask

through the condenser. The vapor temperature was controlled by a thermostat set to 1° C to return to the flask any components boiling at a higher temperature than chloroprene. The temperature of the remaining chloroprene-saturated nitrogen vapor was monitored by a sensor at the top of the column; the vapor pressure was calculated and used to determine the vapor output. Detailed descriptions of the inhalation suites and vapor generation system are provided in Appendix K.

Vapor entering the distribution manifold was diluted with HEPA- and charcoal-filtered air (16-day and 13-week studies) or with additional nitrogen (2-year studies). Flow to each chamber was controlled by compressed-air-driven vacuum pumps; vapor flowed through separate metering valves for each exposure chamber and was diluted with air before entering the chamber.

The study laboratory designed the stainless steel inhalation exposure chambers (Hazleton H-2000®, Harford Systems Division of Lab Products, Inc., Aberdeen, MD) so that uniform vapor concentrations could be maintained throughout the chamber when catch pans were in place. A small particle detector (Type CN, Gardner Associates, Schenectady, NY) was used with and without animals in the exposure chambers to ensure that chloroprene vapor, and not aerosol, was produced. No particle counts above the minimum resolvable level (approximately 200 particles/cm^3) were detected.

VAPOR CONCENTRATION MONITORING

Chamber concentrations of chloroprene were monitored by an on-line gas chromatograph. Samples were drawn from the exposure chambers at least once every hour by a 12-port stream selection valve. During the 16-day and 2-year studies, samples from the distribution line were monitored for purity with a second gas chromatograph; during the 13-week studies, distribution line samples were monitored by the same gas chromatograph that was used to monitor the exposure chambers. The on-line chromatograph was calibrated based on qualitative analysis of grab samples collected in dimethylformaldehyde-filled bubblers. Results were compared to those of an off-line gas chromatograph calibrated with gravimetrically prepared chloroprene standards in dimethylformaldehyde. Chamber concentration uniformity was maintained throughout the studies. Summaries of the chamber concentrations for the 16-day, 13-week, and 2-year studies are listed in Tables K1 through K3.

CHAMBER ATMOSPHERE CHARACTERIZATION

The times for the exposure concentration to build up to 90% of the final exposure concentration (T_{90}) and to decay to 10% of the exposure concentration (T_{10}) were measured in all studies with and without animals present. For the various studies, these values ranged from 7 to 15 minutes. The T_{90} used during all the studies was 12 minutes.

Studies of chloroprene degradation and monitoring for impurities, inhibitors, and stabilizers were conducted throughout the 13-week and 2-year studies by analyzing bubbler samples with gas chromatography or with a fluorescence detector. No significant degradation of chloroprene was observed during the studies.

16-DAY STUDIES

Male and female F344/N rats and B6C3F_1 mice were obtained from Taconic Farms (Germantown, NY). On receipt, the rats and mice were 4 to 5 weeks old. Animals were quarantined for 10 to 13 days and were 6 to 7 weeks old at the beginning of the studies. Groups of 10 male and 10 female rats and mice were exposed to chloroprene by inhalation at concentrations of 0, 32, 80, 200, or 500 ppm (rats) or 0, 12, 32, 80, or 200 ppm (mice). Additional groups of 10 male and 10 female mice designated for day 5 hematology and clinical chemistry analyses were exposed to 0, 12, 32, 80, or 200 ppm chloroprene. Rats and mice were exposed for 6 hours plus T_{90} (12 minutes) per day, 5 days per week, for 16 days. Feed was available *ad libitum* except during exposure periods and urine collection periods, and water was available *ad libitum*. Rats and mice were housed individually. Clinical findings were recorded twice daily. Animals were weighed initially, after one week, and at the end of the studies. Details of the study design and animal maintenance are summarized in Table 1.

On day 4 of exposure, rats were placed in metabolism cages for 16-hour urine collection. Specific gravity was determined with an A/O refractometer, urine

protein concentration was determined using the Coomassie blue reaction, and thioethers were measured as described by Summer *et al*. (1979). All other urine parameters were measured using Abbott VP (Abbott Laboratories, Abbott Park, IL) methodologies. At the end of the urine collection period, rats were anesthetized with 70% CO_2 and blood was collected from the retroorbital sinus for hematology and clinical chemistry analyses. On exposure day 8, mice designated for hematology and clinical chemistry analyses were anesthetized with 70% CO_2 and blood was collected from the retroorbital sinus. Blood for hematology determinations was placed in tubes containing potassium EDTA as an anticoagulant and the analyses were performed with an Ortho ELT-8/ds hematology analyzer (Ortho Instruments, Westwood, MA). Blood smears were stained with Wright/Giemsa stain. The Miller disc method was used to determine the reticulocyte count. Blood for clinical chemistry analyses was placed in tubes with no anticoagulant; Abbott VP methodologies were used to perform the serum chemistry analyses. The hematology and clinical chemistry parameters measured are listed in Table 1.

A necropsy was performed on all core animals. The brain, heart, right kidney, liver, lungs, spleen, thymus, and right testis were weighed. Histopathologic examinations were performed on chamber controls, 80 ppm female rats, 200 and 500 ppm male and female rats, and 80 and 200 ppm male and female mice. Histopathologic examination was also performed on all target organs in other exposure groups to a no-effect level. Table 1 lists the tissues and organs examined.

13-WEEK STUDIES

The 13-week studies were conducted to evaluate the cumulative toxic effects of repeated exposure to chloroprene 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 Farms (Germantown, NY). On receipt, the rats and mice were 4 to 5 weeks old. Animals were quarantined for 12 to 15 days and were 6 to 7 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 sentinel rats and mice using the protocols of the NTP Sentinel Animal Program (Appendix M).

Groups of 10 male and 10 female rats were exposed to chloroprene by inhalation at concentrations of 0, 5, 12, 32, 80, or 200 ppm (core study). Groups of 10 male and 10 female mice were exposed to chloroprene at concentrations of 0, 5, 12, 32, or 80 ppm (core study). Additional study groups of 10 male and 10 female rats designated for clinical pathology analyses were exposed to 0, 5, 12, 32, 80, or 200 ppm. Additional study groups of five male and five female rats exposed to 0, 5, 32, or 200 ppm and groups of five male and five female mice exposed to 0, 12, 32, or 80 ppm were designated for tissue glutathione studies. Additional study groups of 10 male and 10 female rats were exposed to 0, 32, 80, or 200 ppm for a coagulation study and for day 2 hematology analyses. Rats and mice were exposed for 6 hours plus T_{90} (12 minutes) per day, 5 days per week, for 13 weeks. Feed was available *ad libitum* except during exposure and urine collection periods, and water was available *ad libitum*. Rats and mice were housed individually. Clinical findings were recorded weekly for rats and mice. The animals were weighed initially, weekly, and at the end of the studies. Blood for hematology and clinical chemistry analyses was collected from the supraorbital sinus of all mice surviving to the end of the study. On day 22 and prior to the end of the study, male and female rats designated for clinical pathology analyses were placed in metabolism cages for 16-hour urine collection. Urinalysis methodologies were similar to those described for the 16-day studies. After urine collection, animals were anesthetized and blood was collected from the retroorbital sinus for hematology and clinical chemistry analyses. Rats were discarded after the final blood collection. For hematology analyses, samples were collected in containers containing EDTA as an anticoagulant. For clinical chemistry, samples were collected in tubes with no anticoagulant. Erythrocyte, leukocyte, and platelet counts; hemoglobin concentrations; volume of packed red cells; mean cell volume; mean cell hemoglobin; and mean cell hemoglobin concentration were measured with an Ortho ELT-8/ds hematology analyzer. Blood smears were stained with Wright/Giemsa; differential leukocyte counts were based on classifying a minimum of 100 white cells. Reticulocytes were enumerated as a reticulocyte/erythrocyte ratio using the Miller disc

method. Clinical chemistry parameters were measured using Abbott VP methodologies. The hematology and clinical chemistry parameters measured are listed in Table 1.

Rats and mice designated for tissue glutathione studies were killed after the first day of exposure or at week 13. The kidney, liver, lung, and thymus were removed from rats and mice designated for tissue glutathione assays for determination of tissue nonprotein sulfhydryl (glutathione) concentrations and total sulfhydryl concentrations. The assay methods for nonprotein sulfhydryl and total sulfhydryl concentrations were similar to those described by Ellman (1959) as modified by Sedlak and Lindsay (1968).

After two days of exposure, blood was collected from supplemental groups designated for coagulation studies. Blood samples were also collected for day 2 hematology analyses. Rats were anesthetized with intraperitoneal pentobarbital sodium, and samples were collected from the lumbar aorta using plastic syringes and placed in tubes containing potassium EDTA as an anticoagulant for hematology and tubes containing 3.8% sodium citrate for the coagulation tests. Prothrombin times and activated partial thromboplastin times were quantitated using a BBL Fibrinometer and Dade methodologies. Commercial kits (Dade) were used for the measurement of euglobulin lysis times and fibrinogen concentrations.

At week 11, all surviving male and female core study rats were administered neurobehavioral tests. Motor activity and exploration/habituation were assessed using New Standard Systems residential mazes. Residential mazes allow the automated measure of horizontal and vertical activity by infrared sensors located throughout the maze. To preclude disturbance of rats during testing, mazes were housed in soundproof cabinets. Motor activity was measured for each rat during a 1-hour session. Forelimb and hindlimb grip strengths were measured on a horizontal platform with calibrated push-pull strain gauges mounted at each end. A rectangular forelimb grip bar was attached to one gauge, and a hindlimb T-bar was attached to the other gauge. Rats were allowed to grip the forelimb grip bar with their front paws and were pulled along the platform until their grip was broken. As the backward motion continued, the rat's hindpaws reached the T-shaped hindlimb grip bar, which it was allowed to grip and then forced to release by further pulling. Gauge needle deflections (grams) were recorded for each trial. The mean of three trials (both forelimb and hindlimb grip strength) for each rat was recorded as the score.

A Socrel Tail Flick Analgesiometer (Socrel, Varese, Italy) was used to conduct the thermal sensitivity measurements. The apparatus consisted of an infrared heat source (100-W bulb) focused by a parabolic mirror on a photocell. Each rat was placed with its tail on the photocell window, occluding the beam. A foot peddle was depressed to activate the heat source and a timer. When the rat flicked its tail out of the path of the beam, the photocell was energized, turning off the timer and the heat source. The time to remove (flick) the tail was recorded in seconds. The startle response to acoustic stimulation was measured using an SR-Lab Startle Response System (SRI, Scientific and Professional Support Group, La Jolla, CA). During test sessions, individual rats were placed in the system, which was then placed in a soundproof cabinet. Following a 3-minute habituation period, the animal was exposed to six 40-millisecond bursts of 120-decibel white noise spaced 15 seconds apart. In each trial, both the maximum response amplitude (startle response, measured as volts) and the time to maximum response (response latency, recorded as milliseconds) were recorded automatically.

At the end of the 13-week studies, samples were collected for sperm morphology and vaginal cytology evaluations on core study rats exposed to 0, 5, 32, or 200 ppm and core study mice exposed to 0, 12, 32, or 80 ppm. The parameters evaluated are listed in Table 1. Methods used were those described in the NTP's sperm morphology and vaginal cytology evaluations protocol (NTP, 1985). For 7 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 morphology, count, and motility. The right testis and right epididymis were isolated and weighed. The tail of the epididymis (cauda epididymis) was then removed from the epididymal body (corpus epididymis) and weighed. Test yolk (rats) or modified Tyrode's buffer (mice) was applied to slides and a small incision was made at

the distal border of the cauda epididymis. The sperm effluxing from the incision were dispersed in the buffer on the slides, and the numbers of motile and nonmotile spermatozoa were counted for five fields per slide by two observers. Following completion of sperm motility estimates, each right cauda epididymis was placed in buffered saline solution. 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. Four sperm morphology slides were prepared for each animal evaluated. An aliquot of killed sperm suspension was stained in a test tube, spread on a microscope slide, coverslipped, and examined.

A necropsy was performed on all core study animals that survived to the end of the 13-week studies. The brain, heart, right kidney, liver, lung, spleen, right testis, and thymus were weighed. Histopathologic examinations were performed on chamber control rats and mice and on 200 ppm rats and 80 ppm mice. The liver of 80 ppm rats and the nose of 12, 32, and 80 ppm rats were examined microscopically. Target organs were examined in 5, 12, and 32 ppm mice to a no-effect level. Lungs of 5, 12, and 32 ppm male mice and forestomachs of 32 ppm male and female mice were examined microscopically. All lesions observed grossly in rats and mice were examined microscopically. Tissues for microscopic examination were fixed and preserved in 10% neutral buffered formalin, processed and trimmed, embedded in paraffin, sectioned to a thickness of 5 to 6 µm, and stained with hematoxylin and eosin. A complete histopathologic examination was performed on chamber control groups of rats and mice, on 200 ppm rats, and on 80 ppm 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 were exposed by inhalation to chloroprene at concentrations of 0, 12.8, 32, or 80 ppm for 6 hours plus T_{90} (12 minutes) per day, 5 days per week, for 105 weeks.

Source and Specification of Animals

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Simonsen Laboratories, Inc. (Gilroy, CA) for use in the 2-year studies. Rats and mice were quarantined for 14 days before the beginning of the studies. Five and five female rats and mice were randomly selected for parasite evaluation and gross observation of disease. Rats and mice were approximately 6 weeks old at the beginning of the studies. The health of the animals was monitored during the studies according to the protocols of the NTP Sentinel Animal Program (Appendix M).

Animal Maintenance

Rats and mice were housed individually. Feed was available *ad libitum* except during exposure periods, and water was available *ad libitum*. Cages and chambers were changed weekly. Further details of animal maintenance are given in Table 1. Information on feed composition and contaminants is provided in Appendix L.

Clinical Examinations and Pathology

All animals were observed twice daily. Body weights were recorded initially, weekly through week 12, approximately every 4 weeks from week 15 through week 91, and every 2 weeks until the end of the study. Clinical findings were recorded initially, at weeks 4, 5 (mice), 8, 12, and 15 (rats), every 4 weeks through week 91, and every 2 weeks until the end of the study.

A complete necropsy and microscopic examination 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 5 to 6 µm, and stained with hematoxylin and eosin for microscopic examination. For all paired organs (i.e., adrenal gland, kidney, ovary), samples from each organ were examined. Tissues examined microscopically are listed in Table 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 rat study, a quality assessment pathologist evaluated slides from all tumors and all potential target organs, which included the esophagus, kidney, larynx, lung, nose, oral mucosa, stomach, tongue, and trachea of male and female rats and the mammary gland of female rats. For the 2-year mouse study, a quality assessment pathologist evaluated slides from all tumors and all potential target organs, which included the esophagus, harderian gland, larynx, liver, lung, mesentery, nose, skin, spleen, stomach and forestomach, and trachea of male and female mice, the kidney of male mice, and the mammary gland and Zymbal's gland of female mice. Step sections were made from the residual kidney wet tissue of male and female rats and male mice because of a slightly increased trend of proliferative lesions in the standard evaluation. Eight additional kidney sections taken at 1-mm intervals were prepared for each male and female.

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

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

16-Day Studies	13-Week Studies	2-Year Studies
Study Laboratory Battelle Pacific Northwest Laboratories (Richland, WA)	Battelle Pacific Northwest Laboratories (Richland, WA)	Battelle Pacific Northwest Laboratories (Richland, WA)
Strain and Species Rats: F344/N Mice: $B6C3F_1$	Rats: F344/N Mice: $B6C3F_1$	Rats: F344/N Mice: $B6C3F_1$
Animal Source Taconic Farms (Germantown, NY)	Taconic Farms (Germantown, NY)	Simonsen Laboratories, Inc. (Gilroy, CA)
Time Held Before Studies Rats: 10 days (males) or 11 days (females) Mice: 12 days (males) or 13 days (females)	Rats: 12 days (males) or 13 days (females) Mice: 14 days (males) or 15 days (females)	14 days
Average Age When Studies Began 6 to 7 weeks	Rats: 6 to 7 weeks Mice: 6 weeks	6 weeks
Date of First Exposure Rats: 28 September 1986 (males) 29 September 1986 (females) Mice: 30 September 1986 (males) 1 October 1986 (females)	Rats: 10 March 1987 (males) 11 March 1987 (females) Mice: 12 March 1987 (males) 13 March 1987 (females)	Rats: 20 September 1990 Mice: 13 September 1990
Duration of Exposure 6 hours plus T_{90} (12 minutes) per day, 5 days per week, for 16 days	6 hours plus T_{90} (12 minutes) per day, 5 days per week, for 13 weeks	6 hours plus T_{90} (12 minutes) per day, 5 days per week, for 105 weeks
Date of Last Exposure Rats: 13 October 1986 (males) 14 October 1986 (females) Mice: 15 October 1986 (males) 16 October 1986 (females)	Rats: 8 June 1987 (males) 9 June 1987 (females) Mice: 10 June 1987 (males) 11 June 1987 (females)	Rats: 18 September 1992 Mice: 11 September 1992
Necropsy Dates Rats: 14 October 1986 (males) 15 October 1986 (females) Mice: 16 October 1986 (males) 17 October 1986 (females)	Rats: 9 June 1987 (males) 10 June 1987 (females) Mice: 11 June 1987 (males) 12 June 1987 (females)	Rats: 21-23 September 1992 Mice: 14-16 September 1992
Average Age at Necropsy 8 to 9 weeks	Rats: 19 to 20 weeks Mice: 20 weeks	111-112 weeks
Size of Study Groups 10 males and 10 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 weight.	Same as 16-day studies	Same as 16-day studies

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

16-Day Studies	13-Week Studies	2-Year Studies
Animals per Cage 1	1	1
Method of Animal Identification Toe clip	Ear tag (core study rats) Toe clip (special study rats and all mice)	Tail tattoo
Diet NIH-07 open formula pelleted diet (Zeigler Brothers, Inc., Gardners, PA), available *ad libitum*, except during exposure and urine collection periods; changed daily	Same as 16-day studies	Same as 16-day studies
Water Tap water (Richland, WA, municipal supply) via automatic watering system (Edstrom Industries, Waterford, WI), available *ad libitum*	Same as 16-day studies	Tap water (Richland, WA, municipal supply) via automatic watering system (System Engineering, Napa, CA), available *ad libitum*
Cages Stainless steel wire bottom (Hazleton Systems, Inc., Aberdeen, MD), changed weekly	Same as 16-day studies	Stainless steel wire bottom (Lab Products, Inc., Maywood, NJ), changed weekly
Cageboard Untreated Techsorb® (Shepherd Specialty Papers, Inc., Kalamazoo, MI), changed daily	Same as 16-day studies	Untreated Techsorb® (Shepherd Specialty Papers, Inc., Kalamazoo, MI) or untreated cageboard (Bunzl Cincinnati Paper Co., Cincinnati, OH), changed daily
Chamber Air Supply Filters Charcoal filter HEPA filters (Flanders Filters, Inc., San Rafael, CA), checked twice per year	Same as 16-day studies	Same as 16-day studies
Chambers Stainless steel, (Hazleton Lab Products, Inc., Aberdeen, MD), changed weekly	Same as 16-day studies	Same as 16-day studies
Chamber Environment Temperature: 21.6°-25.2° C (rats) 21.9°-25.1° C (mice) Relative humidity: 35%-82% (rats) 35%-87% (mice) Room fluorescent light: 12 hours/day Chamber air changes: 15/hour	Temperature: 21.9°-25.6° C (rats) 21.6°-25.1° C (mice) Relative humidity: 29%-79% Room fluorescent light: 12 hours/day Chamber air changes: 15/hour	Temperature: 20.2°-26.9° C (rats) 20.5°-28.5° C (mice) Relative humidity: 28%-89% (rats) 26%-88% (mice) Room fluorescent light: 12 hours/day Chamber air changes: 15/hour
Exposure Concentrations Rats: 0, 32, 80, 200, or 500 ppm Mice: 0, 12, 32, 80, or 200 ppm	Rats: 0, 5, 12, 32, 80, or 200 ppm Mice: 0, 5, 12, 32, or 80 ppm	0, 12.8, 32, or 80 ppm

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

16-Day Studies	13-Week Studies	2-Year Studies
Type and Frequency of Observation Observed twice daily; animals were weighed initially, after one week, and at the end of the studies; clinical findings were recorded twice daily.	Observed twice daily; animals were weighed initially, after one week, and at the end of the studies; clinical finding were recorded weekly.	Observed twice daily; animals were weighed initially, weekly through week 12, approximately every 4 weeks from week 15 through week 91, and every 2 weeks until the end of the study; clinical findings were recorded initially, at weeks 4, 5 (mice), 8, 12, and 15 (rats), every 4 weeks through week 91, and every 2 weeks until the end of the study.
Method of Sacrifice 70% CO_2 asphyxiation	Same as 16-day studies	Same as 16-day studies
Necropsy Necropsy was performed on all animals. Organs weighed were the brain, heart, right kidney, liver, lungs, spleen, thymus, and right testis.	Necropsy was performed on all core animals. Organs weighed were brain, heart, right kidney, liver, lungs, spleen, thymus, and right testis.	Necropsy was performed on all animals.
Clinical Pathology On day 4 of exposure, rats were placed in metabolism cages for 16-hour urine collection. After urine collection, rats were anesthetized with CO_2 and blood was collected from the retroorbital sinus. Additional groups of 10 male and 10 female mice designated for day 5 hematology analyses were exposed to 0, 12, 32, 80, or 200 ppm. On exposure day 8, mice were anesthetized with CO_2 and blood was collected. ***Hematology:*** hematocrit; hemoglobin concentration; erythrocyte, nucleated erythrocyte, reticulocyte, and platelet counts; Howell-Jolly bodies (mice); mean cell volume; mean cell hemoglobin; mean cell hemoglobin concentration; leukocyte count and differentials ***Clinical chemistry:*** urea nitrogen, creatinine, alanine aminotransferase, glutamate dehydrogenase, and sorbitol dehydrogenase ***Urinalysis:*** volume, specific gravity, creatinine, glucose, protein, alkaline phosphatase, aspartate aminotransferase, urea, and thioethers	Rats bled for hematology and clinical chemistry were first placed in metabolism cages for 16-hour urine collection. Separate groups of 10 male and 10 female rats were exposed to 0, 5, 12, 32, 80, or 200 ppm for 22 days or 13 weeks for hematology, clinical chemistry, and urinalysis evaluations. Blood was collected from the retroorbital sinus of rats designated for clinical pathology on day 23 and at week 14 from the supraorbital sinus of all core study mice surviving to the end of the study for hematology and clinical chemistry. Blood for hematology analyses was also collected from the lumbar aorta of groups of 10 male and 10 female rats (designated for coagulation studies) exposed to 0, 32, 80, or 200 ppm for 2 days. ***Hematology:*** hematocrit; hemoglobin concentration; erythrocyte, nucleated erythrocyte, reticulocyte, and platelet counts; Howell-Jolly bodies (mice); mean cell volume; mean cell hemoglobin; mean cell hemoglobin concentrations; leukocytes and differentials (reticulocytes and nucleated erythrocytes were not counted on day 2) ***Clinical chemistry:*** urea nitrogen, creatinine, alanine aminotransferase, glutamate dehydrogenase, and sorbitol dehydrogenase ***Urinalysis:*** creatinine, glucose, protein, alkaline phosphatase, aspartate aminotransferase, volume, specific gravity, urea, and alanine aminotransferase	None

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

16-Day Studies	13-Week Studies	2-Year Studies
Histopathology		
Histopathology was performed on 0, 200, and 500 ppm male rats, 0, 80, 200, and 500 ppm female rats, and 0, 80, and 200 ppm mice, as well as on target organs in other exposure groups to a no-effect level. In addition to gross lesions and tissue masses, the following tissues were examined: bone marrow, brain, heart, kidney, larynx, liver, lung, lymph nodes (tracheobronchial), nose, spleen, stomach (forestomach and glandular stomach), testis and epididymis, thymus, and trachea.	Complete histopathology was performed on 0 and 200 ppm rats and 0 and 80 ppm mice. The liver of 80 ppm rats and the nose of 12, 32, and 80 ppm rats were examined microscopically. Target organs were examined in 5, 12, and 32 ppm mice to a no-effect level. Lungs of 5, 12, and 32 ppm male mice and forestomachs of 32 ppm male mice were examined microscopically. The forestomachs of 32 ppm female mice were also examined microscopically. In addition to gross lesions and tissue masses, the following tissues were examined: adrenal gland, bone and marrow, brain, clitoral gland (rats), esophagus, gallbladder (mice), heart, large intestine (cecum, colon, and rectum), small intestine (duodenum, jejunum, and ileum), kidney, liver, lung, lymph nodes (bronchial, mandibular, mediastinal, and mesenteric), mammary gland, nose, ovary, pancreas, parathyroid gland, pituitary gland, preputial gland (rats), prostate gland, salivary gland, spleen, stomach (forestomach and glandular stomach), testis with epididymis and seminal vesicle, thymus, thyroid gland, trachea, urinary bladder, and uterus.	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 and marrow, brain, clitoral gland, esophagus, gallbladder (mice), heart, large intestine (cecum, colon, and rectum), small intestine (duodenum, jejunum, and ileum), kidney, liver, lung, lymph nodes (bronchial, mandibular, mediastinal, and mesenteric), mammary gland, nose, ovary, pancreas, parathyroid gland, pituitary gland, preputial gland, prostate gland, salivary gland, spleen, stomach (forestomach and glandular stomach), testis with epididymis and seminal vesicle, thymus, thyroid gland, trachea, urinary bladder, and uterus.
Sperm Morphology and Vaginal Cytology		
None	Groups of 10 male and 10 female rats were exposed to 0, 5, 32, or 200 ppm and groups of 10 male and 10 female mice were exposed to 0, 12, 32, or 80 ppm. At the end of the studies, sperm samples were collected from male rats and mice for sperm morphology evaluations. The following parameters were evaluated: sperm morphology, count, and motility. The right cauda and right epididymis were weighed. Vaginal samples were collected for up to 7 consecutive days prior to the end of the studies for vaginal cytology evaluations. The following parameters were evaluated: relative frequency of estrous stages and estrous cycle length.	None

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

16-Day Studies	13-Week Studies	2-Year Studies
Glutathione Evaluation		
None	Five male and five female rats were exposed to 0, 5, 32, or 200 ppm and five male and five female mice were exposed to 0, 12, 32, or 80 ppm for 1 day. Additional groups of five male and five female rats and mice were exposed to the same concentrations for 12 weeks. After exposure, animals were killed and the kidney, liver, lung, and thymus were collected and homogenized for determination of total and nonprotein sulfhydryl concentrations.	None
Coagulation Study		
None	Ten male and 10 female rats were exposed to 0, 32, 80, or 200 ppm for two days. Blood samples were collected from the lumbar aorta and animals were discarded. The following parameters were evaluated: prothrombin time, activated partial thromboplastin time, euglobulin lysis time, and platelet and fibrinogen concentration.	None
Neurobehavioral Evaluation		
None	At week 11, all male and female core study rats were administered neurobehavioral tests. The following parameters were measured: forelimb/hindlimb grip strength, horizontal activity, rearing activity, total activity, tailflick latency, startle response latency, and startle response amplitude.	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 pregnant were censored from the survival analyses; animals dying from natural causes were not censored. Statistical analyses for possible dose-related effects on survival used Cox's (1972) method for testing two groups for equality and Tarone's (1975) life table test to identify dose-related trends. All reported P values for the survival analyses are two sided.

Calculation of Incidence

The incidences of neoplasms or nonneoplastic lesions as presented in Tables A1, A5, B1, B5, C1, C5, D1, and D5 are given as the number of animals bearing such lesions at a specific anatomic site and the number of animals with that site examined microscopically. For calculation of statistical significance, the incidences of most neoplasms (Tables A3, B3, C3, and D3) and all nonneoplastic lesions are given as the numbers of animals affected at each site examined microscopically. However, when macroscopic examination was required to detect neoplasms in certain tissues (e.g., 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, i.e., the Kaplan-Meier estimate of the neoplasm incidence that would have been observed at the end of the study in the absence of mortality from all other competing risks (Kaplan and Meier, 1958).

Analysis of Neoplasm Incidences

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

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

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

Because of the increased mortality in the chloroprene-exposed groups of mice, supplemental analyses were performed by the survival-adjusted Poly-3 quantal response test (Bailer and Portier, 1988; Portier and Bailer, 1989). This procedure, which is currently being evaluated by the NTP, modifies the Cochran-Armitage/Fisher exact test by adjusting the denominators of the neoplasm rates to take into account survival differences. This adjustment was derived by Portier and Bailer (1989), based on their fitting a Weibull model to historical control neoplasm data for a variety of site-specific neoplasms. The use of the power of $k = 3$ in the poly-k adjustment for intercurrent mortality in the chloroprene study is justified by the following: (1) For liver and lung neoplasms in historical control animals, the observed survival-adjusted value of k that best fits the data is approximately 3 in both male and female mice (Portier *et al.*,

1986). In male mice, the value of k for all neoplasms combined was approximately 3, and for females it was approximately 4.5. (2) Simulations have shown that it is better (in terms of preserving false positive error rate) to underestimate the value of k than to overestimate it. Thus, for example, it is better to use k = 3 when in truth k = 6 than it is to use k = 6 when in truth k = 3. Because none of the values for k estimated by Portier *et al*. (1986) were significantly less than 3, and few were significantly greater than 3, the choice of 3 seems reasonable.

Determining Dose-Response Shape and ED_{10} Values for Chloroprene

For those neoplasms showing chemical-related effects in mice, the shape of the dose-response curve was estimated by fitting the following modified Weibull model (Portier *et al.*, 1986) to the data:

$$P(dose) = 1 - e^{-(intercept + scale \cdot dose^{shape})}$$

where *P(dose)* is the probability of a neoplasm for animals administered dose *dose* of chloroprene. The parameters *intercept*, *scale*, and *shape* are estimated via maximum likelihood estimation using the likelihood

$$L = \sum_{i=0}^{3} x_i \log[P(d_i)] + (n_i - x_i)\log[1-P(d_i)]$$

where x_i is the number of animals with neoplasm in dose group d_i, and n_i is the Poly-3 adjusted number of animals at risk in dose group d_i. A likelihood ratio test is used to test the hypothesis that the shape parameter equals 1. The test statistic is given as –2 times the differences in the log-likelihoods. A one-sided test was used so that the critical values are 2.706 for P = 0.05 and 5.410 for P = 0.01 (these are the squares of the critical regions from standard normal distribution). The shape parameter was restricted to be less than or equal to 10.

If the estimated shape parameter is greater than 1, the resulting dose response has more curvature than a linear model and exhibits "threshold-like" behavior. If the estimated shape parameter is less than 1, then the dose-response curve is very steep in the low-dose region. The ED_{10} values obtained from these dose-response curves represent the exposure concentrations associated with an excess cancer risk of 10%.

Analysis of Nonneoplastic Lesion Incidences

Because all nonneoplastic lesions in this study were considered to be incidental to the cause of death or not rapidly lethal, the primary statistical analysis used was a logistic regression analysis in which nonneoplastic lesion prevalence was modeled as a logistic function of chemical exposure and time.

Analysis of Continuous Variables

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

Historical Control Data

Although the concurrent control group is always the first and most appropriate control group used for evaluation, historical control data can be helpful in the overall assessment of neoplasm incidence in certain instances. Consequently, neoplasm incidences from the NTP historical control database, which is updated

yearly, are included in the NTP reports for neoplasms appearing to show compound-related effects.

QUALITY ASSURANCE METHODS

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

GENETIC TOXICOLOGY

The genetic toxicity of chloroprene was assessed by testing the ability of the chemical to induce mutations in various strains of *Salmonella typhimurium*, sex-linked recessive lethal mutations in *Drosophila melanogaster*, sister chromatid exchanges and chromosomal aberrations in cultured mouse bone marrow cells, and increases in the frequency of micronucleated erythrocytes in peripheral blood cells of mice. The protocols for these studies and the results are given in Appendix E.

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

There is a strong correlation between a chemical's potential electrophilicity (structural alert to DNA reactivity), mutagenicity in *Salmonella*, and carcinogenicity in rodents. The combination of electrophilicity and *Salmonella* mutagenicity is highly correlated with the induction of carcinogenicity in rats and mice and/or at multiple tissue sites (Ashby and Tennant, 1991). Other *in vitro* genetic toxicity tests correlate less well with rodent carcinogenicity (Tennant *et al.*, 1987; Zeiger *et al.*, 1990), although these other tests can provide information on the types of DNA and chromosome effects that can be induced by the chemical being investigated. Data from NTP studies show that a positive response in *Salmonella* is the most predictive *in vitro* test for rodent carcinogenicity (89% of the *Salmonella* mutagens are rodent carcinogens), and that there is no complementarity among the *in vitro* genetic toxicity tests. That is, no battery of tests that included the *Salmonella* test improved the predictivity of the *Salmonella* test alone.

The predictivity for carcinogenicity of a positive response in bone marrow chromosome aberration or micronucleus tests appears to be less than the *Salmonella* test (Shelby *et al.*, 1993; Shelby and Witt, 1995). Positive responses in long-term peripheral blood micronucleus tests have not been formally evaluated for their predictivity for rodent carcinogenicity. But, 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.

RESULTS

RATS

16-DAY STUDY

Three male rats exposed to 500 ppm died on day 2 or 3 of the study. Twenty-three deaths on day 5 (10 males and 13 females) occurred when blood was withdrawn for clinical pathology evaluations; hence, the mortality pattern in this study did not reflect the effect of chloroprene exposure. Mean body weight gains of 200 ppm males and females and 500 ppm females were significantly less than those of the chamber control groups (Table 2). On the first day of exposure, rats exposed to 500 ppm were hypoactive and unsteady and had rapid shallow breathing. These effects were also observed to some degree in animals exposed to 200 ppm. After the second day of exposure, the effects in these groups became more severe, and blood was observed on the noses of many animals.

TABLE 2
Survival and Body Weights of Rats in the 16-Day Inhalation Study of Chloroprene

Dose (ppm)	Survival[a]	Mean Body Weight[b] (g)			Final Weight Relative to Controls (%)
		Initial	Final	Change	
Male					
0	7/10[c]	115 ± 4	139 ± 5	20 ± 2	
32	10/10	113 ± 4	134 ± 6	20 ± 2	96
80	10/10	118 ± 5	136 ± 5	18 ± 1	98
200	9/10[c]	114 ± 4	127 ± 5	11 ± 2**	91
500	1/10[d]	114 ± 4	104[e]	4[e]	75
Female					
0	9/10[c]	100 ± 2	110 ± 3	9 ± 1	
32	9/10[c]	100 ± 2	109 ± 3	8 ± 1	99
80	9/10[c]	103 ± 2	112 ± 2	9 ± 1	102
200	3/10[c]	101 ± 2	101 ± 4	4 ± 1**	92
500	7/10[c]	102 ± 2	103 ± 3	−1 ± 1**	94

** Significantly different ($P \leq 0.01$) from the chamber control group by Williams' or Dunnett's test
[a] Number of animals surviving at 16 days/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] Day of death: 5
[d] Day of death: 2, 2, 3, 5, 5, 5, 5, 5, 5
[e] No standard error calculated due to high mortality

The day 4 hematology, clinical chemistry, and urinalysis data for rats are listed in Table G1. A mild to marked anemia, evidenced by decreases in hematocrit values, hemoglobin concentrations, and erythrocyte counts occurred in the 200 ppm female and 500 ppm male and female rats. The anemia was characterized as normocytic and normochromic, as evidenced by the lack of alterations in mean cell volume and mean cell hemoglobin concentration values. Also, there was evidence of an hematopoietic response to the anemia, characterized by increased reticulocyte and nucleated erythrocyte counts. A thrombocytopenia, evidenced by a reduction in circulating platelet numbers, occurred in the 200 ppm female and 500 ppm male and female rats.

The 200 ppm female and 500 ppm male and female rats had increased serum activities of alanine aminotransferase, glutamate dehydrogenase, and sorbitol dehydrogenase relative to the chamber controls; these findings would be consistent with increased hepatocellular permeability and leakage. Changes in other clinical pathology variables were sporadic and did not demonstrate a treatment relationship; they were not considered toxicologically relevant.

Absolute and relative right kidney weights of 80 and 500 ppm females were significantly greater than those of the chamber control group (Table F1). The absolute and relative liver weights of 200 and 500 ppm females and the absolute liver weight of 80 ppm females were significantly greater than those of the chamber control group.

The incidences of minimal to mild olfactory epithelial degeneration in all exposed groups of males and females were significantly greater than those in the chamber control groups (Table 3). These effects were most prominent in the posterior portion of the nasal cavity, which consists primarily of the ethmoid turbinates covered by olfactory epithelium. The olfactory epithelium lining the dorsal meatus, median septum, and tips of the ethmoturbinates was most often affected. Olfactory degeneration consisted of focal thinning or disorganization of normally stratified olfactory neurons and sustentacular cells. In some areas of degeneration, there were focal erosions of the olfactory epithelium and mineralizations within the mucosa. Frequently, the olfactory epithelium along the median septum, dorsal meatus, or tips of the ethmoturbinates was replaced by a simple columnar respiratory-like epithelium (metaplasia) in males and females exposed to chloroprene. Other lesions in the nasal cavity included squamous metaplasia of the respiratory epithelium in males and females exposed 500 ppm. Mild to moderate, centrilobular to random hepatocellular necrosis was observed in rats exposed to 200 or 500 ppm. The incidences of centrilobular necrosis in 500 ppm males and 200 ppm females were significantly greater than those in the chamber control groups. Scattered chronic centrilobular inflammation characterized by focal aggregates of lymphocytes and macrophages was also present in the liver of females exposed to 200 or 500 ppm and in one male exposed to 500 ppm.

TABLE 3
Incidences of Selected Nonneoplastic Lesions in Rats in the 16-Day Inhalation Study of Chloroprene

	Chamber Control	32 ppm	80 ppm	200 ppm	500 ppm
Male					
Nose[a]	10	10	10	10	10
Degeneration, Olfactory Epithelium[b]	1 (1.0)[c]	10** (1.0)	10** (1.1)	10** (1.9)	10** (3.8)
Metaplasia, Squamous, Olfactory Epithelium	0	0	0	1 (2.0)	4* (1.8)
Metaplasia, Respiratory, Olfactory Epithelium	0	2 (1.0)	5* (1.0)	6** (1.0)	1 (2.0)
Metaplasia, Squamous, Respiratory Epithelium	1 (1.0)	1 (1.0)	0	0	7** (1.7)
Liver	10	1	10	10	10
Necrosis, Centrilobular	0	0	0	1 (2.0)	9** (3.4)
Inflammation, Chronic	0	0	0	0	1 (2.0)
Female					
Nose	10	10	10	10	10
Degeneration, Olfactory Epithelium	0	9** (1.2)	10** (1.6)	10** (3.4)	10** (3.3)
Metaplasia, Squamous, Olfactory Epithelium	0	1 (1.0)	1 (1.0)	4* (1.0)	0
Metaplasia, Respiratory, Olfactory Epithelium	0	7** (1.0)	8** (1.2)	3 (1.0)	7** (1.4)
Metaplasia, Squamous, Respiratory Epithelium	1 (2.0)	1 (1.0)	0	0	4 (1.3)
Liver	10	3	10	10	10
Necrosis, Centrilobular	0	0	0	7** (2.6)	3 (2.0)
Inflammation, Chronic	0	0	0	2 (1.0)	5* (1.0)

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

13-WEEK STUDY

One male exposed to 200 ppm died during the study (Table 4). The final mean body weights and body weight gains of all exposed groups of males and females were similar to those of the chamber control groups. In the 200 ppm male group, clinical findings related to chloroprene exposure included red or clear discharge around the nose and eye region and blood on the feet.

TABLE 4
Survival and Body Weights of Rats in the 13-Week Inhalation Study of Chloroprene

Dose (ppm)	Survival[a]	Mean Body Weight[b] (g)			Final Weight Relative to Controls (%)
		Initial	Final	Change	
Male					
0	10/10	109 ± 4	311 ± 9	202 ± 8	
5	10/10	119 ± 2*	323 ± 11	204 ± 10	104
12	10/10	116 ± 1	306 ± 9	190 ± 8	98
32	10/10	117 ± 2	327 ± 11	209 ± 10	105
80	10/10	116 ± 1	301 ± 8	184 ± 7	97
200	9/10[c]	116 ± 3	304 ± 8	185 ± 7	98
Female					
0	10/10	102 ± 2	191 ± 4	89 ± 3	
5	10/10	101 ± 1	193 ± 4	92 ± 3	101
12	10/10	102 ± 2	199 ± 5	97 ± 4	104
32	10/10	101 ± 2	195 ± 4	94 ± 4	102
80	10/10	103 ± 1	192 ± 3	90 ± 3	101
200	10/10	102 ± 1	183 ± 3	81 ± 3	96

* Significantly different ($P \leq 0.05$) from the chamber control group by Williams' or Dunnett's test
[a] Number of animals surviving at 13 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.
[c] Day of death: 2

The hematology, clinical chemistry, and urinalysis data for rats are listed in Table G2. On day 2, minimal increases in hematocrit values, hemoglobin concentrations, and erythrocyte counts occurred in males exposed to 32 ppm or greater and in females exposed to 200 ppm; these findings are consistent with a minimal relative erythrocytosis related to hemoconcentration. At week 13, however, a minimal anemia, evidenced by decreased hematocrit values, hemoglobin concentrations, and erythrocyte counts occurred in 200 ppm male and female rats. The anemia was characterized as normocytic, normochromic, and nonresponsive, as evidenced by the lack of alterations in mean cell volume, mean cell hemoglobin concentration, and reticulocyte values, respectively. A thrombocytopenia, evidenced by a reduction in circulating platelet numbers, occurred in the 200 ppm male and female rats on days 2 and 80 and 200 ppm females on day 22. At study termination, platelet counts rebounded and were minimally increased in 200 ppm male and female rats, suggesting an increase in platelet production. On day 2, minimal to mild increases in activated partial thromboplastin time and prothrombin time occurred in 200 ppm male and female rats.

The 200 ppm male and female rats also had increased serum activities of alanine aminotransferase, glutamate dehydrogenase, and sorbitol dehydrogenase on day 22; these increases were transient, and by week 13, the serum activities of these enzymes were similar to those of the chamber controls. There were increases in urine volume on day 22 and at week 13 in the 200 ppm male and female rats; the significance of these increases was tempered by the inappropriately high urine volumes for the chamber control animals which suggested that the urine may have been contaminated with water. The urine volume increase for the 200 ppm animals, however, was substantial and extreme; this suggested that the marked increase in urine volume in the 200 ppm animals was not of renal origin but was probably related to excessive manipulation of water bottles (for example, due to nasal or pharyngeal irritation) exacerbating water contamination of the urine collected. Additionally, there was no indication of severe renal injury, as evidenced by the lack of increases in the serum concentration of urea nitrogen or creatinine. Regardless of the apparent water contamination, the data for the urine constituents could be evaluated based on a urine constituent/urine creatinine ratio, thus ameliorating the effects of variable urine volumes. An alkaline phosphatase enzymeuria, evidenced by increased urine alkaline phosphatase activity, occurred in the 200 ppm female rats on day 22. At week 13, an alkaline phosphatase enzymeuria occurred in the males exposed to 32 ppm or greater and females exposed to 200 ppm. At week 13, a proteinuria, evidenced by increased urine protein concentration, also occurred in the 200 ppm male rats. Changes in other clinical pathology variables were sporadic, did not demonstrate a treatment relationship, and were not considered toxicologically relevant.

Tissue nonprotein sulfhydryl (glutathione) determinations are listed in Table H1. Significant reductions in nonprotein sulfhydryl concentrations were observed in the liver of male rats immediately following 1 day or 12 weeks of exposure to 200 ppm and in the liver of females exposed to 200 ppm for 12 weeks. Nonprotein sulfhydryl concntrations were also reduced in the lung of 200 ppm female rats after 1 day but not after 12 weeks of exposure to 200 ppm. Nonprotein sulfhydryl concentrations in the kidney and thymus were not reduced by exposure to chloroprene.

The absolute and relative kidney weights of 200 ppm males and females and 80 ppm females were significantly greater than those of the chamber control groups (Table F2). The sperm motility of males exposed to 200 ppm was significantly less than that of the chamber control group (Table I1).

Neurobehavioral parameters are listed in Table J1. Compared to chamber controls, horizontal activity was increased in male rats exposed to 32 ppm or greater. Total activity was increased in 32 and 200 ppm males. Other neurobehavioral parameters measured in male rats as well as all parameters measured in female rats were not affected by chloroprene exposure.

Increased incidences of minimal to mild olfactory epithelial degeneration and respiratory metaplasia occurred in males and females exposed to 80 or 200 ppm (Table 5). The incidence of olfactory epithelial degeneration in 32 ppm females was also significantly greater than that in the chamber control group. These effects were most prominent in the posterior portion of the nasal cavity (Level III), which consists primarily of the ethmoid turbinates covered by olfactory epithelium. The olfactory epithelium lining the dorsal meatus, median septum, and tips of the ethmoturbinates was most often affected. Olfactory degeneration consisted of focal thinning or disorganization of the normally stratified olfactory neurons and sustentacular cells. In some areas of degeneration, there were focal erosions of the olfactory epithelium and mineralization within the mucosa. A minimal, suppurative inflammatory cell exudate was sometimes present in the nasal cavity adjacent to these erosions. Frequently, the olfactory epithelium along the median septum, dorsal meatus, or tips of the ethmoturbinates was replaced by a simple columnar respiratory-like epithelium (metaplasia). Minimal to mild, centrilobular to random hepatocellular necrosis was observed only in rats exposed to 200 ppm.

In 200 ppm females, the incidence of hepatocellular necrosis was significantly greater than that in the chamber control group. Scattered chronic inflammation characterized by focal aggregates of lymphocytes and macrophages was also present in the liver of male and female rats in the 200 ppm groups; the incidence in 200 ppm females was significantly greater than that in the chamber control group. Minimal to

mild, variably sized aggregates of yellow or brown material consistent with hemosiderin appeared in small vessels or lymphatics in or near portal triads or in Kupffer cells of rats exposed to 200 ppm. The incidences of hemosiderin pigmentation were significantly increased in males and females exposed to 200 ppm.

Exposure Concentration Selection Rationale: Based on anemia and hepatocellular necrosis caused by exposure to 200 ppm chloroprene, the highest exposure concentration selected for the 2-year study was 80 ppm. The range of exposure concentrations selected for the 2-year study included a no-observable-effect level for degenerative lesions of the olfactory epithelium.

TABLE 5
Incidences of Selected Nonneoplastic Lesions in Rats in the 13-Week Inhalation Study of Chloroprene

	Chamber Control	5 ppm	12 ppm	32 ppm	80 ppm	200 ppm
Male						
Nose[a]	10	0	10	10	10	10
Degeneration, Olfactory Epithelium[b]	0	—	0	3 (1.0)[c]	10** (1.6)	10** (2.0)
Metaplasia, Respiratory, Olfactory Epithelium	0	—	0	0	4* (1.3)	4* (1.3)
Liver	10	2	1	1	10	10
Necrosis, Centrilobular	0	0	0	0	0	3 (2.0)
Inflammation, Chronic	0	1 (1.0)	0	0	1 (1.0)	2 (1.0)
Hemosiderin Pigmentation	0	0	0	0	0	5* (1.6)
Female						
Nose	10	0	10	10	10	10
Degeneration, Olfactory Epithelium	0	—	0	4* (1.0)	9** (1.9)	10** (1.9)
Metaplasia, Respiratory, Olfactory Epithelium	0	—	0	0	8** (2.0)	9** (2.0)
Liver	10	2	5	3	10	10
Necrosis, Centrilobular	0	0	0	0	0	5* (1.0)
Inflammation, Chronic	2 (2.0)	0	1 (2.0)	0	1 (2.0)	8* (1.3)
Hemosiderin Pigmentation	3 (1.0)	0	1 (3.0)	0	0	9** (1.7)

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

2-YEAR STUDY

Survival

Estimates of 2-year survival probabilities for male and female rats are shown in Table 6 and in the Kaplan-Meier survival curves (Figure 1). Survival of males exposed to 32 or 80 ppm was significantly less than that of the chamber control group.

Body Weights and Clinical Findings

Mean body weights of males exposed to 80 ppm were less than those of the chamber controls after week 93 (Figure 2 and Tables 7 and 8). Masses of the torso in exposed female groups were observed during the study, and these findings correlated with mammary gland fibroadenomas observed at necropsy.

TABLE 6
Survival of Rats in the 2-Year Inhalation Study of Chloroprene

	Chamber Control	12.8 ppm	32 ppm	80 ppm
Male				
Animals initially in study	50	50	50	50
Moribund	34	40	41	41
Natural deaths	3	1	4	5
Animals surviving to study termination	13	9	5	4
Percent probability of survival at end of study[a]	26	18	10	8
Mean survival (days)[b]	646	638	609	609
Survival analysis[c]	P = 0.013	P = 0.615	P = 0.025	P = 0.025
Female				
Animals initially in study	50	50	50	50
Moribund	19	21	23	27
Natural deaths	1	1	1	2
Pregnant[d]	1	0	0	0
Animals surviving to study termination	29	28	26	21
Percent probability of survival at end of study	59	56	52	42
Mean survival (days)	686	685	672	673
Survival analysis	P = 0.085	P = 1.000	P = 0.473	P = 0.151

[a] Kaplan-Meier determinations
[b] Mean of all deaths (uncensored, censored, and terminal sacrifice)
[c] The result of the life table trend test (Tarone, 1975) is in the chamber control column, and the results of the life table pairwise comparisons (Cox, 1972) with the chamber controls are in the exposed group columns.
[d] Censored from survival analyses

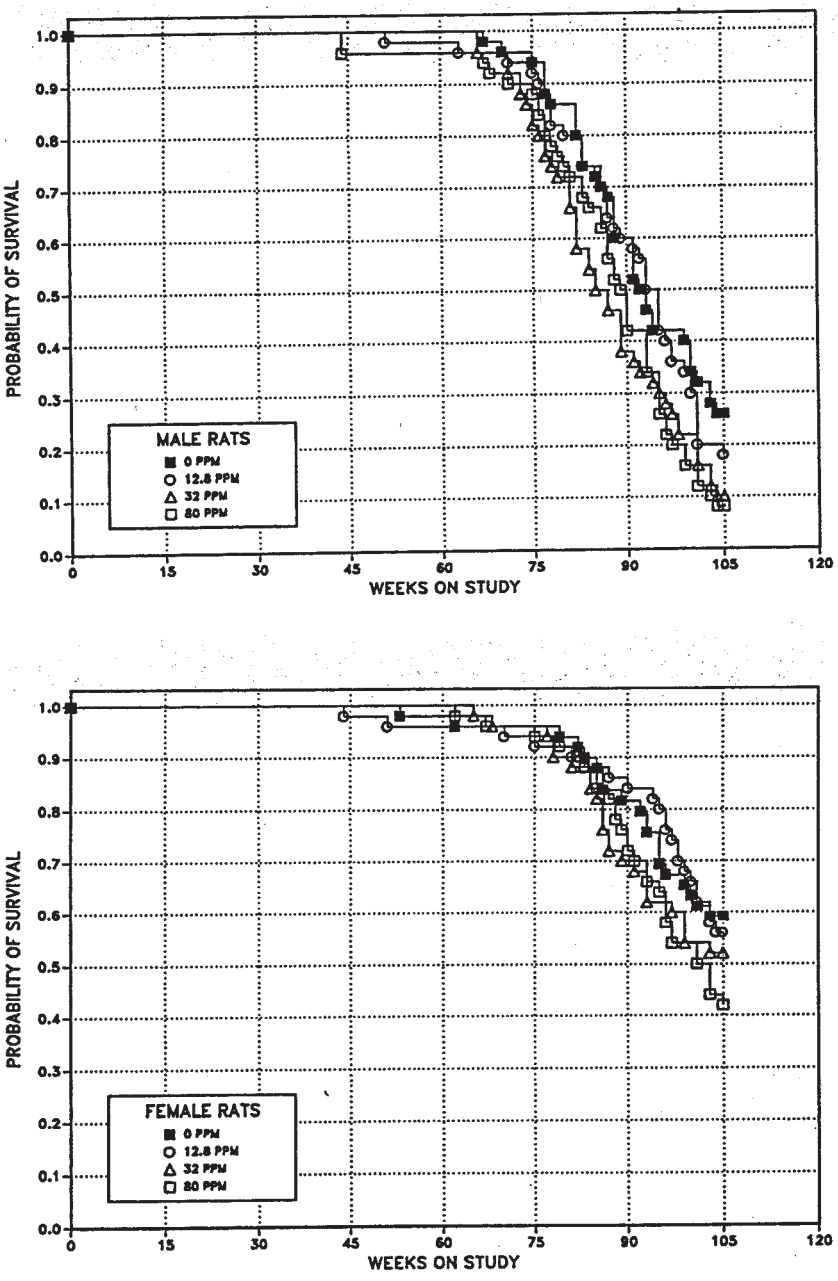


FIGURE 1
Kaplan-Meier Survival Curves for Male and Female Rats Exposed to Chloroprene by Inhalation for 2 Years

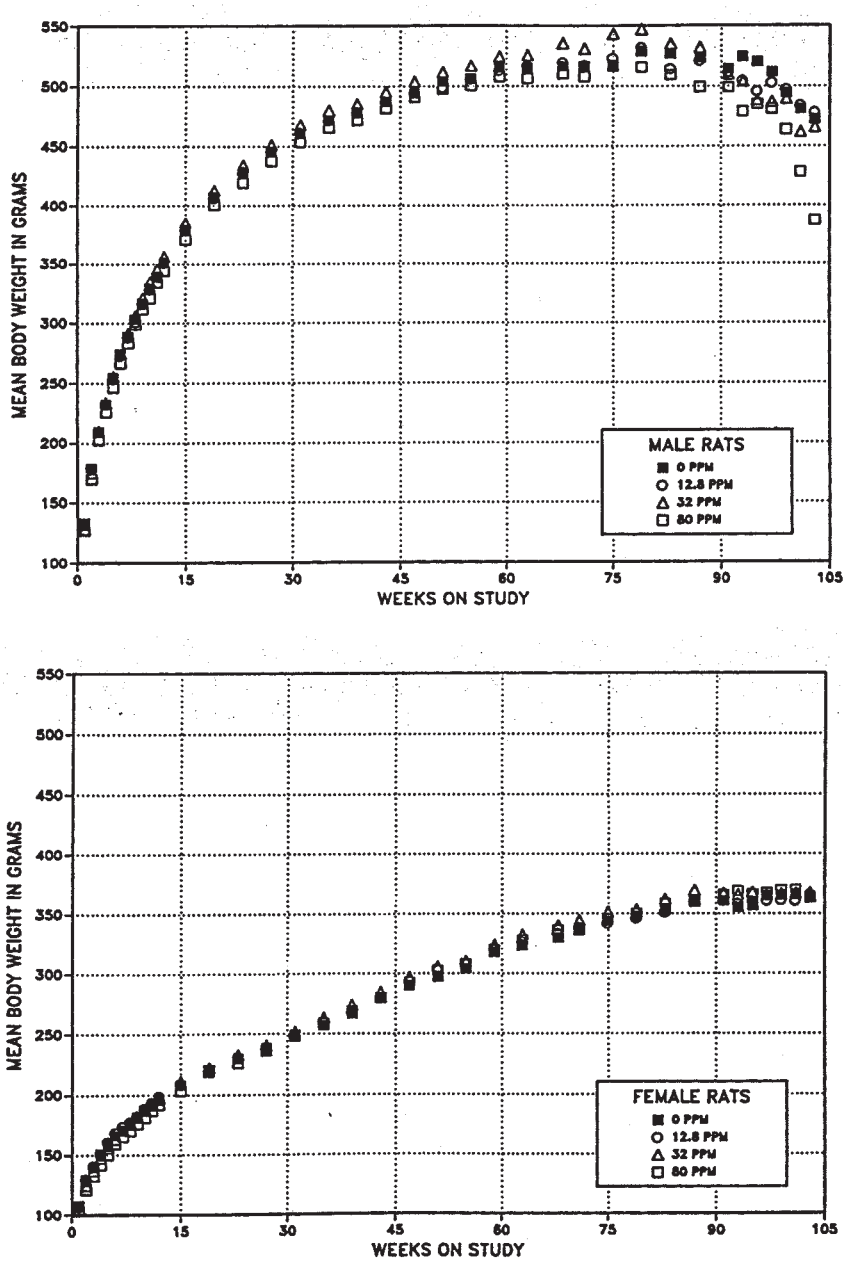


FIGURE 2
Growth Curves for Male and Female Rats Exposed to Chloroprene by Inhalation for 2 Years

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

Weeks on Study	Chamber Control		12.8 ppm			32 ppm			80 ppm		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	133	50	132	99	50	129	97	50	127	95	50
2	179	50	179	100	50	175	98	50	170	95	50
3	209	50	210	100	50	210	101	50	203	97	50
4	232	50	232	100	50	234	101	50	226	97	50
5	254	50	253	100	50	256	101	50	246	97	50
6	274	50	273	99	50	275	100	50	267	97	50
7	289	50	288	100	50	292	101	50	283	98	50
8	303	50	301	99	50	307	101	50	299	99	50
9	317	50	316	100	50	321	102	50	312	99	50
10	330	50	328	100	50	335	102	50	321	98	50
11	339	50	339	100	50	346	102	50	334	99	50
12	351	50	351	100	50	356	102	50	344	98	50
15	380	50	379	100	50	386	102	50	371	98	50
19	407	50	406	100	50	413	101	50	401	98	50
23	428	50	427	100	50	434	101	50	419	98	50
27	446	50	446	100	50	451	101	50	438	98	50
31	460	50	461	100	50	468	102	50	454	99	50
35	471	50	471	100	50	480	102	50	466	99	50
39	478	50	478	100	50	485	102	50	472	99	50
43	487	50	487	100	50	495	102	50	481	99	50
47	494	50	494	100	50	504	102	50	491	99	48
51	504	50	499	99	50	512	102	50	498	99	48
55	506	50	506	100	49	517	102	50	500	99	48
59	516	50	513	99	49	525	102	50	508	98	48
63	515	50	517	100	48	526	102	50	506	98	48
68	516	49	520	101	48	536	104	48	510	99	47
71	516	48	517	100	48	531	103	48	508	98	46
75	518	48	523	101	47	544	105	41	517	100	44
79	529	43	532	101	41	548	104	36	516	98	38
83	527	37	514	98	39	535	102	29	510	97	34
87	524	34	521	100	33	532	102	25	499	95	29
91	514	28	511	99	30	510	99	19	499	97	21
93	525	23	504	96	26	504	96	17	479	91	19
95	520	21	495	95	24	488	94	16	485	93	13
97	511	21	502	98	19	487	95	14	481	94	10
99	494	21	497	101	17	489	99	11	464	94	9
101	481	16	484	101	11	462	96	9	428	89	6
103	472	14	478	101	10	466	99	7	387	82	5
Mean for weeks											
1-13	268		267	100		270	101		261	97	
14-52	456		455	100		463	102		449	99	
53-103	512		508	99		513	100		487	95	

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

Weeks on Study	Chamber Control		12.8 ppm			32 ppm			80 ppm		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	107	50	106	99	50	105	98	50	103	96	50
2	129	50	129	101	50	125	97	50	121	94	50
3	140	50	140	101	50	137	98	50	133	95	50
4	151	50	151	100	50	147	98	50	142	94	50
5	159	50	161	101	50	156	98	50	150	95	50
6	166	50	168	101	50	163	98	50	159	96	50
7	171	50	174	102	50	171	100	50	165	97	50
8	175	50	177	101	50	175	100	50	170	97	50
9	181	50	183	101	50	181	100	50	176	97	50
10	187	50	189	101	50	188	101	50	181	97	50
11	191	50	193	102	50	193	101	50	187	98	50
12	195	50	198	102	50	197	101	50	192	98	50
15	208	50	209	101	50	211	102	50	203	98	50
19	219	50	219	100	50	222	102	50	220	101	50
23	230	50	231	101	50	233	101	50	226	99	50
27	238	50	237	100	50	241	101	50	236	99	50
31	249	50	248	100	50	252	101	50	248	100	50
35	257	49	260	101	50	263	103	50	258	101	50
39	267	49	269	101	50	274	103	50	269	101	50
43	280	49	280	100	50	284	102	50	280	100	50
47	290	49	293	101	49	297	102	50	293	101	50
51	297	49	304	102	48	306	103	50	302	102	50
55	304	48	308	101	48	310	102	50	308	101	50
59	318	48	320	101	48	324	102	50	320	101	50
63	323	47	326	101	48	332	103	50	328	101	49
68	330	47	333	101	48	340	103	49	336	102	48
71	336	47	338	101	47	344	103	48	336	100	48
75	344	47	342	99	47	351	102	48	345	100	48
79	348	47	346	99	46	353	102	45	350	101	47
83	353	45	351	100	44	362	103	44	358	102	44
87	359	41	360	100	43	370	103	36	361	100	42
91	360	40	360	100	42	367	102	34	365	101	36
93	355	39	358	101	42	366	103	33	369	104	33
95	356	36	360	101	41	368	103	31	366	103	32
97	365	33	360	99	38	366	100	31	367	101	28
99	365	32	361	99	34	366	100	29	369	101	27
101	366	30	361	99	33	367	100	27	370	101	25
103	364	30	366	101	31	367	101	27	363	100	23
Mean for weeks											
1-13	163		164	101		162	99		157	96	
14-52	254		255	101		258	102		254	100	
53-103	347		347	100		353	102		351	101	

Pathology and Statistical Analysis

This section describes the statistically significant or biologically noteworthy changes in the incidences of neoplasms and/or nonneoplastic lesions of the oral cavity, thyroid gland, lung, mammary gland, kidney, urinary bladder, and nose. Summaries of the incidences of neoplasms and nonneoplastic lesions, individual animal tumor diagnoses, statistical analysis of primary neoplasms that occurred with an incidence of at least 5% in at least one 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.

Oral Cavity (Oral Mucosa, Tongue, Pharynx, and Gingiva): The incidences of squamous cell papilloma and squamous cell papilloma or squamous cell carcinoma (combined) in male rats exposed to 32 ppm and male and female rats exposed to 80 ppm were significantly greater than those in the chamber controls and exceeded the historical control ranges (Tables 9, A3, A4a, B3, and B4a). Squamous cell carcinoma, squamous cell papilloma, and squamous hyperplasia involved the palate, pharynx, gingiva, cheek, and tongue. One squamous cell papilloma was located in the upper esophagus of an 80 ppm female. Squamous cell carcinomas were characterized by multiple papillary projections covered by several layers of well-differentiated to anaplastic squamous epithelium overlying a fibrovascular core (Plates 1 and 2). Islands of anaplastic epithelium invaded the stalk and/or underlying connective tissue; keratin "pearls" were often present. Mitotic activity was sometimes increased in the neoplastic cells. Squamous cell papillomas were well differentiated and did not invade adjacent tissues (Plates 3 and 4). In most cases papillomas had a narrow base or stalk connecting to adjacent unaffected mucosa. Squamous hyperplasia observed in three males in the 80 ppm group was characterized by focal thickening and folding of the squamous epithelium with a few blunt papillary projections.

TABLE 9
Incidences of Neoplasms and Nonneoplastic Lesions of the Oral Cavity in Rats in the 2-Year Inhalation Study of Chloroprene

	Chamber Control	12.8 ppm	32 ppm	80 ppm
Male				
Number Necropsied	50	50	50	50
Squamous Cell Hyperplasia[a]	0	0	0	3 (2.7)[b]
Squamous Cell Papilloma[c]				
Overall rate[d]	0/50 (0%)	2/50 (4%)	4/50 (8%)	10/50 (20%)
Adjusted rate[e]	0.0%	13.8%	25.4%	71.7%
Terminal rate[f]	0/13 (0%)	0/9 (0%)	0/5 (0%)	2/4 (50%)
First incidence (days)	—[h]	701	620	539
Logistic regression test[g]	P < 0.001	P = 0.217	P = 0.040	P < 0.001
Squamous Cell Carcinoma				
Overall rate	0/50	0/50	1/50 (2%)	2/50 (4%)
Squamous Cell Papilloma or Squamous Cell Carcinoma[i]				
Overall rate	0/50 (0%)	2/50 (4%)	5/50 (10%)	12/50 (24%)
Adjusted rate	0.0%	13.8%	28.4%	74.9%
Terminal rate	0/13 (0%)	0/9 (0%)	0/5 (0%)	2/4 (50%)
First incidence (days)	—	701	609	539
Logistic regression test	P < 0.001	P = 0.217	P = 0.022	P < 0.001
Female				
Squamous Cell Papilloma[j]				
Overall rate	1/49 (2%)	2/50 (4%)	2/50 (4%)	7/50 (14%)
Adjusted rate	3.0%	6.2%	7.7%	29.5%
Terminal rate	0/29 (0%)	1/28 (4%)	2/26 (8%)	5/21 (24%)
First incidence (days)	687	681	733 (T)	660
Logistic regression test	P = 0.003	P = 0.508	P = 0.469	P = 0.020
Squamous Cell Carcinoma				
Overall rate	0/49 (0%)	1/50 (2%)	3/50 (6%)	4/50 (8%)
Squamous Cell Papilloma or Squamous Cell Carcinoma[k]				
Overall rate	1/49 (2%)	3/50 (6%)	5/50 (10%)	11/50 (22%)
Adjusted rate	3.0%	9.2%	17.4%	40.8%
Terminal rate	0/29 (0%)	1/28 (4%)	4/26 (15%)	6/21 (29%)
First incidence (days)	687	681	588	660
Logistic regression test	P < 0.001	P = 0.315	P = 0.093	P = 0.001

(T)Terminal sacrifice
[a] Number of animals with lesion
[b] Average severity grade of lesions in affected animals: 1 = minimal; 2 = mild; 3 = moderate; 4 = marked
[c] Historical incidence for 2-year inhalation studies with chamber controls (mean ± standard deviation): 8/655 (1.2% ± 1.9%); range 0%-6%
[d] Number of animals with neoplasm per number of animals necropsied
[e] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[f] Observed incidence in animals surviving until the end of the study
[g] In the chamber control column are the P values associated with the trend test. In the exposed group columns are the P values corresponding to the pairwise comparisons between the chamber controls and that exposed group. The logistic regression test regards lesions in animals dying prior to terminal kill as nonfatal.
[h] Not applicable; no neoplasms in animal group
[i] Historical incidence: 9/655 (1.4% ± 1.9%); range 0%-6%
[j] Historical incidence: 3/653 (0.5% ± 0.9%); range 0%-2%
[k] Historical incidence: 8/653 (1.2% ± 1.7%); range 0%-6%

Thyroid Gland: The incidences of follicular cell adenoma or carcinoma (combined) in males exposed to 32 or 80 ppm were significantly greater than that in the chamber control group and exceeded the historical control range (Tables 10, A3, and A4b). Although the incidences of follicular cell adenoma and follicular cell adenoma or carcinoma (combined) in 80 ppm females were not significantly greater than those in the chamber controls, they did exceed the historical control range for these neoplasms (Tables 10, B3, and B4b). Follicular cell carcinomas obliterated the thyroid gland and sometimes invaded the capsule or adjacent structures. Patterns varied from solid to papillary to follicular, with a mixture of these patterns present in most neoplasms. Cells were pleomorphic and cuboidal to high columnar, with a high nucleus:cytoplasm ratio and varying degrees of atypia. Mitoses were common in carcinomas, as were areas of necrosis, mineralization, and cholesterol clefts.

Follicular cell adenomas were characterized by branching papillary or follicular patterns of relatively uniform cuboidal to columnar cells on a delicate fibrovascular stroma. Adenomas were well demarcated and cells were hyperchromatic, while mitotic figures were rare. The incidence of follicular cell hyperplasia was significantly increased in 32 ppm males. Follicular cell hyperplasia was focal and characterized by one or a few enlarged follicles with several much smaller follicles inside and to one side. The increased number of cells resulted in a few simple papillary projections into the lumen.

TABLE 10
Incidences of Neoplasms and Nonneoplastic Lesions of the Thyroid Gland in Rats in the 2-Year Inhalation Study of Chloroprene

	Chamber Control	12.8 ppm	32 ppm	80 ppm
Male				
Number Examined Microscopically	50	50	49	50
Follicular Cell Hyperplasia[a]	0	2 (2.0)[b]	4* (1.8)	1 (1.0)
Follicular Cell Adenoma[c]				
Overall rate[d]	0/50 (0%)	2/50 (4%)	2/49 (4%)	4/50 (8%)
Follicular Cell Carcinoma				
Overall rate	0/50 (0%)	0/50 (0%)	2/49 (4%)	1/50 (2%)
Follicular Cell Adenoma or Carcinoma[e]				
Overall rate	0/50 (0%)	2/50 (4%)	4/49 (8%)	5/50 (10%)
Adjusted rate[f]	0.0%	13.5%	29.5%	36.3%
Terminal rate[g]	0/13 (0%)	1/9 (11%)	1/5 (20%)	1/4 (25%)
First incidence (days)	—[i]	597	569	307
Logistic regression test[h]	P = 0.029	P = 0.232	P = 0.050	P = 0.044
Female				
Number Examined Microscopically	49	50	50	50
Follicular Cell, Hyperplasia	0	0	0	2 (2.5)
Follicular Cell Adenoma[j]				
Overall rate	1/49 (2%)	1/50 (2%)	0/50 (0%)	3/50 (6%)
Follicular Cell Carcinoma				
Overall rate	0/49 (0%)	0/50 (0%)	1/50 (2%)	2/50 (4%)
Follicular Cell Adenoma or Carcinoma[k]				
Overall rate	1/49 (2%)	1/50 (2%)	1/50 (2%)	5/50 (10%)
Adjusted rate	3.4%	3.2%	3.8%	16.8%
Terminal rate	1/29 (3%)	0/28 (0%)	1/26 (4%)	1/21 (5%)
First incidence (days)	733 (T)	721	733 (T)	617
Logistic regression test	P = 0.017	P = 0.753N	P = 0.738	P = 0.098

* Significantly different ($P \leq 0.05$) from the chamber control group by the logistic regression test
(T)Terminal sacrifice
[a] Number of animals with lesion
[b] Average severity grade of lesions in affected animals: 1 = minimal; 2 = mild; 3 = moderate; 4 = marked
[c] Historical incidence for 2-year inhalation studies with chamber controls (mean ± standard deviation): 3/641 (0.5% ± 0.9%); range 0%-2%
[d] Number of animals with neoplasm per number of animals with thyroid gland examined microscopically
[e] Historical incidence: 11/641 (1.7% ± 1.6%); range 0%-4%
[f] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[g] Observed incidence in animals surviving until the end of the study
[h] In the chamber control column are the P values associated with the trend test. In the exposed group columns are the P values corresponding to the pairwise comparisons between the chamber controls and that exposed group. The logistic regression test regards lesions in animals dying prior to terminal kill as nonfatal. A lower incidence in an exposure group is indicated by **N**.
[i] Not applicable; no neoplasms in animal group
[j] Historical incidence: 2/642 (0.3% ± 0.8%); range 0%-2%
[k] Historical incidence: 8/642 (1.3% ± 1.9%); range 0%-6%

Lung: The incidences of alveolar epithelial hyperplasia were significantly greater in all exposed groups of males and females than in the chamber control groups (Table 11). Most hyperplasia was graded minimal; however, exposed rats had more foci of hyperplasia per lung section than did chamber controls. The incidences of alveolar/bronchiolar carcinoma and alveolar/bronchiolar adenoma or carcinoma (combined) in 80 ppm males were slightly greater than those in the chamber control group (Tables 11 and A1). Although these incidences were not significant, they exceeded the historical control range for these neoplasms (Table A4c). Furthermore, one male exposed to 80 ppm had multiple alveolar/bronchiolar carcinomas, and one male exposed to 80 ppm and one exposed to 32 ppm had carcinomas which metastasized to mediastinum or bronchial lymph nodes (Table A1). Although not significant, the incidence of alveolar/bronchiolar adenoma was greater in 80 ppm females than in the chamber controls. Alveolar/bronchiolar carcinomas were solid or papillary, obliterated normal pulmonary architecture, and sometimes invaded the pleura or other adjacent structures. A scirrhous response was seen in some carcinomas. Cells were cuboidal to columnar but often pleomorphic, with a high nucleus:cytoplasm ratio and numerous mitoses. Alveolar adenomas were usually papillary and distorted the alveolar architecture. Cells were cuboidal to columnar and well differentiated.

TABLE 11
Incidences of Neoplasms and Nonneoplastic Lesions of the Lung in Rats in the 2-Year Inhalation Study of Chloroprene

	Chamber Control	12.8 ppm	32 ppm	80 ppm
Male				
Number Examined Microscopically	50	50	49	50
Alveolar Epithelium, Hyperplasia[a]	5 (1.4)[b]	16** (1.4)	14* (1.9)	25** (1.4)
Alveolar/bronchiolar Adenoma				
Overall rate[c]	2/50 (4%)	0/50 (0%)	3/49 (6%)	3/50 (6%)
Alveolar/bronchiolar Carcinoma[d]				
Overall rate	0/50 (0%)	2/50 (4%)	1/49 (2%)	4/50 (8%)
Adjusted rate[e]	0.0%	17.9%	6.7%	35.1%
Terminal rate[f]	0/13 (0%)	1/9 (11%)	0/5 (0%)	1/4 (25%)
First incidence (days)	—[h]	702	667	540
Logistic regression test[g]	P = 0.023	P = 0.200	P = 0.452	P = 0.052
Alveolar/bronchiolar Adenoma or Carcinoma[i]				
Overall rate	2/50 (4%)	2/50 (4%)	4/49 (8%)	6/50 (12%)
Adjusted rate	6.9%	17.9%	19.9%	59.3%
Terminal rate	0/13 (0%)	1/9 (11%)	0/5 (0%)	2/4 (50%)
First incidence (days)	616	702	505	540
Logistic regression test	P = 0.039	P = 0.684	P = 0.366	P = 0.094
Female				
Number Examined Microscopically	49	50	50	50
Alveolar Epithelium, Hyperplasia	6 (1.8)	22** (1.4)	22** (1.5)	34** (1.3)
Alveolar/bronchiolar Adenoma[j]				
Overall rate	1/49 (2%)	0/50 (0%)	0/50 (0%)	3/50 (6%)
Adjusted rate	3.4%	0.0%	0.0%	9.6%
Terminal rate	1/29 (3%)	0/28 (0%)	0/26 (0%)	1/21 (5%)
First incidence (days)	733 (T)	—	—	613
Logistic regression test	P = 0.066	P = 0.507N	P = 0.522N	P = 0.314

* Significantly different ($P \leq 0.05$) from the chamber control group by the logistic regression 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
[c] Number of animals with neoplasm per number of animals with lung examined microscopically
[d] Historical incidence for 2-year inhalation studies with chamber controls (mean ± standard deviation): 6/654 (0.9% ± 1.0%); range 0%-2%
[e] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[f] Observed incidence in animals surviving until the end of the study
[g] In the chamber control column are the P values associated with the trend test. In the exposed group columns are the P values corresponding to the pairwise comparisons between the chamber controls and that exposed group. The logistic regression test regards lesions in animals dying prior to terminal kill as nonfatal. A lower incidence in an exposure group is indicated by **N**
[h] Not applicable; no neoplasms in animal group
[i] Historical incidence: 23/654 (3.5% ± 3.7%); range 0%-10%
[j] Historical incidence: 7/650 (1.1% ± 1.6%); range 0%-4%

Mammary Gland: The incidences of multiple fibroadenoma in all exposed groups of female rats were greater than that in the chamber control group (Tables 12 and B1). The incidences of fibroadenoma (including multiple fibroadenoma) in 32 and 80 ppm females were significantly greater than that in the chamber controls (Tables 12, B1, and B3). The incidences of fibroadenoma in the chamber control group and in all exposed groups of females exceeded the historical control range (Tables 12 and B4d). Fibroadenomas were characterized by collections of glandular epithelium arranged in acini and ducts and surrounded by fibrous connective tissue. The relative amounts of glandular and fibrous elements varied greatly among neoplasms. Epithelial cells were usually uniform and arranged in a single layer; a few fibroadenomas had small areas of cellular atypia.

TABLE 12
Incidences of Neoplasms of the Mammary Gland in Female Rats in the 2-Year Inhalation Study of Chloroprene

	Chamber Control	12.8 ppm	32 ppm	80 ppm
Fibroadenoma (multiple)				
Overall rate[a]	5/49 (10%)	12/50 (24%)	15/50 (30%)**	19/50 (38%)*
Fibroadenoma (includes multiple)[b]				
Overall rate	24/49 (49%)	32/50 (64%)	36/50 (72%)	36/50 (72%)
Adjusted rate[c]	65.4%	86.0%	85.3%	89.7%
Terminal rate[d]	17/29 (59%)	23/28 (82%)	20/26 (77%)	17/21 (81%)
First incidence (days)	366	302	470	433
Logistic regression test[e]	P = 0.005	P = 0.130	P = 0.011	P = 0.009

* Significantly different ($P \leq 0.05$) from the chamber control group by the logistic regression test
** $P \leq 0.01$
[a] Number of animals with neoplasm per number of animals necropsied
[b] Historical incidence for 2-year inhalation studies with chamber controls (mean ± standard deviation): 180/653 (27.6% ± 7.7%); range 16%-42%
[c] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[d] Observed incidence in animals surviving until the end of the study
[e] In the chamber control column are the P values associated with the trend test. In the exposed group columns are the P values corresponding to the pairwise comparisons between the chamber controls and that exposed group. The logistic regression test regards lesions in animals dying prior to terminal kill as nonfatal.

Kidney: The severity of nephropathy in exposed groups of male and female rats was slightly greater than in the chamber controls (Table 13). The incidences of renal tubule nephropathy in 32 and 80 ppm females were significantly increased relative to that in the chamber control group (Tables 13 and B5). Initially, a single hematoxylin- and eosin-stained section of each kidney was prepared. Primarily because of the slightly increased trends and incidences of renal tubule hyperplasia and renal tubule adenoma identified in male and female rats by the standard evaluation, additional step sections of kidney were prepared from the remaining formalin-fixed tissues. Eight additional kidney sections taken at 1-mm intervals were prepared for each male and female. Additional males and females with focal hyperplasia or adenomas and one 12.8 ppm male with a carcinoma were identified. The incidences of these proliferative lesions in standard and extended evaluations are presented in Table 13.

The step-section and combined single- and step-section incidences of renal tubule hyperplasia in 32 ppm males and 80 ppm males and females were significantly greater than those in the chamber controls. In all exposed groups of males, the step-section and combined single- and step-section incidences of

TABLE 13
Incidences of Neoplasms and Nonneoplastic Lesions of the Kidney in Rats in the 2-Year Inhalation Study of Chloroprene

	Chamber Control	12.8 ppm	32 ppm	80 ppm
Male				
Number Examined Microscopically	50	50	50	50
Single Sections (Standard Evaluation)				
Nephropathy[a]	50 (2.8)[b]	50 (3.0)	50 (3.1)	50 (3.5)**
Renal Tubule Hyperplasia	2 (2.5)	3 (2.3)	6 (2.5)	6 (1.8)
Oncocytic Hyperplasia	0	0	0	2 (2.5)
Mesenchymal Tumor, NOS				
Overall rate[c]	0/50 (0%)	0/50 (0%)	0/50 (0%)	2/50 (4%)
Renal Tubule Adenoma[d]				
Overall rate	0/50 (0%)	1/50 (0%)	1/50 (2%)	2/50 (4%)
Step Sections (Extended Evaluation)				
Renal Tubule Hyperplasia	12 (1.9)	19 (2.6)	27** (2.0)	34** (2.8)
Renal Tubule Adenoma				
Overall rate	1/50 (2%)	6/50 (12%)	6/50 (12%)	7/50 (14%)
Adjusted rate[e]	7.7%	37.0%	52.5%	65.9%
Terminal rate[f]	1/13 (8%)	2/9 (22%)	0/5 (0%)	2/4 (50%)
First incidence (days)	733 (T)	600	679	625
Logistic regression test[g]	P = 0.010	P = 0.047	P = 0.007	P = 0.005
Renal Tubule Adenoma or Carcinoma				
Overall rate	1/50 (2%)	7/50 (14%)	6/50 (12%)	7/50 (14%)
Adjusted rate	7.7%	39.8%	52.5%	65.9%
Terminal rate	1/13 (8%)	2/9 (22%)	0/5 (0%)	2/4 (50%)
First incidence (days)	733 (T)	600	679	625
Logistic regression test	P = 0.016	P = 0.025	P = 0.007	P = 0.005
Single Sections and Step Sections (Combined)				
Renal Tubule Hyperplasia	14 (2.0)	20 (2.6)	28** (2.1)	34** (2.9)
Renal Tubule Adenoma				
Overall rate	1/50 (2%)	7/50 (14%)	6/50 (12%)	8/50 (16%)
Adjusted rate	7.7%	40.7%	52.5%	70.7%
Terminal rate	1/13 (8%)	2/9 (22%)	0/5 (0%)	2/4 (50%)
First incidence (days)	733 (T)	600	679	625
Logistic regression test	P = 0.005	P = 0.024	P = 0.007	P = 0.002
Renal Tubule Adenoma or Carcinoma				
Overall rate	1/50 (2%)	8/50 (16%)	6/50 (12%)	8/50 (16%)
Adjusted rate	7.7%	43.4%	52.5%	70.7%
Terminal rate	1/13 (8%)	2/9 (22%)	0/5 (0%)	2/4 (50%)
First incidence (days)	733 (T)	600	679	625
Logistic regression test	P = 0.008	P = 0.013	P = 0.007	P = 0.002

TABLE 13
Incidences of Neoplasms and Nonneoplastic Lesions of the Kidney in Rats in the 2-Year Inhalation Study of Chloroprene

	Chamber Control	12.8 ppm	32 ppm	80 ppm
Female				
Number Examined Microscopically	49	50	50	50
Single Sections (Standard Evaluation)				
Nephropathy	43 (1.9)	48 (2.0)	49* (2.0)	49* (2.2)*
Renal Tubule Hyperplasia	0	0	1 (2.0)	4 (1.5)
Oncocytic Hyperplasia	0	0	0	1 (2.0)
Mesenchymal Tumor, NOS				
Overall rate	0/49 (0%)	0/50 (0%)	0/50 (0%)	1/50 (2%)
Renal Tubule Adenoma[h]				
Overall rate	0/49 (0%)	0/50 (0%)	0/50 (0%)	2/50 (4%)
Step Sections (Extended Evaluation)				
Renal Tubule Hyperplasia	6 (1.3)	6 (1.8)	11 (2.1)	19** (1.9)
Renal Tubule Adenoma				
Overall rate	0/49 (0%)	0/50 (0%)	0/50 (0%)	2/50 (4%)
Single Sections and Step Sections (Combined)				
Renal Tubule Hyperplasia	6 (1.3)	6 (1.8)	11 (2.1)	21** (2.0)
Renal Tubule Adenoma or Carcinoma				
Overall rate	0/49 (0%)	0/50 (0%)	0/50 (0%)	4/50 (8%)

* Significantly different ($P \leq 0.05$) from the chamber control group by the logistic regression test (incidences) or by the Mann-Whitney U test (severity)
** $P \leq 0.01$
(T)Terminal sacrifice
[a] Number of animals with lesion
[b] Average severity grade of lesions in affected animals: 1 = minimal; 2 = mild; 3 = moderate; 4 = marked
[c] Number of animals with lesion per number of animals microscopically examined
[d] Historical incidence for 2-year inhalation studies with chamber controls (mean ± standard deviation): 6/652 (0.9% ± 1.3%); range 0%-4%
[e] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[f] Observed incidence in animals surviving until the end of the study
[g] In the chamber control column are the P values associated with the trend test. In the exposed group columns are the P values corresponding to the pairwise comparisons between the chamber controls and that exposed group. The logistic regression test regards lesions in animals dying prior to terminal kill as nonfatal.
[h] Historical incidence: 1/650 (0.2% ± 0.6%); range 0%–2%

renal tubule adenoma and renal tubule adenoma or carcinoma (combined) were significantly greater than those in the chamber control group. Renal tubule hyperplasia, as defined in the present study, was distinguished from regenerative epithelial changes commonly seen as a part of nephropathy and was considered a preneoplastic lesion. Renal tubule hyperplasia, adenoma, and carcinoma constitute a morphologic continuum. Hyperplasia was generally a focal, minimal to mild lesion consisting of tubules that were dilated to l.5 to 2 times the normal diameter and were lined by increased numbers of tubule epithelial cells that partially or totally filled the tubule lumen. Cells within hyperplastic lesions varied slightly in size and sometimes stained more basophilic then normal cells but otherwise appeared similar to normal tubule epithelial cells. Renal tubule adenomas were larger, discrete lesions ranging from greater than five tubule diameters to 1 mm or more in size. Cells within adenomas were mildly to moderately pleomorphic,

sometimes had vacuolated cytoplasm, and tended to form complex patterns, particularly microtubular structures. Renal tubule carcinoma was well differentiated from adenoma in that it was larger and less discrete and had a prominent vascular supply, more anaplasia, and more cellular atypia. Renal tubule carcinoma was characterized by vesiculate nuclei with prominent nucleoli and increased numbers of mitotic figures. Oncocytic hyperplasia was observed at the end of the study in two males and one female exposed to 80 ppm. This lesion was characterized by individual tubules or small clusters of tubules that were somewhat dilated and totally filled by large polygonal cells with abundant, brightly eosinophilic, granular cytoplasm and small, centrally located, basophilic nuclei (oncocytes). These lesions are thought to arise from the distal tubule epithelium. Transitional cell neoplasms were also observed in one male and one female in the 12.8 ppm groups. In addition, mesenchymal tumors of the kidney were observed in one male and one female exposed to 80 ppm (Tables A1 and B1).

Urinary Bladder: Two 80 ppm females had transitional epithelium carcinomas (Table B1). One transitional epithelium carcinoma was observed in a 32 ppm male, and one transitional cell papilloma was observed in an 80 ppm male (Table A1). These findings are noteworthy because no urinary bladder neoplasms have been seen in chamber control male or female F344/N rats (Tables A4e and B4f).

Nose (Olfactory Epithelium): The incidences of atrophy, basal cell hyperplasia, metaplasia, and necrosis of the olfactory epithelium in 32 and 80 ppm males and females and atrophy and necrosis in 12.8 ppm males were significantly greater than those in the chamber control groups (Tables 14, A5, and B5). The incidences of chronic inflammation were significantly increased in males exposed to 12.8 or 32 ppm and in males and females exposed to 80 ppm. The incidences of fibrosis and adenomatous hyperplasia in 80 ppm males and females were significantly greater than those in the chamber controls. Lesions in the nasal cavity were generally minimal to mild in severity. Necrosis of the olfactory epithelium was characterized by areas of karyorrhexis and sloughing of olfactory epithelium with cell debris in the lumen in the dorsal meatus. Chronic inflammation was characterized by serofibrinous exudate (neutrophils, fibrin, proteinaceous fluid, cell debris) in the lumen of Levels II and III with necrosis and fusion of turbinates. Most often involved were the dorsal meatus, dorsal septum, and adjacent portions of ethmoid turbinates. Atrophy of the olfactory epithelium was characterized by decreased numbers of layers of olfactory epithelium and included loss of Bowman's glands and olfactory axons in more severe cases. Atrophy was usually accompanied by respiratory metaplasia. Metaplasia of the olfactory epithelium was characterized by replacement of olfactory epithelium with ciliated, columnar, respiratory-like epithelium. Adenomatous hyperplasia of the olfactory epithelium was characterized by proliferation of respiratory-like epithelium in areas of inflammation, usually involving the dorsal septum and adjacent portions of turbinates (Plates 5 and 6). The epithelium was taller than normal and had increased numbers of cells, including goblet cells; underlying glands were often lined by goblet cells and dilated by mucus. The hyperplasia varied in severity from forming a few folds in the epithelium, to folds with accompanying hyperplastic glands, to extensive papillary formations. It was primarily observed in the 80 ppm groups. Basal cell hyperplasia of the olfactory epithelium was characterized by proliferation or increased thickness of the basal cell layer in turbinates and septum of Level III and dorsally in Level II (Plates 7 and 8). Fibrosis of the olfactory epithelium was characterized by replacement of normal lamina propria in turbinates and septum of Level III with collagenous connective tissue. It was usually associated with basal cell hyperplasia. Focal fibrosis of the turbinate was characterized by turbinates that were abnormally fused with the septum or each other, and there was no active inflammation in the section. Such fusion was found in a few rats exposed to 12.8 or 32 ppm and may have represented a healed site of previous necrosis.

TABLE 14
Incidences of Nonneoplastic Lesions of the Olfactory Epithelium in Rats in the 2-Year Inhalation Study of Chloroprene

	Chamber Control		12.8 ppm		32 ppm		80 ppm	
Male								
Number Examined Microscopically	50		50		49		49	
Atrophy[a]	3	(1.7)[b]	12*	(1.8)	46**	(2.2)	48**	(3.6)
Fibrosis	0		0		0		47**	(2.7)
Hyperplasia, Adenomatous	2	(2.0)	0		1	(2.0)	42**	(2.0)
Hyperplasia, Basal Cell	0		0		38**	(1.6)	46**	(2.2)
Inflammation, Chronic Active	0		5*	(1.0)	9**	(1.6)	49**	(2.7)
Metaplasia	6	(1.7)	5	(1.0)	45**	(1.8)	48**	(3.1)
Necrosis	0		11**	(2.0)	26**	(2.0)	19**	(2.2)
Female								
Number Examined Microscopically	49		50		50		50	
Atrophy	0		1	(1.0)	40**	(1.3)	50**	(2.9)
Fibrosis	0		0		0		49**	(2.2)
Hyperplasia, Adenomatous	0		0		0		27**	(2.0)
Hyperplasia, Basal Cell	0		0		17**	(1.1)	49**	(2.3)
Inflammation, Chronic Active	0		0		2	(1.0)	33**	(2.0)
Metaplasia	0		1	(1.0)	35**	(1.0)	50**	(2.7)
Necrosis	0		0		8**	(2.0)	12**	(1.3)

* Significantly different ($P \leq 0.05$) from the chamber control group by the logistic regression 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

16-DAY STUDY

All males and females exposed to 200 ppm died on day 2 or day 3 of the study (Table 15). Mean body weight gains of males exposed to 32 or 80 ppm were significantly less than that of the chamber control group. Mice exposed to 200 ppm exhibited narcosis during exposure and were hypoactive with reduced body tone after the first day of exposure. There were no other clinical findings related to chloroprene exposure.

TABLE 15
Survival and Body Weights of Mice in the 16-Day Inhalation Study of Chloroprene

Dose (ppm)	Survival[a]	Mean Body Weight[b] (g)			Final Weight Relative to Controls (%)
		Initial	Final	Change	
Male					
0	10/10	24.7 ± 0.5	27.0 ± 0.5	2.3 ± 0.1	
12	10/10	24.8 ± 0.5	27.1 ± 0.6	2.3 ± 0.3	100
32	10/10	25.3 ± 0.3	26.5 ± 0.3	1.2 ± 0.3**	98
80	10/10	24.8 ± 0.5	26.1 ± 0.6	1.3 ± 0.2**	97
200	0/10[c]	24.2 ± 0.4	—	—	—
Female					
0	10/10	19.5 ± 0.7	22.6 ± 0.5	2.3 ± 0.3	
12	10/10	20.4 ± 0.8	23.1 ± 0.4	2.6 ± 0.3	102
32	10/10	19.9 ± 1.0	22.1 ± 0.2	1.8 ± 0.3	98
80	10/10	20.1 ± 0.8	22.5 ± 0.3	2.7 ± 0.3	100
200	0/10[d]	20.0 ± 0.6	—	—	—

** Significantly different ($P \leq 0.01$) from the chamber control group by Williams' or Dunnett's test
[a] Number of animals surviving at 16 days/number initially in group
[b] Weights and weight changes are given as mean ± standard error. No data were calculated for groups with 100% mortality.
[c] Day of death: 2, 2, 2, 2, 2, 3, 3, 3, 3, 3
[d] Day of death: 2, 2, 2, 2, 2, 2, 3, 3, 3, 3

In general, hematology and clinical chemistry parameters measured for exposed males and females were similar to those of the chamber control group (Table G3).

The absolute and relative thymus weights of 80 ppm rats were significantly less than those of the chamber control groups (Table F3). The absolute and relative liver weights of 80 ppm females and relative liver weights of 80 ppm males were significantly greater than those of the chamber control groups.

Increased incidences of multifocal random hepatocellular necrosis occurred in males and females exposed to 200 ppm. Hypertrophy of the myocardium, foci of hemorrhage, and mucosal erosion were observed in three males and three females exposed to 200 ppm. Squamous epithelial hyperplasia of the forestomach was observed in two males and two females exposed to 80 ppm. Thymic necrosis, characterized by karyorrhexis of thymic lymphocytes, was observed in all males and females in the 200 ppm groups.

13-WEEK STUDY

All male and female mice survived to the end of the study (Table 16). The final mean body weight and body weight gain of males exposed to 80 ppm were significantly less than those of the chamber control group. There were no clinical findings attributed to chloroprene exposure.

TABLE 16
Survival and Body Weights of Mice in the 13-Week Inhalation Study of Chloroprene

Dose (ppm)	Survival[a]	Mean Body Weight[b] (g)			Final Weight Relative to Controls (%)
		Initial	Final	Change	
Male					
0	10/10	25.5 ± 0.4	35.9 ± 0.9	10.5 ± 0.7	
5	10/10	25.2 ± 0.3	35.1 ± 0.9	10.0 ± 0.7	98
12	10/10	25.2 ± 0.2	34.9 ± 0.6	9.7 ± 0.6	97
32	10/10	25.4 ± 0.2	36.0 ± 0.9	10.6 ± 0.9	100
80	10/10	24.7 ± 0.3	32.7 ± 0.6*	7.9 ± 0.5*	91
Female					
0	10/10	20.4 ± 0.2	30.3 ± 1.0	9.9 ± 0.9	
5	10/10	20.9 ± 0.3	32.2 ± 0.9	11.3 ± 0.9	106
12	10/10	20.4 ± 0.3	30.1 ± 0.6	9.7 ± 0.6	99
32	10/10	20.8 ± 0.2	32.6 ± 0.8	11.8 ± 0.7	108
80	10/10	20.5 ± 0.2	30.2 ± 1.3	9.7 ± 1.2	100

* Significantly different ($P \leq 0.05$) from the chamber control group by Williams' or Dunnett's test
[a] Number of animals surviving at 13 weeks/number initially in group
[b] Weights and weight changes are given as mean ± standard error.

The hematology and clinical chemistry data are listed in Table G4. In general, changes in the hematology variables were similar to, albeit milder than, what occurred in the 13-week rat study. At week 13, a minimal anemia evidenced by decreases of hematocrit values and erythrocyte counts occurred in 32 and 80 ppm female mice. The anemia was characterized as normocytic, normochromic, and nonresponsive, as evidenced by the lack of alterations in mean cell volume, mean cell hemoglobin concentration, and reticulocyte values. Additionally, platelet counts were minimally increased in 32 and 80 ppm females, suggesting an increase in platelet production.

No biologically significant organ weight effects were observed (Table F4). Sperm morphology and vaginal cytology parameters of exposed male and female mice were similar to those of the chamber controls (Table I2).

Significantly increased incidences of squamous epithelial hyperplasia of the forestomach occurred in males and females exposed to 80 ppm (Table 17). Hyperplasia was characterized by minimal to mild thickening and folding of the forestomach epithelium. Most of the lesions were somewhat multifocal to diffuse and were located at the pole of the forestomach. Hyperplasia was usually limited to acanthosis and minimal hyperkeratosis. The underlying muscular layers of the forestomach tended to be thickened, and the submucosa occasionally had a minimal to mild mixed inflammatory cell infiltrate.

Exposure Concentration Selection Rationale: Based on mortality in mice exposed to 200 ppm chloroprene in the 16-day study, the highest exposure concentration selected for the 2-year study was 80 ppm. Squamous epithelial hyperplasia of the forestomach, observed at 80 ppm in the 13-week study, was not considered to be life threatening.

TABLE 17
Incidences of Forestomach Lesions in Mice in the 13-Week Inhalation Study of Chloroprene

	Chamber Control	5 ppm	12 ppm	32 ppm	80 ppm	
Male						
Number Examined Microscopically	10	3	0	10	10	
Squamous Epithelial Hyperplasia[a]	0	0	0	0	4*	(1.5)[b]
Female						
Number Examined Microscopically	10	0	0	10	10	
Squamous Epithelial Hyperplasia	0	0	0	0	9**	(1.9)

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

2-YEAR STUDY

Survival

Estimates of 2-year survival probabilities for male and female mice are shown in Table 18 and in the Kaplan-Meier survival curves (Figure 3). Survival of males exposed to 32 or 80 ppm and all groups of exposed females was significantly less than that of the chamber controls.

Body Weights and Clinical Findings

The mean body weights of 80 ppm females were less than those of the chamber control group after week 75 (Tables 19 and 20 and Figure 4). The mean body weights of 32 ppm females were greater than those of the chamber control group after week 97, but the body weights were based on, at the most, three animals. Clinical findings included masses of the head, which correlated with harderian gland adenoma and/or carcinoma in 32 ppm males and 80 ppm males and females. Dorsal and lateral torso masses of female mice correlated with mammary gland neoplasms in 32 and 80 ppm females and subcutaneous sarcoma in 12.8, 32, and 80 ppm females.

TABLE 18
Survival of Mice in the 2-Year Inhalation Study of Chloroprene

	Chamber Control	12.8 ppm	32 ppm	80 ppm
Male				
Animals initially in study	50	50	50	50
Moribund	15	16	26	34
Natural deaths	8	7	10	3
Animals surviving to study termination	27	27	14	13
Percent probability of survival at end of study[a]	54	54	28	26
Mean survival (days)[b]	689	683	646	646
Survival analysis[c]	P < 0.001	P = 1.000	P = 0.007	P = 0.003
Female				
Animals initially in study	50	50	50	50
Accidental death[d]	0	1	0	1
Moribund	13	27	38	41
Natural deaths	2	6	11	5
Animals surviving to study termination	35	16	1	3[e]
Percent probability of survival at end of study	70	33	2	6
Mean survival (days)	686	641	558	562
Survival analysis	P < 0.001	P < 0.001	P < 0.001	P < 0.001

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

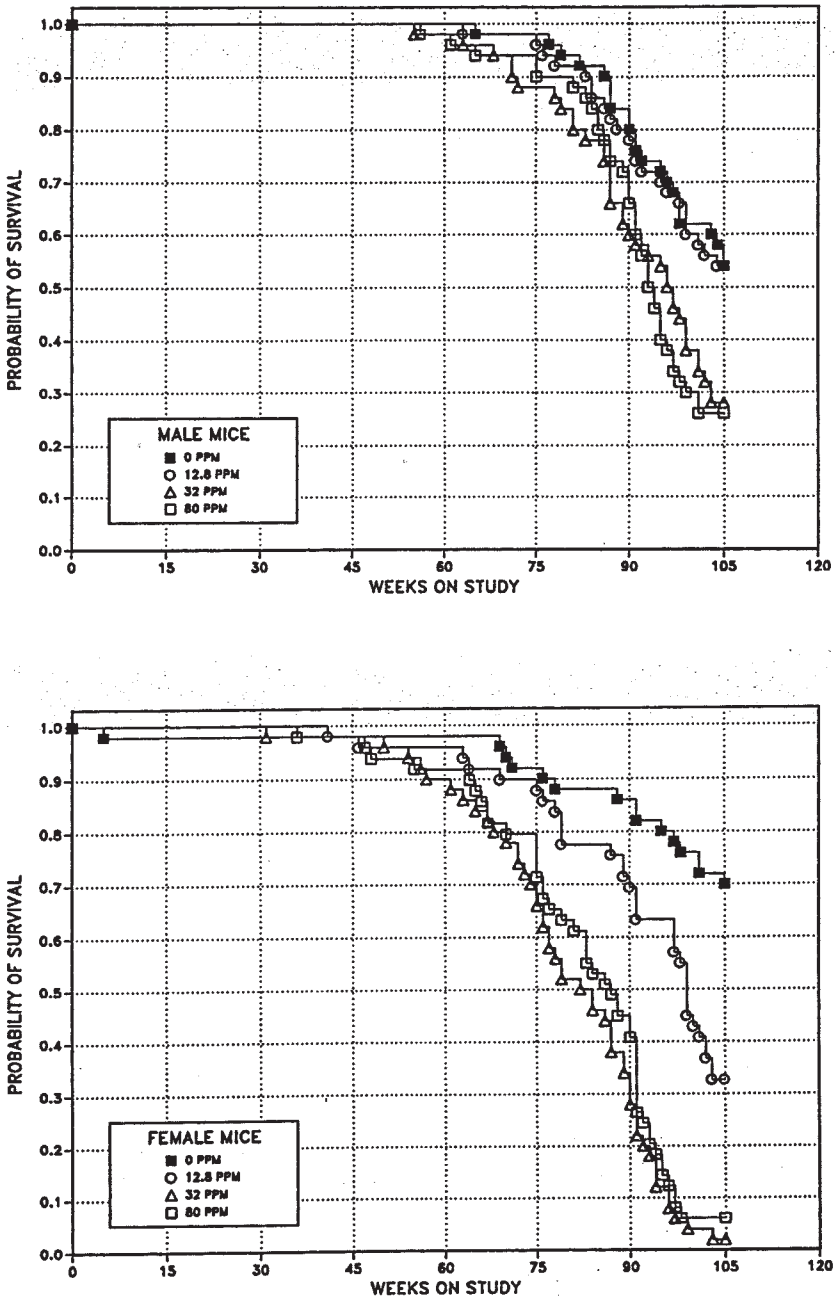


FIGURE 3
Kaplan-Meier Survival Curves for Male and Female Mice Exposed to Chloroprene by Inhalation for 2 Years

TABLE 19
Mean Body Weights and Survival of Male Mice in the 2-Year Inhalation Study of Chloroprene

Weeks on Study	Chamber Control		12.8 ppm			32 ppm			80 ppm		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	24.9	50	25.0	100	50	24.5	98	50	24.4	98	50
2	26.6	50	27.0	102	50	26.0	98	50	25.9	97	50
3	27.4	50	27.6	101	50	27.2	99	50	26.8	98	50
4	27.9	50	28.4	102	50	28.1	101	50	27.9	100	50
5	28.8	50	29.0	101	50	28.9	100	50	28.6	99	50
6	29.7	50	29.9	101	50	29.7	100	50	29.5	99	50
7	30.2	50	30.3	100	50	30.4	101	50	29.5	98	50
8	30.7	50	30.9	101	50	30.5	99	50	30.1	98	50
9	31.5	50	31.3	99	50	31.0	98	50	30.5	97	50
10	32.1	50	32.2	100	50	31.8	99	50	31.2	97	50
11	32.6	50	32.8	101	50	32.3	99	50	31.9	98	50
12	32.4	50	33.7	104	50	33.3	103	50	32.4	100	50
15	34.3	50	35.6	104	50	35.0	102	50	34.0	99	50
19	36.9	50	38.8	105	50	37.8	102	50	37.1	101	50
23	38.7	50	40.1	104	50	39.6	102	50	38.6	100	50
27	40.4	50	42.1	104	50	41.6	103	50	40.9	101	50
31	42.2	50	44.0	104	50	43.2	102	50	42.8	101	50
35	43.9	50	45.6	104	50	44.6	102	50	44.5	101	50
39	45.3	50	46.6	103	50	45.8	101	50	45.3	100	50
43	46.4	50	47.0	101	50	46.8	101	50	45.5	98	50
47	46.1	50	47.1	102	50	47.4	103	50	46.3	100	50
51	47.0	50	47.5	101	50	47.7	102	50	46.8	100	50
55	47.2	50	48.4	103	50	48.3	102	49	47.4	100	50
59	48.3	50	49.1	102	50	49.2	102	49	48.5	100	49
63	48.8	50	48.7	100	50	49.4	101	49	48.6	100	48
67	49.3	49	49.6	101	49	49.9	101	48	49.1	100	47
71	48.8	49	49.2	101	49	49.5	101	46	48.1	99	47
75	49.3	49	50.1	102	48	50.4	102	44	48.7	99	46
79	49.4	48	50.4	102	46	50.3	102	43	48.8	99	45
83	49.0	46	49.5	101	46	49.6	101	40	47.9	98	44
87	48.5	43	49.5	102	42	50.2	104	35	47.1	97	38
91	47.5	40	49.8	105	39	51.2	108	30	45.8	96	33
93	47.6	37	50.0	105	36	51.1	107	29	45.3	95	28
95	47.2	37	49.6	105	35	49.8	106	28	45.3	96	21
97	47.0	34	48.6	103	34	49.1	105	25	44.3	94	19
99	46.4	31	47.5	102	32	48.4	104	20	44.9	97	15
101	46.4	31	46.6	100	29	47.0	101	18	43.7	94	13
103	44.8	31	45.1	101	28	46.1	103	14	42.4	95	13
Mean for weeks											
1-13	29.6		29.9	101		29.5	100		29.1	98	
14-52	42.1		43.4	103		43.0	102		42.2	100	
53-103	47.8		48.9	102		49.3	103		46.6	97	

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

Weeks on Study	Chamber Control		12.8 ppm			32 ppm			80 ppm		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	19.8	50	20.1	102	50	20.0	101	50	19.7	100	50
2	21.8	50	21.8	100	50	21.9	101	50	21.5	99	49
3	22.9	50	22.7	99	50	23.1	101	50	22.2	97	49
4	23.4	50	23.8	102	50	23.8	102	50	23.1	99	49
5	24.2	50	24.5	101	50	24.6	102	50	23.9	99	49
6	25.1	49	25.2	100	50	25.8	103	50	25.0	100	49
7	26.0	49	25.8	99	50	26.4	102	50	25.2	97	49
8	26.1	49	26.2	100	50	26.3	101	50	25.8	99	49
9	26.0	49	26.6	102	50	26.4	102	50	26.1	100	49
10	27.0	49	27.1	100	50	27.4	102	50	26.9	100	49
11	27.7	49	28.1	101	50	28.1	101	50	27.1	98	49
12	27.8	49	28.8	104	50	28.4	102	50	27.6	99	49
15	29.8	49	31.0	104	50	29.8	100	50	28.4	95	49
19	31.6	49	33.3	105	50	32.2	102	50	30.6	97	49
23	34.1	49	35.5	104	50	34.5	101	50	32.3	95	49
27	36.9	49	38.3	104	50	37.1	101	50	35.5	96	49
31	38.0	49	40.3	106	50	38.4	101	50	37.2	98	49
35	40.2	49	42.8	107	50	41.2	103	49	39.9	99	49
39	42.1	49	44.8	106	50	42.9	102	49	41.7	99	48
43	44.6	49	45.7	103	49	45.2	101	49	42.6	96	48
47	44.8	49	46.9	105	47	47.0	105	49	45.2	101	47
51	46.5	49	48.3	104	47	47.6	102	48	46.1	99	46
55	47.3	49	50.3	106	47	49.8	105	47	47.6	101	46
59	49.4	49	52.3	106	47	51.6	105	45	49.4	100	45
63	50.7	49	53.7	106	47	53.1	105	44	50.1	99	45
67	51.8	49	54.3	105	45	54.6	105	41	51.7	100	41
71	52.4	46	55.1	105	44	55.6	106	39	52.0	99	39
75	54.6	46	56.4	103	43	56.5	104	34	52.1	95	38
79	56.2	44	57.2	102	40	57.7	103	28	53.1	95	31
83	56.1	44	57.0	102	38	57.4	102	25	51.7	92	29
87	56.0	44	57.0	102	38	54.5	97	21	51.6	92	25
91	54.7	43	57.7	106	32	55.0	101	11	48.7	89	15
93	54.9	41	57.9	106	31	53.3	97	10	47.7	87	12
95	54.2	41	56.2	104	31	56.5	104	6	47.6	88	8
97	53.6	40	54.9	102	29	57.3	107	3	47.4	88	4
99	52.8	38	52.2	99	24	54.0	102	3	46.0	87	3
101	51.8	38	52.5	101	19	55.3	107	2	46.6	90	3
103	51.1	36	51.7	101	18	60.0	117	1	46.7	91	3
Mean for weeks											
1-13	24.8		25.1	101		25.2	102		24.5	99	
14-52	38.9		40.7	105		39.6	102		38.0	98	
53-103	53.0		54.8	104		55.1	104		49.4	93	

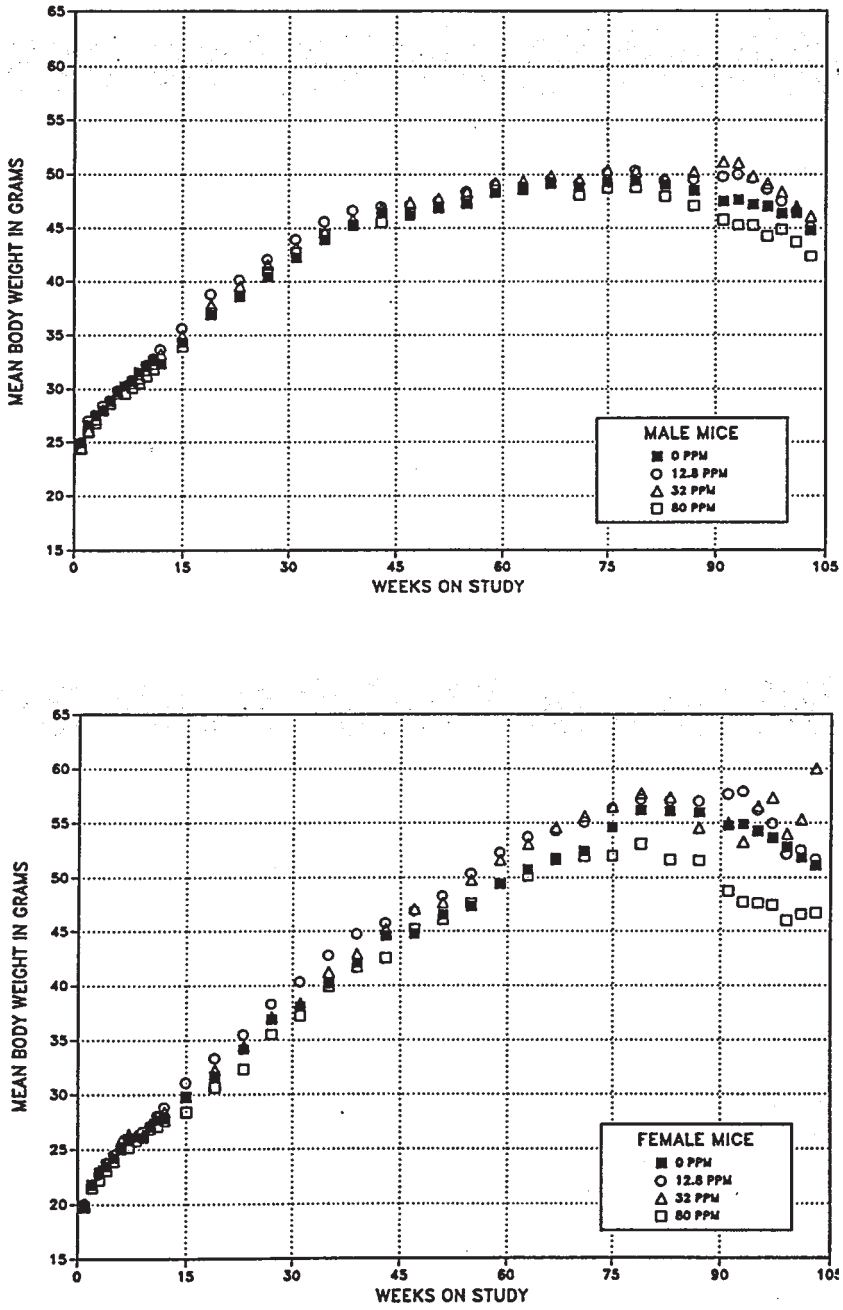


FIGURE 4
Growth Curves for Male and Female Mice Exposed to Chloroprene by Inhalation for 2 Years

Pathology and Statistical Analysis

This section describes the statistically significant or biologically noteworthy changes in the incidences of neoplasms and/or nonneoplastic lesions of the lung, circulatory system, harderian gland, mammary gland, liver, skin and mesentery, forestomach, Zymbal's gland, kidney, nose, trachea, and spleen. Summaries of the incidences of neoplasms and nonneoplastic lesions, individual animal tumor diagnoses, statistical analysis of primary neoplasms that occurred with an incidence of at least 5% in at least one group, and historical incidences for the neoplasms mentioned in this section are presented in Appendix C for male rats and Appendix D for female rats.

Lung: The incidences of alveolar/bronchiolar neoplasms in all exposed male and female groups were significantly greater than those in the chamber control groups (Tables 21, C3, and D3). The incidences of alveolar/bronchiolar neoplasms generally exceeded the historical control ranges (Tables 21, C4a, and D4a). The incidences of multiple alveolar/bronchiolar adenoma and carcinoma were increased in all exposed groups of males and females (Plates 9 and 10). The morphology of lung neoplasms was similar in control and exposed groups. Alveolar/bronchiolar adenoma was a discrete neoplasm that replaced and compressed adjacent lung parenchyma and consisted of solid and papillary patterns composed of single layers of well-differentiated cuboidal to columnar epithelial cells. Alveolar/bronchiolar carcinoma was usually larger than an adenoma and consisted of solid and papillary patterns and clusters of moderately pleomorphic cuboidal to columnar epithelial cells that generally formed multiple layers and/or solid masses. Carcinomas had increased cellular pleomorphism, increased numbers of mitoses, and evidence of local invasion.

The incidences of bronchiolar hyperplasia in all groups of exposed males and females were significantly greater than those in the chamber control groups (Tables 21, C5, and D5). Bronchiolar hyperplasia was characterized by diffuse thickening of the cuboidal cells lining the terminal bronchioles and in some cases caused papillary projections into the lumen. Accompanying this change was extension of cuboidal cells into alveolar ducts or alveolar sacs immediately adjacent to the bronchiolar epithelium. The incidences of histiocytic cell infiltration in 80 ppm males and in all exposed groups of females were significantly greater than those in the chamber control groups. This change consisted of histiocytes within alveolar lumens, usually adjacent to alveolar/bronchiolar neoplasms. The histiocyte infiltrate was very commonly seen in lungs with alveolar/bronchiolar neoplasms and was considered to be secondary to the presence of the neoplasm.

Lung neoplasms from chamber control and exposed mice were analyzed for genetic alterations in K-*ras* and H-*ras* proto-oncogenes. DNA was isolated from paraffin embedded tissues and analyzed by several assays based on polymerase chain reaction (PCR), including restriction fragment length polymorphism (RFLP) analysis, single-strand conformation polymorphism analysis, and direct sequencing (Appendix N). In comparison to spontaneous lung neoplasms, a higher frequency of K-*ras* mutations, with a predominance of unique A to T transversions at codon 61, was detected in the chloroprene-induced lung neoplasms.

TABLE 21
Incidences of Neoplasms and Nonneoplastic Lesions of the Lung in Mice in the 2-Year Inhalation Study of Chloroprene

	Chamber Control	12.8 ppm	32 ppm	80 ppm
Male				
Number Examined Microscopically	50	50	50	50
Bronchiole Hyperplasia[a]	0	10** (2.0)[b]	18** (1.7)	23** (2.2)
Histiocytic Cell Infiltration	7 (1.6)	8 (3.3)	11 (2.5)	22** (2.9)
Alveolar/bronchiolar Adenoma, Multiple				
Overall rate[c]	0/50 (0%)	6/50 (12%)*	7/50 (14%)**	13/50 (26%)**
Alveolar/bronchiolar Adenoma (includes multiple)[d]				
Overall rate	8/50 (16%)	18/50 (36%)	22/50 (44%)	28/50 (56%)
Adjusted rate[e]	23.8%	54.8%	68.3%	84.7%
Terminal rate[f]	4/27 (15%)	13/27 (48%)	6/14 (43%)	9/13 (69%)
First incidence (days)	635	530	382	523
Logistic regression test[g]	P < 0.001	P = 0.016	P = 0.002	P < 0.001
Alveolar/bronchiolar Carcinoma, Multiple				
Overall rate	2/50 (4%)	4/50 (8%)	10/50 (20%)**	15/50 (30%)**
Alveolar/bronchiolar Carcinoma (includes multiple)[h]				
Overall rate	6/50 (12%)	12/50 (24%)	23/50 (46%)	28/50 (56%)
Adjusted rate	21.3%	37.9%	76.7%	85.1%
Terminal rate	5/27 (19%)	8/27 (30%)	8/14 (57%)	9/13 (69%)
First incidence (days)	729	638	567	524
Logistic regression test	P < 0.001	P = 0.075	P < 0.001	P < 0.001
Alveolar/bronchiolar Adenoma or Carcinoma[i]				
Overall rate	13/50 (26%)	28/50 (56%)	36/50 (72%)	43/50 (86%)
Adjusted rate	39.2%	79.4%	89.0%	100.0%
Terminal rate	8/27 (30%)	20/27 (74%)	10/14 (71%)	13/13 (100%)
First incidence (days)	635	530	382	523
Logistic regression test	P < 0.001	P < 0.001	P < 0.001	P < 0.001
Female				
Number Examined Microscopically	50	49	50	50
Bronchiole Hyperplasia	0	15** (2.0)	12** (2.2)	30** (2.2)
Histiocytic Cell Infiltration	1 (3.0)	14** (2.0)	18** (2.3)	23** (2.4)
Alveolar/bronchiolar Adenoma, Multiple				
Overall rate	0/50 (0%)	6/49 (12%)*	12/50 (24%)**	16/50 (32%)**
Alveolar/bronchiolar Adenoma (includes multiple)[j]				
Overall rate	2/50 (4%)	16/49 (33%)	29/50 (58%)	26/50 (52%)
Adjusted rate	5.7%	57.9%	100.0%	100.0%
Terminal rate	2/35 (6%)	6/16 (38%)	1/1 (100%)	3/3 (100%)
First incidence (days)	734 (T)	447	346	453
Logistic regression test	P < 0.001	P < 0.001	P < 0.001	P < 0.001
Alveolar/bronchiolar Carcinoma, Multiple				
Overall rate	0/50 (0%)	6/49 (12%)*	8/50 (16%)**	17/50 (34%)**

TABLE 21
Incidences of Neoplasms and Nonneoplastic Lesions of the Lung in Mice in the 2-Year Inhalation Study of Chloroprene

	Chamber Control	12.8 ppm	32 ppm	80 ppm
Female (continued)				
Alveolar/bronchiolar Carcinoma (includes multiple)[k]				
Overall rate	2/50 (4%)	14/49 (29%)	16/50 (32%)	28/50 (56%)
Adjusted rate	5.5%	51.9%	100.0%	95.4%
Terminal rate	1/35 (3%)	6/16 (38%)	1/1 (100%)	2/3 (67%)
First incidence (days)	706	447	524	324
Logistic regression test	P < 0.001	P < 0.001	P < 0.001	P < 0.001
Alveolar/bronchiolar Adenoma or Carcinoma[l]				
Overall rate	4/50 (8%)	28/49 (57%)	34/50 (68%)	42/50 (84%)
Adjusted rate	11.0%	83.5%	100.0%	100.0%
Terminal rate	3/35 (9%)	11/16 (69%)	1/1 (100%)	3/3 (100%)
First incidence (days)	706	447	346	324
Logistic regression test	P < 0.001	P < 0.001	P < 0.001	P < 0.001

* Significantly different (P≤0.05) from the chamber control group by the logistic regression test
** P≤0.01
(T)Terminal sacrifice
[a] Number of animals with lesion
[b] Average severity grade of lesions in affected animals: 1 = minimal; 2 = mild; 3 = moderate; 4 = marked
[c] Number of animals with neoplasm per number of animals with lung examined microscopically
[d] Historical incidence for 2-year inhalation studies with chamber controls (mean ± standard deviation): 141/947 (14.9% ± 7.0%); range 6%-36%
[e] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[f] Observed incidence in animals surviving until the end of the study
[g] In the chamber control column are the P values associated with the trend test. In the exposed group columns are the P values corresponding to the pairwise comparisons between the chamber controls and that exposed group. The logistic regression test regards lesions in animals dying prior to terminal kill as nonfatal.
[h] Historical incidence: 75/947 (7.9% ± 5.7%); range 0%-16%
[i] Historical incidence: 205/947 (21.7% ± 8.0%); range 10%-42%
[j] Historical incidence: 61/939 (6.5% ± 3.2%); range 0%-14%
[k] Historical incidence: 38/939 (4.1% ± 3.2%); range 0%-12%
[l] Historical incidence: 97/939 (10.3% ± 3.7%); range 0%-16%

Circulatory System: The incidences of hemangiosarcoma and hemangioma or hemangiosarcoma (combined) in all groups of exposed males and in 32 ppm females were significantly greater than those in the chamber control groups. These incidences were significant even when hemangioma and hemangiosarcoma of the liver in male mice were excluded because of the possible complication from *Helicobacter hepaticus* infection (see liver pathology section). The incidences of hemangiosarcoma and hemangioma or hemangiosarcoma (combined) exceeded the historical control ranges (Tables 22, C3, C4b, D3, and D4b). Hemangiosarcomas in males and females occurred primarily in the mesentery, subcutis of the skin, and liver; the bone and spleen were also affected occasionally. In some cases, hemangiosarcomas occurred in more than one organ in the same animal. Hemangiosarcomas consisted of multiple, variably sized, blood-filled spaces that were lined by abundant, plump, mildly to moderately pleomorphic endothelial cells. A number of hemangiosarcomas of the mesentery invaded adjacent tissues such as the pancreas, prostate gland, mesenteric lymph node, and kidney. In the liver, these blood-filled spaces were sometimes separated by cords of hepatocytes. Hemangiomas were found only in the mesentery. Hemangiomas consisted of discrete clusters of blood-filled spaces lined by small numbers of relatively normal-appearing endothelial cells.

TABLE 22

Incidences of Hemangioma and Hemangiosarcoma in Mice in the 2-Year Inhalation Study of Chloroprene

	Chamber Control	12.8 ppm	32 ppm	80 ppm
Male				
Hemangioma, All Organs (excludes liver)				
Overall rate[a]	0/50	1/50	2/50	2/50
Hemangioma, All Organs[b]				
Overall rate	0/50	1/50	2/50	2/50
Hemangiosarcoma, Bone Marrow[c]				
Overall rate	0/50	1/49	2/50	1/50
Hemangiosarcoma, Liver				
Overall rate	2/50	5/50	6/50	8/49*
Hemangiosarcoma, Mesentery				
Overall rate	0/50	3/50	13/50**	7/50**
Hemangiosarcoma, Skin				
Overall rate	1/50	4/50	1/50	7/50*
Hemangiosarcoma, All Organs (excludes liver)				
Overall test	1/50	11/50*	16/50**	15/50**
Hemangiosarcoma, All Organs[d]				
Overall rate	3/50 (6%)	13/50 (26%)	22/50 (44%)	19/50 (38%)
Adjusted rate[e]	11.1%	38.6%	69.8%	68.0%
Terminal rate[f]	3/27 (11%)	7/27 (26%)	6/14 (43%)	6/13 (46%)
First incidence (days)	733 (T)	659	495	454
Logistic regression test[g]	P < 0.001	P = 0.006	P < 0.001	P < 0.001
Hemangioma or Hemangiosarcoma, All Organs (excludes liver)				
Overall rate	1/50	12/50**	18/50**	17/50**
Hemangioma or Hemangiosarcoma, All Organs[h]				
Overall rate	3/50 (6%)	14/50 (28%)	23/50 (46%)	21/50 (42%)
Adjusted rate	11.1%	41.7%	70.7%	74.1%
Terminal rate	3/27 (11%)	8/27 (30%)	6/14 (43%)	7/13 (54%)
First incidence (days)	733 (T)	659	495	454
Logistic regression test	P < 0.001	P = 0.003	P < 0.001	P < 0.001

TABLE 22
Incidences of Hemangioma and Hemangiosarcoma in Mice in the 2-Year Inhalation Study of Chloroprene

	Chamber Control	12.8 ppm	32 ppm	80 ppm
Female				
Hemangioma, All Organs[i]				
Overall rate	0/50 (0%)	0/50 (0%)	2/50 (4%)	3/50 (6%)
Adjusted rate	0.0%	0.0%	100.0%	39.5%
Terminal rate	0/35 (0%)	0/16 (0%)	1/1 (100%)	1/3 (33%)
First incidence (days)	—[j]	—	607	624
Logistic regression test	P = 0.004	—[k]	P = 0.072	P = 0.037
Hemangiosarcoma, Bone Marrow				
Overall rate	0/50	1/49	1/49	0/50
Hemangiosarcoma, Liver				
Overall rate	1/50	0/49	1/50	0/50
Hemangiosarcoma, Mesentery				
Overall rate	0/50	4/50*	13/50**	4/50
Hemangiosarcoma, Skin				
Overall rate	2/50	1/50	2/50	1/50
Hemangiosarcoma, All Organs[l]				
Overall rate	4/50 (8%)	6/50 (12%)	17/50 (34%)	5/50 (10%)
Adjusted rate	10.6%	25.7%	100.0%	18.3%
Terminal rate	3/35 (9%)	2/16 (13%)	1/1 (100%)	0/3 (0%)
First incidence (days)	541	482	216	523
Logistic regression test	P = 0.493N	P = 0.330	P = 0.009	P = 0.486
Hemangioma or Hemangiosarcoma, All Organs[m]				
Overall rate	4/50 (8%)	6/50 (12%)	18/50 (36%)	8/50 (16%)
Adjusted rate	10.6%	25.7%	100.0%	50.8%
Terminal rate	3/35 (9%)	2/16 (13%)	1/1 (100%)	1/3 (33%)
First incidence (days)	541	482	216	523
Logistic regression test	P = 0.248	P = 0.330	P = 0.005	P = 0.110

* Significantly different ($P \leq 0.05$) from the chamber control group by the logistic regression test
** $P \leq 0.01$
(T) Terminal sacrifice
[a] Number of animals with neoplasm per number of animals examined. Denominator is number examined microscopically for bone marrow and liver; for other tissues, denominator is number of animals necropsied.
[b] Historical incidence for 2-year inhalation studies with chamber control groups: 8/950 (0.8% ± 1.0%); range 0%-2%
[c] Historical incidence: 0/938
[d] Historical incidence: 26/950 (2.7% ± 2.9%); range 0%-9%
[e] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[f] Observed incidence in animals surviving until the end of the study
[g] In the chamber control column are the P values associated with the trend test. In the exposed group columns are the P values corresponding to the pairwise comparisons between the chamber controls and that exposed group. The logistic regression test regards lesions in animals dying prior to terminal kill as nonfatal. A negative trend is indicated by **N**.
[h] Historical incidence: 34/950 (3.6% ± 3.4%); range 0%-10%
[i] Historical incidence: 15/941 (1.6% ± 1.9%); range 0%-4%
[j] Not applicable; no neoplasms in animal group
[k] Value of statistic cannot be computed.
[l] Historical incidence: 28/941 (3.0% ± 2.3%); range 0%-6%
[m] Historical incidence: 43/941 (4.6% ± 3.2%); range 0%-10%

Harderian Gland: The incidences of harderian gland adenoma and harderian gland adenoma or carcinoma (combined) in males exposed to 32 or 80 ppm and females exposed to 80 ppm were significantly greater than those in the chamber controls (Tables 23, C3, and D3). The incidences of harderian gland adenoma or carcinoma (combined) in 32 ppm males and 80 ppm males and females exceeded the historical control ranges (Tables 23, C4c, and D4c). Adenomas were composed of large, irregular glandular struc-tures, which often formed papillary structures con-sisting of one to three layers of cuboidal to tall columnar epithelial cells with eosinophilic to finely vacuolated cytoplasm. Carcinomas were composed of solid to papillary, irregular clusters of pleomorphic cells with moderately to markedly vacuolated cytoplasm; neoplastic cells often invaded the adjacent stroma and occasionally metastasized to the lung.

TABLE 23
Incidences of Neoplasms of the Harderian Gland in Mice in the 2-Year Inhalation Study of Chloroprene

	Chamber Control	12.8 ppm	32 ppm	80 ppm
Male				
Adenoma[a]				
Overall rate[b]	2/50 (4%)	5/50 (10%)	8/50 (16%)	10/50 (20%)
Adjusted rate[c]	5.8%	17.7%	36.8%	46.4%
Terminal rate[d]	1/27 (4%)	4/27 (15%)	4/14 (29%)	4/13 (31%)
First incidence (days)	596	701	596	589
Logistic regression test[e]	P = 0.004	P = 0.205	P = 0.035	P = 0.007
Carcinoma				
Overall rate	0/50 (0%)	0/50 (0%)	2/50 (4%)	2/50 (4%)
Adenoma or Carcinoma[f]				
Overall rate	2/50 (4%)	5/50 (10%)	10/50 (20%)	12/50 (24%)
Adjusted rate	5.8%	17.7%	42.3%	58.3%
Terminal rate	1/27 (4%)	4/27 (15%)	4/14 (29%)	6/13 (46%)
First incidence (days)	596	701	596	589
Logistic regression test	P < 0.001	P = 0.205	P = 0.010	P = 0.001
Female				
Adenoma[g]				
Overall rate	1/50 (2%)	3/50 (6%)	3/50 (6%)	8/50 (16%)
Adjusted rate	2.9%	14.9%	12.0%	74.4%
Terminal rate	1/35 (3%)	2/16 (13%)	0/1 (0%)	2/3 (67%)
First incidence (days)	734 (T)	621	524	467
Logistic regression test	P = 0.001	P = 0.225	P = 0.293	P = 0.007
Carcinoma				
Overall rate	1/50 (2%)	2/50 (4%)	0/50 (0%)	1/50 (2%)
Adenoma or Carcinoma[h]				
Overall rate	2/50 (4%)	5/50 (10%)	3/50 (6%)	9/50 (18%)
Adjusted rate	5.0%	23.8%	12.0%	77.0%
Terminal rate	1/35 (3%)	3/16 (19%)	0/1 (0%)	2/3 (67%)
First incidence (days)	527	621	524	467
Logistic regression test	P = 0.004	P = 0.186	P = 0.577	P = 0.016

(T)Terminal sacrifice
[a] Historical incidence for 2-year inhalation studies with chamber controls (mean ± standard deviation): 47/950 (5.0% ± 4.5%); range 0%-14%
[b] Number of animals with neoplasm per number of animals necropsied
[c] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[d] Observed incidence in animals surviving until the end of the study
[e] In the chamber control column are the P values associated with the trend test. In the exposed group columns are the P values corresponding to the pairwise comparisons between the chamber controls and that exposed group. The logistic regression test regards lesions in animals dying prior to terminal kill as nonfatal.
[f] Historical incidence: 49/950 (5.2% ± 4.5%); range 0%-14%
[g] Historical incidence: 26/941 (2.8% ± 4.1%); range 0%-16%
[h] Historical incidence: 32/941 (3.4% ± 4.4%); range 0%-16%

Mammary Gland: The incidence of mammary gland carcinoma in 80 ppm females was significantly greater than in the chamber control group (Tables 24 and D3). The incidences of mammary gland carcinoma in 32 and 80 ppm females exceeded the historical control range (Table D4d). Multiple mammary gland carcinomas occurred in exposed females. The incidence of adenoacanthoma was not significantly increased in any exposed group, but in the 32 and 80 ppm groups, the incidences exceeded the historical control range. Carcinomas consisted of highly irregular acinar and ductlike structures composed of densely packed, relatively well-differentiated appearing epithelial cells separated by a small to moderate amount of fibrous stroma (Plate 11). Some mammary gland neoplasms consisted of solid clusters of basophilic epithelial cells admixed with large areas of keratinizing stratified squamous epithelium and were classified as adenoacanthoma (Plate 12). Adenoacanthomas are uncommon neoplasms usually seen as a result of chemical exposure. Mammary gland hyperplasia was present in a few females exposed to chloroprene but not in the chamber controls (Tables 24 and D5).

TABLE 24
Incidences of Neoplasms and Nonneoplastic Lesions of the Mammary Gland in Female Mice in the 2-Year Inhalation Study of Chloroprene

	Chamber Control	12.8 ppm	32 ppm	80 ppm
Number Examined Microscopically	49	49	50	50
Hyperplasia[a]	0	1 (1.0)[b]	1 (1.0)	3 (2.0)
Adenoacanthoma[c]				
Overall rate[d]	0/50 (0%)	1/50 (2%)	3/50 (6%)	2/50 (4%)
Adjusted rate[e]	0.0%	2.1%	7.7%	7.9%
Terminal rate[f]	0/35 (0%)	0/16 (0%)	0/1 (0%)	0/3 (0%)
First incidence (days)	—[h]	440	425	582
Logistic regression test[g]	P = 0.355	P = 0.496	P = 0.205	P = 0.252
Carcinoma, Multiple				
Overall rate	3/50 (6%)	4/50 (8%)	6/50 (12%)	11/50 (22%)
Carcinoma (includes multiple)[i]				
Overall rate	3/50 (6%)	4/50 (8%)	7/50 (14%)	12/50 (24%)
Adjusted rate	7.4%	13.6%	35.1%	56.4%
Terminal rate	1/35 (3%)	1/16 (6%)	0/1 (0%)	1/3 (33%)
First incidence (days)	527	447	394	336
Logistic regression test	P = 0.008	P = 0.553	P = 0.207	P = 0.036
Adenoacanthoma or Carcinoma				
Overall rate	3/50 (6%)	5/50 (10%)	10/50 (20%)	14/50 (28%)
Adjusted rate	7.4%	15.4%	40.1%	59.8%
Terminal rate	1/35 (3%)	1/16 (6%)	0/1 (0%)	1/3 (33%)
First incidence (days)	527	440	394	336
Logistic regression test	P = 0.006	P = 0.427	P = 0.093	P = 0.012

[a] Number of animals with lesion
[b] Average severity grade of lesions in affected animals: 1 = minimal; 2 = mild; 3 = moderate; 4 = marked
[c] Historical incidence for 2-year inhalation studies with chamber controls (mean ± standard deviation): 1/941 (0.1% ± 0.5%); range 0%-2%
[d] Number of animals with neoplasm per number of animals necropsied
[e] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[f] Observed incidence in animals surviving until the end of the study
[g] In the chamber control column are the P values associated with the trend test. In the exposed group columns are the P values corresponding to the pairwise comparisons between the chamber controls and that exposed group. The logistic regression test regards lesions in animals dying prior to terminal kill as nonfatal.
[h] Not applicable; no neoplasms in animal group
[i] Historical incidence: 29/941 (3.1% ± 2.6%); range 0%-8%

Liver: The incidences of hepatocellular carcinoma in all exposed groups of females and hepatocellular adenoma or carcinoma (combined) in 32 and 80 ppm females were significantly greater than those in the chamber controls; in the 80 ppm group, the incidences exceeded the historical control ranges for carcinoma and adenoma or carcinoma (combined) (Tables 25, D3, and D4e). The incidence of eosinophilic foci in 80 ppm females was also significantly greater than that in the chamber controls. Eosinophilic foci were discrete spherical lesions composed of normal-sized to enlarged cells with eosinophilic cytoplasm which produced no compression of the surrounding parenchyma. Hepatocellular adenomas had discrete borders, compressed the surrounding parenchyma, and were composed of disorganized cords which intersected at sharp angles with the hepatic cords of the surrounding parenchyma. Hepatocellular carcinomas differed from adenomas in that the neoplastic hepatocytes within carcinomas often were more atypical than in adenomas and formed solid sheets and/or trabeculae that were three or more cells thick; a number of carcinomas metastasized to the lung. The increased incidences of hematopoietic cell proliferation of the liver in 32 and 80 ppm females were most likely secondary to the presence of the sarcomas and mammary gland neoplasms in exposed females.

The livers of most control and exposed males contained a spectrum of lesions consistent with *Helicobacter* infection; these changes, which generally occurred together in the same liver, included bile duct hyperplasia, karyomegaly, and regeneration of hepatocytes (Plates 13 and 14). Liver sections from five of five males with liver lesions were positive for bacterial organisms consistent with *H. hepaticus* when examined using Steiner's modification of the Warthin-Starry stain. Using a PCR-RFLP-based assay, frozen liver sections from 5 of 10 mice (chamber control and exposed males and females) were found to be positive for the presence of a *Helicobacter* organism compatible with *H. hepaticus*. Also, the spectrum of nonneoplastic liver lesions was consistent with that observed with *H. hepaticus* infection. In contrast to males, liver lesions typical of *H. hepaticus* infection were not present in females. Bile duct hyperplasia was mild to moderate and consisted of multifocal proliferation of small to moderate numbers of oval cells and bile ducts, which extended outwardly from portal areas and sometimes extended between adjacent portal areas.

Slight chronic inflammation consisting of aggregates of small numbers of lymphocytes and macrophages around proliferating bile ducts and oval cells was also seen. Karyomegaly was usually minimal to mild and diffuse, was characterized by enlargement of the nucleus from approximately 1.5 to 2 times the normal size and was sometimes accompanied by enlargement of the entire hepatocyte due to an increase in the amount of cytoplasm. Regeneration was generally mild to marked and characterized by the presence of one or more nodules, ranging in size from less than 1 mm up to 1 cm in diameter, which were composed of a mixture of varying numbers of small, normal-sized, and enlarged hepatocytes containing oval cells and bile ducts and sometimes chronic inflammatory cell infiltrates.

The incidences of hepatoceulluar adenoma or carcinoma (combined) in chamber control and exposed groups of male mice and 80 ppm female mice exceeded the historical control ranges [males: 358/947 (37.8% ± 12.5%), range 11%-60%; females: Table D4e]. The incidences of hemangiosarcoma of the liver were increased in exposed groups of male mice (Tables 22 and C3) and exceeded the historical control range [12/947 (1.3% ± 1.7%), range 0%-6%]. Hemangiosarcomas were morphologically similar to those observed spontaneously and in other tissues in this study. Based upon a retrospective analysis of the recent 2-year studies showing evidence of an active hepatitis resulting from *H. hepaticus* infection, it has been determined that the incidences of hepatocellular adenomas, hepatocellular carcinomas, and hemangiosarcomas are increased under these conditions. Interpretation of the increased incidence of hemangiosarcoma in the liver of male mice in this study was confounded by the *H. hepaticus*-associated liver disease. Neoplastic responses (including hemangiosarcomas) at other sites were not considered to be affected by this infection.

TABLE 25
Incidences of Neoplasms and Nonneoplastic Lesions of the Liver in Mice in the 2-Year Inhalation Study of Chloroprene

	Chamber Control	12.8 ppm	32 ppm	80 ppm
Male				
Number Examined Microscopically	50	50	50	49
Karyomegaly[a]	19 (1.5)[b]	13 (1.5)	20 (1.7)	29* (1.9)
Regeneration	22 (2.8)	25 (3.1)	25 (3.0)	27* (3.0)
Bile Duct, Hyperplasia	34 (2.1)	31 (2.3)	34 (2.4)	36 (2.9)
Hepatocellular Adenoma or Carcinoma				
Overall rate[c]	43/50 (86%)	37/50 (74%)	42/50 (84%)	41/49 (84%)
Female				
Number Examined Microscopically	50	49	50	50
Eosinophilc Focus	13	12	15	28**
Hematopoietic Cell Proliferation	1 (1.0)	5 (1.6)	9* (1.6)	12** (1.5)
Hepatocellular Adenoma, Multiple				
Overall rate	5/50 (10%)	7/49 (14%)	2/50 (4%)	9/50 (18%)
Hepatocellular Adenoma (includes multiple)[d]				
Overall rate	17/50 (34%)	19/49 (39%)	11/50 (22%)	16/50 (32%)
Adjusted rate[e]	47.0%	69.1%	100.0%	85.1%
Terminal rate[f]	16/35 (46%)	9/16 (56%)	1/1 (100%)	1/3 (33%)
First incidence (days)	637	523	505	383
Logistic regression test[g]	P = 0.070	P = 0.157	P = 0.064	P = 0.141
Hepatocellular Carcinoma, Multiple				
Overall rate	0/50 (0%)	1/49 (2%)	7/50 (14%)*	4/50 (8%)
Hepatocellular Carcinoma (includes multiple)[h]				
Overall rate	4/50 (8%)	11/49 (22%)	14/50 (28%)	19/50 (38%)
Adjusted rate	10.3%	41.8%	100.0%	91.5%
Terminal rate	2/35 (6%)	4/16 (25%)	1/1 (100%)	2/3 (67%)
First incidence (days)	493	440	503	524
Logistic regression test	P < 0.001	P = 0.040	P = 0.002	P < 0.001
Hepatocellular Adenoma or Carcinoma[i]				
Overall rate	20/50 (40%)	26/49 (53%)	20/50 (40%)	30/50 (60%)
Adjusted rate	52.2%	81.8%	100.0%	100.0%
Terminal rate	17/35 (49%)	11/16 (69%)	1/1 (100%)	3/3 (100%)
First incidence (days)	493	440	503	383
Logistic regression test	P < 0.001	P = 0.051	P = 0.011	P < 0.001

* Significantly different ($P \leq 0.05$) from the chamber control group by the logistic regression 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
[c] Number of animals with neoplasm per number of animals with liver examined microscopically
[d] Historical incidence for 2-year inhalation studies with chamber controls (mean ± standard deviation): 114/937 (12.2% ± 9.7%); range 0%-40%
[e] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[f] Observed incidence in animals surviving until the end of the study
[g] In the chamber control column are the P values associated with the trend test. In the exposed group columns are the P values corresponding to the pairwise comparisons between the chamber controls and that exposed group. The logistic regression test regards lesions in animals dying prior to terminal kill as nonfatal.
[h] Historical incidence: 103/937 (11.0% ± 6.7%); range 0%-30%
[i] Historical incidence: 200/937 (21.3% ± 11.9%); range 3%-54%

Skin and Mesentery: The incidences of sarcoma of the skin in all exposed groups of females were significantly greater than in the chamber controls (Tables 26 and D3). The sarcomas occurred primarily in the subcutis and consisted of sheets and interlacing bundles of undifferentiated and highly pleomorphic mesenchymal cells. In exposed females, morphologically similar sarcomas were also present in the mesentery, and the incidence in 32 ppm females was significantly greater than that in the chamber control group. These sarcomas were pleomorphic and highly invasive. Increased incidences of mesentery sarcoma were present in exposed groups of female mice (Tables 26 and D3). These neoplasms generally occurred in females that did not have either mesentery hemangiosarcoma or skin (subcutaneous) sarcoma. Incidences of sarcomas of the skin and mesentery exceeded the historical control ranges (Tables 26, D4f, and D4g).

TABLE 26
Incidences of Sarcoma of the Skin and Mesentery in Female Mice in the 2-Year Inhalation Study of Chloroprene

	Chamber Control	12.8 ppm	32 ppm	80 ppm
Skin[a]				
Overall rate[b]	0/50 (0%)	11/50 (22%)	11/50 (22%)	18/50 (36%)
Adjusted rate[c]	0.0%	35.3%	100.0%	69.6%
Terminal rate[d]	0/35 (0%)	2/16 (13%)	1/1 (100%)	0/3 (0%)
First incidence (days)	—[f]	285	524	462
Logistic regression test[e]	P < 0.001	P = 0.001	P < 0.001	P < 0.001
Mesentery[g]				
Overall rate	0/50 (0%)	4/50 (8%)	8/50 (16%)	3/50 (6%)
Adjusted rate	0.0%	16.3%	46.5%	12.6%
Terminal rate	0/35 (0%)	1/16 (6%)	0/1 (0%)	0/3 (0%)
First incidence (days)	—	523	463	443
Logistic regression test	P = 0.308	P = 0.060	P = 0.004	P = 0.157

[a] Historical incidence for 2-year inhalation studies with chamber controls (mean ± standard deviation): 5/941 (0.5% ± 0.9%); range 0%-2%
[b] Number of animals with neoplasm per number of animals necropsied
[c] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[d] Observed incidence in animals surviving until the end of the study
[e] In the chamber control column are the P values associated with the trend test. In the exposed group columns are the P values corresponding to the pairwise comparisons between the chamber controls and that exposed group. The logistic regression test regards lesions in animals dying prior to terminal kill as nonfatal.
[f] Not applicable; no neoplasms in animal group
[g] Historical incidence: 0/941

Forestomach: The incidence of squamous cell papilloma in 80 ppm females was greater than that in the chamber controls; the difference was not significant but exceeded the historical control range (Tables 27, D3, and D4h). Male mice exhibited a positive trend in squamous cell papilloma of the forestomach (Tables 27 and C3). Squamous cell papilloma was characterized as an arboriform structure consisting of a branching core of fibrous tissue, which was connected to the submucosa of the forestomach by a thin stalk and was covered by multiple layers of hyperplastic epithelial cells (Plate 15). In males and females exposed to 80 ppm, the incidences of hyperplasia of the forestomach epithelium were significantly greater than those in chamber controls, and the lesions were similar to those seen in the 13-week study. Hyperplasia was a focal to multifocal change characterized by an increase in the number of cell layers in the epithelium (Plate 16).

TABLE 27
Incidences of Neoplasms and Nonneoplastic Lesions of the Forestomach in Mice in the 2-Year Inhalation Study of Chloroprene

	Chamber Control	12.8 ppm	32 ppm	80 ppm
Male				
Number Examined Microscopically	50	48	49	50
Epithelial Hyperplasia[a]	4 (3.0)[b]	6 (1.8)	7 (2.3)	29** (2.2)
Squamous Cell Papilloma[c]				
Overall rate[d]	1/50 (2%)	0/50 (0%)	2/50 (4%)	4/50 (8%)
Adjusted rate[e]	3.7%	0.0%	14.3%	12.7%
Terminal rate[f]	1/27 (4%)	0/27 (0%)	2/14 (14%)	0/13 (0%)
First incidence (days)	733 (T)	—[h]	733 (T)	587
Logistic regression test[g]	P = 0.030	P = 0.500N	P = 0.276	P = 0.216
Female				
Number Examined Microscopically	50	49	49	50
Epithelial Hyperplasia	4 (2.0)	3 (3.7)	8 (1.6)	27** (2.7)
Squamous Cell Papilloma[i]				
Overall rate	0/50 (0%)	0/50 (0%)	0/50 (0%)	4/50 (8%)
Adjusted rate	0.0%	0.0%	0.0%	18.8%
Terminal rate	0/35 (0%)	0/16 (0%)	0/1 (0%)	0/3 (0%)
First incidence (days)	—	—	—	576
Logistic regression test	P = 0.001	—[j]	—	P = 0.053
Squamous Cell Papilloma or Carcinoma[k]				
Overall rate	1/50 (2%)	0/50 (0%)	0/50 (0%)	4/50 (8%)
Adjusted rate	2.9%	0.0%	0.0%	18.8%
Terminal rate	1/35 (3%)	0/16 (0%)	0/1 (0%)	0/3 (0%)
First incidence (days)	734 (T)	—	—	576
Logistic regression test	P = 0.007	P = 0.656N	P = 0.998N	P = 0.120

** Significantly different ($P \leq 0.01$) from the chamber control group by the logistic regression test
(T)Terminal sacrifice
[a] Number of animals with lesion
[b] Average severity grade of lesions in affected animals: 1 = minimal; 2 = mild; 3 = moderate; 4 = marked
[c] Historical incidence for 2-year inhalation studies with chamber controls (mean ± standard deviation): 6/950 (0.6% ± 1.2%); range 0%-4%
[d] Number of animals with neoplasm per number of animals necropsied
[e] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[f] Observed incidence in animals surviving until the end of the study
[g] In the chamber control column are the P values associated with the trend test. In the exposed group columns are the P values corresponding to the pairwise comparisons between the chamber controls and that exposed group. The logistic regression test regards lesions in animals dying prior to terminal kill as nonfatal. A lower incidence in an exposure group is indicated by **N**.
[h] Not applicable; no neoplasms in animal group
[i] Historical incidence: 11/941 (1.2% ± 1.8%); range 0%-6%
[j] Value of statistic cannot be computed.
[k] Historical incidence: 13/941 (1.4% ± 1.8%); range 0%-6%

Zymbal's Gland: Carcinomas of the Zymbal's gland were seen in three 80 ppm females (Table D1); two of these carcinomas metastasized to the lung. These neoplasms were characterized by multiple variably sized cellular clusters admixed with multiple large duct-like structures that were lined with stratified squamous epithelium and contained eosinophilic material, separated by small to moderate amounts of fibrous stroma. The cellular clusters consisted of densely packed, deeply basophilic, basal-like cells surrounding a centrally located cluster of large sebaceous-like cells with abundant foamy cytoplasm. Zymbal's gland carcinomas have not been reported in the NTP historical database for control female mice (Table D4i).

Kidney: Although not significantly increased, the incidence of renal tubule adenoma in 80 ppm males was greater than that in the chamber control group and exceeded the historical control range (Tables 28, C3, and C4e). In addition, incidences of renal tubule hyperplasia were significantly increased in 32 and 80 ppm males relative to the chamber control group. Initially, a single hematoxylin- and eosin-stained section of each kidney was prepared. Primarily because of the slightly positive trend and increased incidences of renal tubule hyperplasia and renal tubule adenoma in the standard evaluation and the rarity of renal proliferative lesions in mice, additional step sections of kidney were prepared from the remaining formalin-fixed tissues. Eight additional kidney sections taken at 0.5-mm intervals were prepared for each male. Additional males with focal hyperplasia or adenomas were identified. The incidences of these proliferative lesions in standard and extended evaluations are presented in Tables 28 and C3. The step-section and step- and single-section (combined) incidences of renal tubule adenoma in 80 ppm males and the step- and single-section (combined) incidences in 32 ppm males were significantly greater than those in the chamber control group (Tables 28 and C3). The step-section and step- and single-section (combined) incidences of renal tubule hyperplasia in all exposed groups of males were significantly greater than those in the chamber controls (Tables 28 and C5).

Renal tubule hyperplasia, adenoma, and carcinoma constitute a morphologic continuum. Hyperplasia was generally a focal, minimal to mild lesion consisting of tubules that were dilated two to five times the normal diameter and were lined by increased numbers of tubule epithelial cells that partially or totally filled the tubule lumen. Cells within hyperplastic lesions varied slightly in size and sometimes stained more basophilic then normal cells but otherwise appeared similar to normal tubule epithelial cells. Renal tubule adenomas were larger, discrete lesions, ranging from greater than five tubule diameters to 1 mm or more in size. Cells within adenomas consisted of relatively normal-appearing tubule epithelial cells that sometimes formed solid masses of multiple clusters of cells. Oncocytic hyperplasia was observed at the end of the study in one male exposed to 12.8 ppm. Oncocytic hyperplasia was characterized by multiple, confluent, discrete foci, which were a few tubule diameters in size, and was composed of oncocytes that were large cells with abundant, brightly eosinophilic, granular cytoplasm and a moderately basophilic, centrally placed nucleus.

TABLE 28
Incidences of Neoplasms and Nonneoplastic Lesions of the Kidney in Male Mice in the 2-Year Inhalation Study of Chloroprene

	Chamber Control	12.8 ppm	32 ppm	80 ppm
Number Examined Microscopically	50	49	50	50
Single Sections (Standard Evaluation)				
Renal Tubule Hyperplasia[a]	0	4 (1.3)[b]	5* (1.2)	5* (1.4)
Renal Tubule Adenoma[c]				
Overall rate[d]	0/50 (0%)	1/49 (2%)	1/50 (2%)	3/50 (6%)
Adjusted rate[e]	0.0%	3.6%	7.1%	13.8%
Terminal rate[f]	0/27 (0%)	0/27 (0%)	1/14 (7%)	1/13 (8%)
First incidence (days)	—[h]	722	733 (T)	587
Logistic regression test[g]	P = 0.039	P = 0.492	P = 0.369	P = 0.121
Step Sections (Extended Evaluation)				
Renal Tubule Hyperplasia	2 (2.0)	12** (1.4)	16** (1.6)	17** (1.5)
Renal Tubule Adenoma				
Overall rate	0/50 (0%)	1/49 (2%)	2/50 (4%)	6/50 (12%)
Adjusted rate	0.0%	3.7%	12.9%	30.2%
Terminal rate	0/27 (0%)	1/27 (4%)	1/14 (7%)	2/13 (15%)
First incidence (days)	—	733 (T)	715	567
Logistic regression test	P < 0.001	P = 0.500	P = 0.135	P = 0.011
Single Sections and Step Sections (Combined)				
Renal Tubule Hyperplasia	2 (2.0)	16** (1.4)	17** (1.6)	18** (1.6)
Renal Tubule Adenoma				
Overall rate	0/50 (0%)	2/49 (4%)	3/50 (6%)	9/50 (18%)
Adjusted rate	0.0%	7.1%	19.6%	40.7%
Terminal rate	0/27 (0%)	1/27 (4%)	2/14 (14%)	3/13 (23%)
First incidence (days)	—	722	715	567
Logistic regression test	P < 0.001	P = 0.227	P = 0.042	P = 0.002

* Significantly different ($P \leq 0.05$) from the chamber control group by the logistic regression test
** $P \leq 0.01$
(T)Terminal sacrifice
[a] Number of animals with lesion
[b] Average severity grade of lesions in affected animals: 1 = minimal; 2 = mild; 3 = moderate; 4 = marked
[c] Historical incidence for 2-year inhalation studies with chamber controls (mean ± standard deviation): 2/946 (0.2% ± 0.5%); range 0%-2%
[d] Number of animals with neoplasm per number of animals with kidney examined microscopically
[e] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[f] Observed incidence in animals surviving until the end of the study
[g] In the chamber control column are the P values associated with the trend test. In the exposed group columns are the P values corresponding to the pairwise comparisons between the chamber controls and that exposed group. The logistic regression test regards lesions in animals dying prior to terminal kill as nonfatal.
[h] Not applicable; no neoplasms in animal group

Nose: The incidences of olfactory epithelium atrophy, adenomatous hyperplasia, and metaplasia in 80 ppm males and females were significantly greater than in the chamber control groups (Table 29). The incidences of suppurative inflammation in 32 and 80 ppm females were significantly greater than that in the chamber control group. These nasal lesions involved the olfactory regions of Levels II and III. Atrophy of the olfactory epithelium was characterized by decreased numbers of layers of olfactory epithelium and included loss of Bowman's glands and olfactory axons in more severe cases. Metaplasia of the olfactory epithelium was characterized by replacement of olfactory epithelium with ciliated columnar respiratory-like epithelium. Adenomatous hyperplasia of the olfactory epithelium was characterized by respiratory-like epithelium which was taller than normal and had increased numbers of cells with multiple folds, including goblet cells; underlying glands were often lined by goblet cells and dilated by mucus (Plates 17 and 18). Adenomas of the respiratory epithelium were present in one 32 ppm female and one 80 ppm male. Both adenomas were very small (0.5 mm in diameter) arboriform masses and consisted of multiple papillary structures covered by multiple layers of cuboidal, nonciliated epithelial cells. These adenomas have not been documented in the NTP historical control database.

Trachea: Single papillary adenomas were detected in one 12.8 ppm male and in one 32 ppm male (Table C1). These lesions consisted of a thin, branching core of fibrous tissue covered by two to three layers of epithelial cells. These adenomas have not been documented in the NTP historical database.

Spleen: The incidences of hematopoietic proliferation in 32 and 80 ppm males and in all exposed groups of females were significantly greater than those in the chamber controls (males: chamber control, 26/50; 12.8 ppm, 22/49; 32 ppm, 35/50; 80 ppm, 31/50; females: 13/50, 25/49, 42/49, 39/50; Tables C5 and D5). The increased incidences of hematopoietic proliferation may have been chemical related.

TABLE 29
Incidences of Nonneoplastic Lesions of the Nose in Mice in the 2-Year Inhalation Study of Chloroprene

	Chamber Control		12.8 ppm		32 ppm		80 ppm	
Male								
Number Examined Microscopically	50		48		50		50	
Suppurative Inflammation[a]	2	(2.0)[b]	1	(1.0)	4	(1.0)	6	(1.5)
Olfactory Epithelium, Atrophy	7	(1.1)	8	(1.4)	7	(1.1)	49**	(2.5)
Olfactory Epithelium, Adenomatous Hyperplasia	3	(1.0)	2	(1.0)	2	(1.0)	48**	(2.0)
Olfactory Epithelium, Metaplasia	6	(1.0)	5	(1.4)	5	(1.0)	49**	(2.5)
Respiratory Epithelium, Hyaline Degeneration	3	(1.3)	4	(1.3)	2	(1.0)	10*	(1.2)
Adenoma, Respiratory Epithelium	0		0		0		1	
Female								
Number Examined Microscopically	50		49		49		50	
Suppurative Inflammation	0		1	(1.0)	3*	(1.7)	4**	(1.5)
Olfactory Epithelium, Atrophy	6	(1.2)	5	(1.2)	4	(1.3)	47**	(2.0)
Olfactory Epithelium, Adenomatous Hyperplasia	2	(1.0)	3	(1.0)	0		44**	(1.9)
Olfactory Epithelium, Metaplasia	2	(1.0)	3	(1.0)	1	(2.0)	44**	(2.0)
Respiratory Epithelium, Hyaline Degeneration	17	(1.0)	9	(1.2)	10	(1.3)	25**	(1.2)
Adenoma, Respiratory Epithelium	0		0		1		0	

* Significantly different ($P \leq 0.05$) from the chamber control group by the logistic regression 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

Supplemental Analyses in Mice

Because of the large number of early deaths of mice exposed to chloroprene, survival-adjusted neoplasm rates were estimated using the Poly-3 survival-adjusted quantal response method of Portier and Bailer (1989) to provide a clearer indication of exposure-response relationships for neoplasms induced by chloroprene. This adjustment accounts for the impact of early mortality on the expression of late-developing neoplasms. The Poly-3 survival-adjusted neoplasm rates for mice in the 2-year inhalation study of chloroprene are presented in Table 30. The neoplasm incidence values in this table represent the ratio of the number of animals in an exposure group bearing the specific neoplasm relative to the adjusted number of animals at risk. These risk-adjusted values were determined by combining the proportion of lifetime neoplasm risk for each animal in a particular group as follows: animals that survived to the end of the study and animals that had the particular neoplasm (including animals that died early and had the neoplasm and animals that lived until the end of the study, at which time the neoplasm was detected) were given a risk weight of one unit; the risk weight for an animal that died before study termination but was free of the particular neoplasm being analyzed was estimated by calculating the fractional survival time on study for that animal raised to the third power. For example, if an animal died after one-half of the study (approximately 52 weeks) and did not have the particular neoplasm being analyzed, it was considered to contribute 0.125 risk for that neoplasm $(½)^3$. The use of the third power was selected because cumulative neoplasm rates have been found to occur generally as a third- to fourth-order function of age in animals. Simulation experiments have shown that this method is valid even when the actual values for the power are as low as 1 or as high as 5 (Bailer and Portier, 1988). This type of analysis had also been performed on neoplasms induced by 1,3-butadiene in B6C3F_1 mice (NTP, 1993).

TABLE 30
Survival-Adjusted Neoplasm Rates for Mice in the 2-Year Inhalation Study of Chloroprene[a]

	Males (%)				Females (%)			
	Chamber Control	12.8 ppm	32 ppm	80 ppm	Chamber Control	12.8 ppm	32 ppm	80 ppm
Lung								
Alveolar/bronchiolar Carcinoma	14.1**	28.3	56.9**	66.4**	4.6**	35.6**	53.8**	76.0**
Alveolar/bronchiolar Adenoma or Carcinoma	29.8**	63.7**	79.2**	92.9**	9.1**	68.3**	85.8**	96.1**
All Organs								
Hemangioma or Hemangiosarcoma[b]	2.4**	28.2**	45.2**	43.6**	9.0*	16.0	53.1**	27.7*
Harderian Gland								
Adenoma or Carcinoma	4.7**	12.0	26.3**	32.0**	4.5**	13.5	11.7	31.2**
Mammary Gland								
Adenoacanthoma or Carcinoma					6.7**	12.9	33.7**	42.5**
Liver								
Hepatocellular Carcinoma					9.0**	28.4*	47.5**	58.2**
Hepatocellular Adenoma or Carcinoma					44.8	62.9	63.3	79.7**
Forestomach								
Squamous Cell Papilloma or Carcinoma	2.4**	0	5.6	13.3	2.3**	0	0	14.6
Kidney								
Renal Tubule Adenoma								
(single section)	0*	2.4	2.8	8.2				
(single + step section)	0**	4.8	8.3	23.9**				
Skin								
Sarcoma					0*	27.5**	39.0**	52.6**
Mesentery								
Sarcoma					0	10.7*	28.9**	11.0

* In the chamber control column, indicates a significant trend ($P < 0.05$) across all dose groups by the Poly-3 quantal response test; in the exposed group columns, indicates a significant difference from the chamber control group by pairwise comparison
** $P < 0.01$
[a] Survival-adjusted neoplasm rates were estimated using the Poly-3 survival-adjusted quantal response method of Portier and Bailer (1989).
[b] Liver hemangiomas and hemangiosarcomas were excluded for male mice.

GENETIC TOXICOLOGY

Chloroprene showed no evidence of mutagenicity in tests performed *in vitro* or *in vivo*. Chloroprene was not mutagenic in any of four strains of *Salmonella typhimurium* (TA98, TA100, TA1535, or TA1537) when tested with a preincubation protocol at concentrations up to 3,333 µg/plate, with and without Aroclor-induced rat or hamster liver S9 (Zeiger *et al.*, 1987; Table E1). No induction of sex-linked recessive lethal mutations was noted in germ cells of male *Drosophila melanogaster* administered chloroprene via feeding or injection (Foureman *et al.*, 1994; Table E2). *In vivo* assays in male mice for induction of chromosomal aberrations, sister chromatid exchanges, and increases in the frequency of micronucleated erythrocytes after 12 inhalation exposures to chloroprene (12, 32, or 80 ppm) all gave negative results (Tice *et al.*, 1988; Tables E3, E4, and E5). In addition, no increase was observed in the frequency of micronucleated erythrocytes in peripheral blood of male and female mice exposed for 13 weeks to chloroprene (5 to 80 ppm) via inhalation (Table E6).

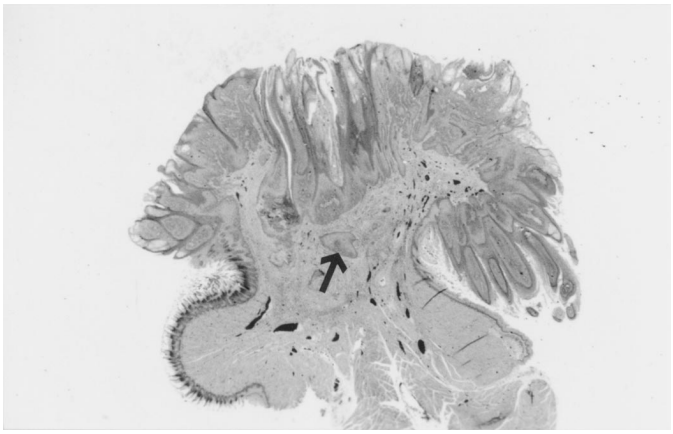


PLATE 1
Squamous cell carcinoma in the tongue of a female F344/N rat exposed to 80 ppm chloroprene by inhalation for 2 years. Note the islands of neoplastic cells that have infiltrated the muscular layers (arrow). H&E; 2.5×

PLATE 2
Higher magnification of the squamous cell carcinoma in Plate 1. Note the islands of neoplastic epithelial cells that have extended through the basal lamina and the associated inflammatory infiltrate. H&E; 13.2×

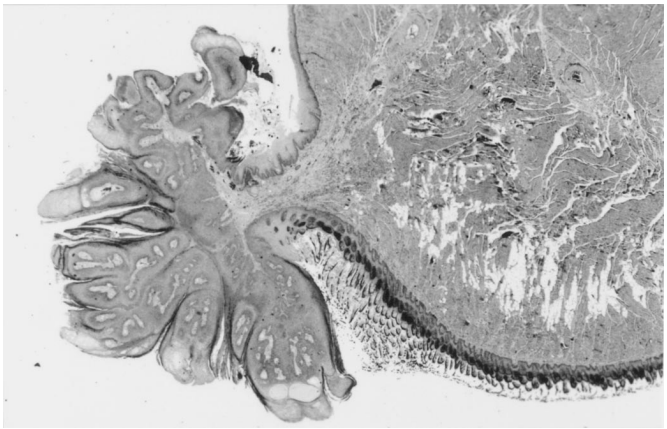


PLATE 3
Squamous cell papilloma in the tongue of a male F344/N rat exposed to 80 ppm chloroprene by inhalation for 2 years. Note the absence of inflammation or hyperplasia in the adjacent tongue mucosa. H&E; 4×

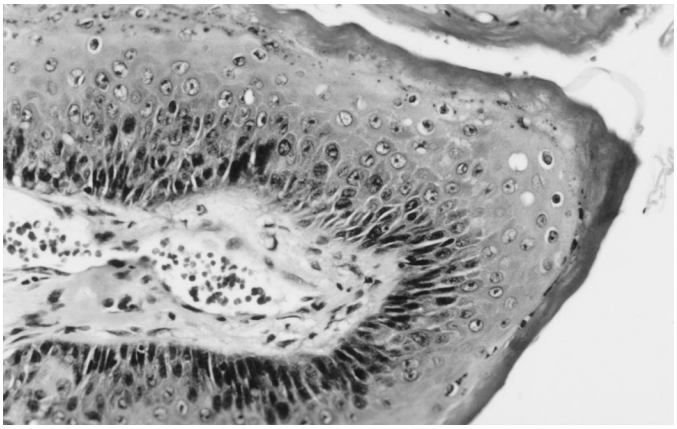


PLATE 4
Higher magnification of Plate 3. Note that the neoplastic cells have not extended beyond the basal lamina of the submucosa. H&E; 80×

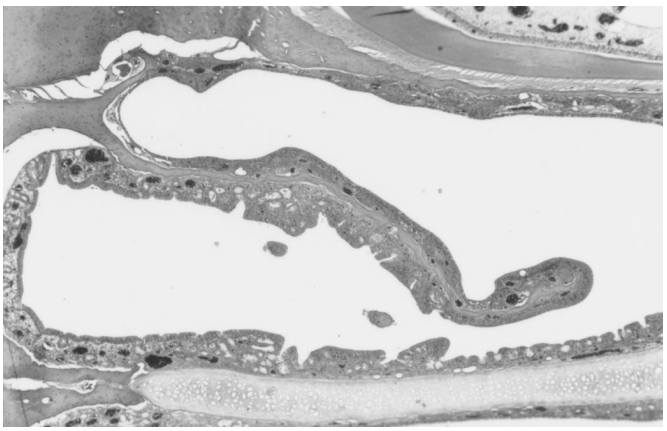


PLATE 5
Adenomatous hyperplasia of the areas of respiratory metaplasia of the septum and turbinates in nasal Level II in the nasal cavity of a female F344/N rat exposed to 80 ppm chloroprene by inhalation for 2 years. Note the numerous folds in the hyperplastic epithelium. H&E; 8×

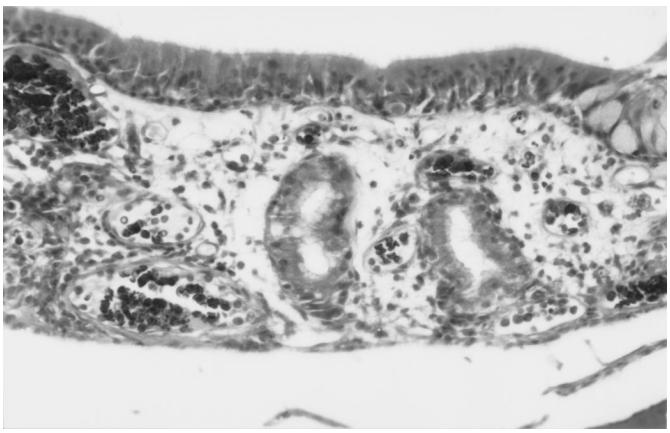


PLATE 6
Higher magnification of Plate 5. Note that the olfactory epithelium is replaced with thickened respiratory epithelium and the underlying glands are dilated in areas of inflammation. H&E; 80×

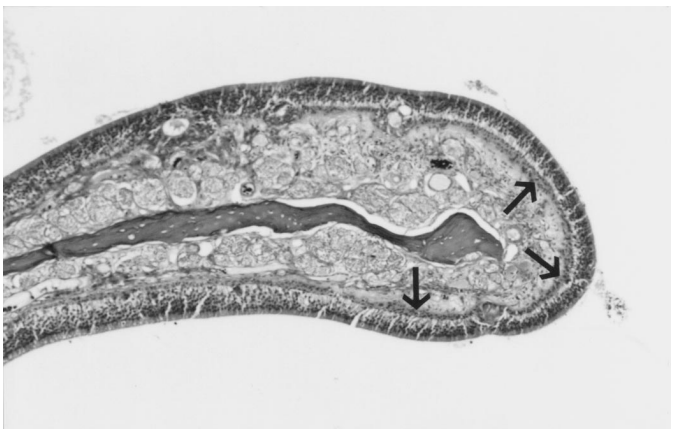


PLATE 7
Basal cell hyperplasia (arrows) and fibrosis in the turbinate of nasal Level III in the nasal cavity of a female F344/N rat exposed to 80 ppm chloroprene by inhalation for 2 years. H&E; 25×

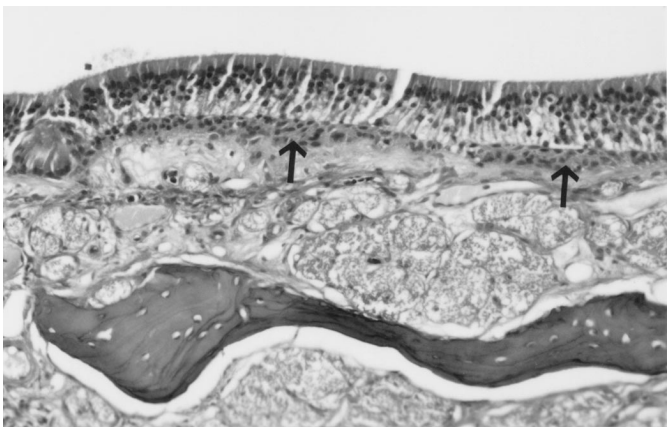


PLATE 8
Higher magnification of Plate 7 showing several layers of basal cells (arrows) and fibrosis. H&E; 66×

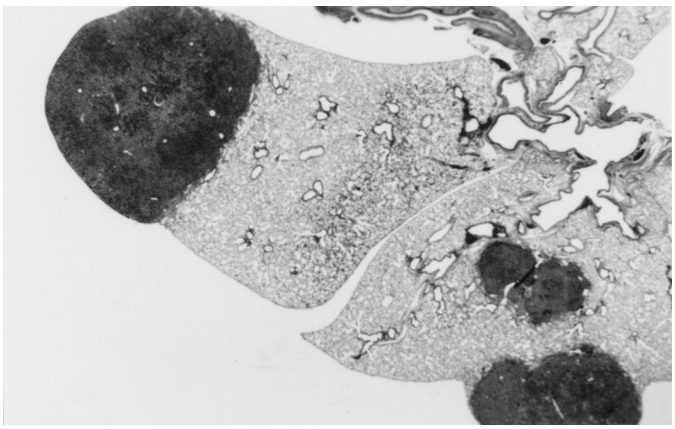


PLATE 9
Lung of a male B6C3F$_1$ mouse exposed to 80 ppm chloroprene by inhalation for 2 years. Note the multiple alveolar/bronchiolar carcinomas. H&E; 2.5×

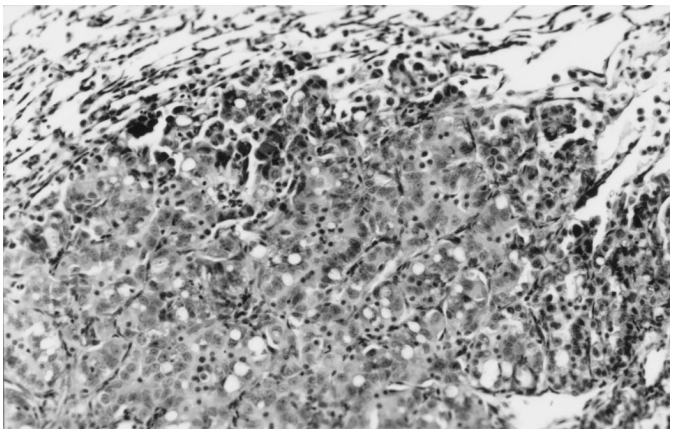


PLATE 10
Higher magnification of Plate 9. Note the mixed pattern of the multiple alveolar/bronchiolar carcinomas consisting of solid and papillary patterns and the vacuolated cytoplasm of malignant cells consistent with type II cells. Note that the neoplastic cells are in filtrating the adjacent normal lung parenchyma. H&E; 50×

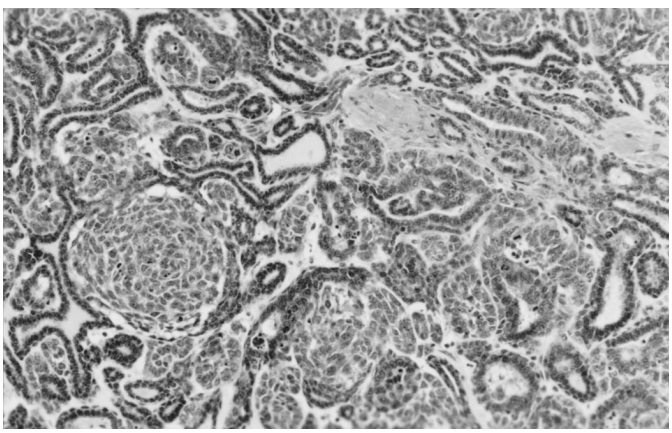


PLATE 11
Mammary gland carcinoma of a female B6C3F$_1$ mouse exposed to 80 ppm chloroprene by inhalation for 2 years. Note that the normal architecture of the mammary gland is replaced by malignant epithelia that are forming glandular patterns. H&E; 5×

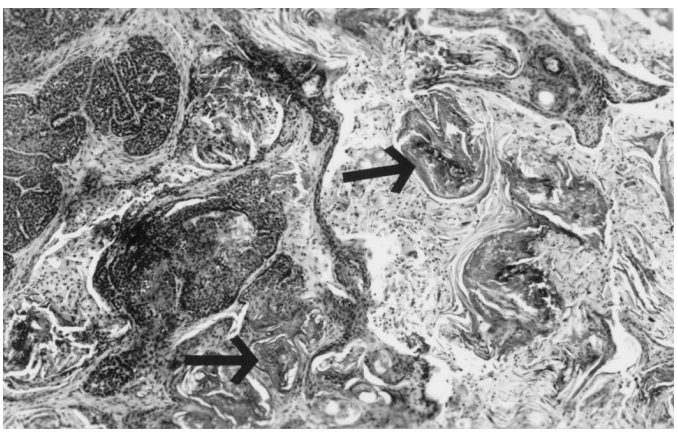


PLATE 12
Mammary gland adenoacanthoma of a female B6C3F$_1$ mouse exposed to 80 ppm chloroprene by inhalation for 2 years. Note that the normal architecture of the mammary gland is replaced by dense cellular solid foci of pleomorphic cells with a high nucleus:cytoplasm ratio. Also note the abundant squamous cell differentiation (arrows), a prominent feature of this neoplasm. H&E; 50×

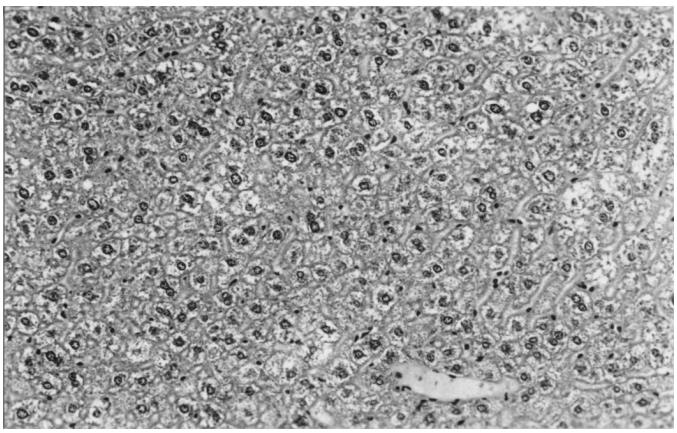


PLATE 13
Normal liver of a male B6C3F$_1$ mouse exposed to filtered air by inhalation for 2 years. H&E; 50×

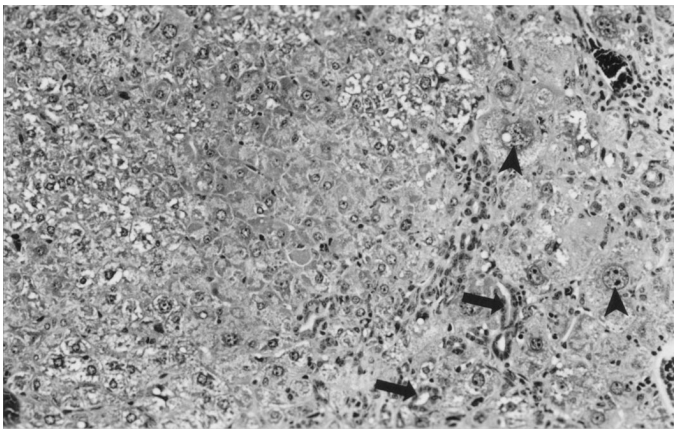


PLATE 14
Liver of a male B6C3F$_1$ mouse exposed to filtered air by inhalation for 2 years with inflammatory lesions consistent with Helicobacter infection. Compare to Plate 13 and note the prominent bile duct hyperplasia (arrows), karyomegaly (arrowheads), and regeneration of hepatocytes. H&E; 50×

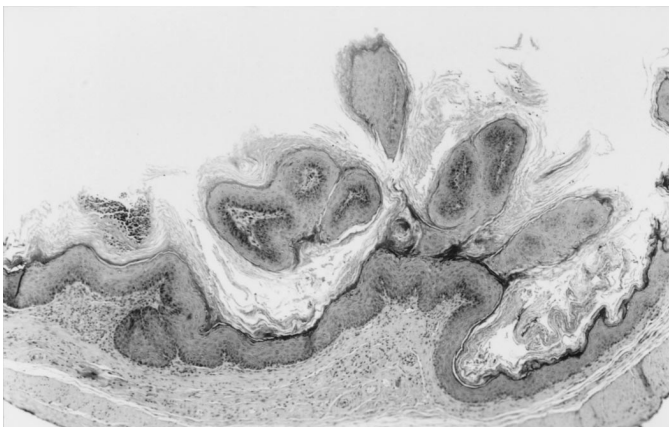


PLATE 15
Squamous cell papilloma in the forestomach of a male B6C3F$_1$ mouse exposed to 80 ppm chloroprene by inhalation for 2 years. The squamous cell papilloma has multiple fronds of thickened epithelium radiating from a central narrow stalk. H&E; 16×

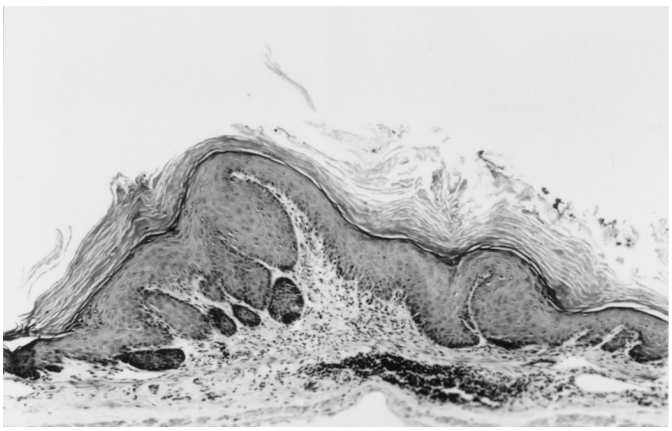


PLATE 16
Squamous cell hyperplasia in the forestomach of a female B6C3F$_1$ mouse exposed to 80 ppm chloroprene by inhalation for 2 years. The epithelium is thickened and is associated with marked hyperkeratosis. H&E; 25×

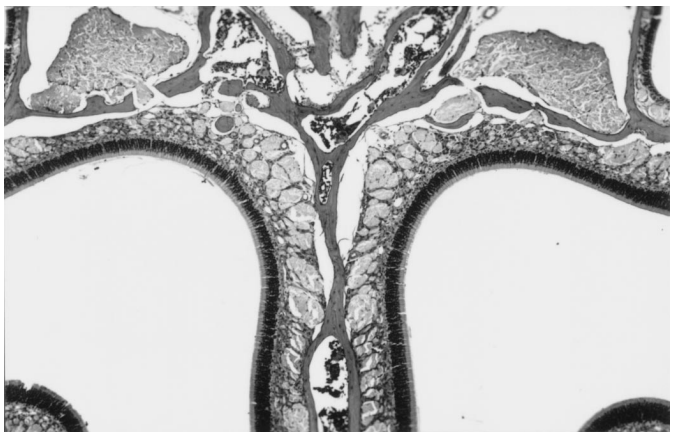


PLATE 17
Nasal cavity of a male B6C3F$_1$ mouse exposed to filtered air by inhalation for 2 years. Note the normal olfactory epithelium lining the septum and dorsal meatus in nasal Level III. H&E; 20×

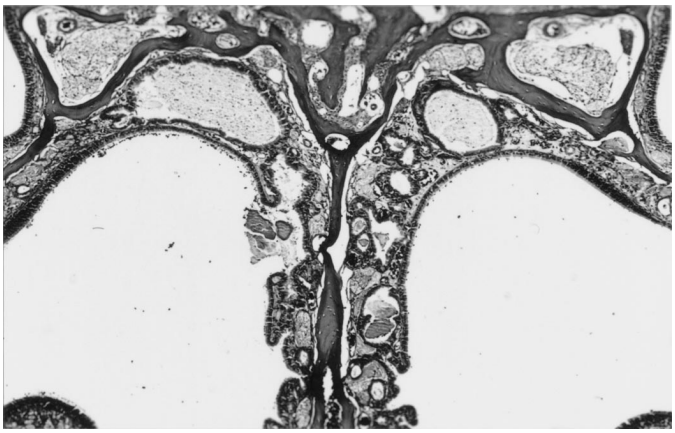


PLATE 18
Nasal cavity of a male B6C3F$_1$ mouse exposed to 80 ppm chloroprene by inhalation for 2 years. Compare to Plate 17 and note the respiratory metaplasia and atrophy of the olfactory epithelium of dorsal meatus in nasal Level III. Note the adenomatous hyperplasia of the septum characterized by numerous folds in the hyperplastic epithelium. H&E; 20×

DISCUSSION AND CONCLUSIONS

Chloroprene was selected for study by the National Toxicology Program (NTP) because it is an important high-volume production chemical with a potential for human exposure, there is limited information available on its carcinogenic potential in experimental animals and humans, and it is the 2-chloro analogue of 1,3-butadiene. Chloroprene is also structurally similar to vinyl chloride, a human carcinogen known to induce hemangiosarcomas in the liver of laboratory animals and exposed workers. Based on results of a previous NTP study of 1,3-butadiene in mice in which neoplasms were induced at multiple organ sites (NTP, 1984; Huff *et al.*, 1985), NTP examined chloroprene and isoprene (2-methyl-1,3-butadiene) to see if either of these structural analogues of 1,3-butadiene produces effects similar to those of 1,3-butadiene. A second study of 1,3-butadiene was also conducted over an expanded exposure range to provide a better characterization of dose-response effects.

1,3-Butadiene has been studied intensely over the past 12 years, and results from those studies have raised the level of concern for humans exposed to this chemical and heightened the importance of understanding the toxicologic and carcinogenic potential of chloroprene and isoprene. This report presents the findings of 16-day, 13-week, and 2-year chloroprene inhalation studies in F344/N rats and B6C3F$_1$ mice and makes comparisons to the toxicologic effects of 1,3-butadiene.

In the two NTP long-term inhalation toxicology/ carcinogenicity studies of 1,3-butadiene in B6C3F$_1$ mice, exposure concentrations ranged from 6.25 to 1,250 ppm (Huff *et al.*, 1985; Melnick *et al.*, 1990a; NTP, 1984, 1993). Particularly noteworthy in these studies were the induction of malignant lymphomas as early as 20 weeks after the start of exposure and uncommon hemangiosarcomas of the heart. Furthermore, malignant lung neoplasms were induced in female mice at all exposure concentrations. Other sites of neoplasm induction in mice included the liver, forestomach, harderian gland, ovary, mammary gland, and preputial gland. A 2-year inhalation study of 1,3-butadiene in Sprague-Dawley rats, sponsored by the International Institute of Synthetic Rubber Producers, used exposure concentrations of 1,000 and 8,000 ppm. In rats, 1,3-butadiene was carcinogenic to the mammary gland, brain, Zymbal's gland, uterus, pancreas, testis, and thyroid gland (Owen *et al.*, 1987). These studies established 1,3-butadiene as a multiple-species, multiple-organ carcinogen, with mice eliciting the more striking response. Because of differences in sites of tumor induction and in the effective exposure-related responses between rats and mice, recent research has focused on trying to understand the basis for this species difference, especially as it may relate to assessment of human risk. Based on available epidemiological and mechanistic data on 1,3-butadiene as well as the similarities in response between 1,3-butadiene and ethylene oxide, Melnick and Kohn (1995) concluded that butadiene should be considered a human carcinogen and that the mouse is an appropriate model for assessing human cancer risk.

Epidemiologic studies have consistently associated excess mortality from lymphatic and hematopoietic cancers with occupational exposure to 1,3-butadiene. Significant increases in incidences of lymphosarcoma have been observed in individuals who work in the 1,3-butadiene production industry (Divine, 1990; Ward *et al.*, 1995), whereas increases in the incidence of leukemia have been found in individuals who work in the styrene-butadiene rubber manufacturing industry (Matanoski *et al.*, 1990; Santos-Burgoa *et al.*, 1992). Recent follow-up studies of synthetic-rubber producers have confirmed the association between exposure to 1,3-butadiene and chronic leukemia (Delzell *et al.*, 1996). The finding that the risk of chronic leukemia in humans exposed to 1,3-butadiene was similar to risk estimates that were based on the induction of lymphocytic lymphoma in exposed mice supports the use of mice in studies for human risk assessment.

Based on data available on 1,3-butadiene, the Occupational Safety and Health Administration (OSHA) has recently lowered the occupational exposure standard for 1,3-butadiene from 1,000 to 1 ppm, expressed as an 8-hour, time-weighted, average work-place exposure limit, and set a 15-minute short-term exposure limit of 5 ppm (29 CFR, Parts 1910, 1915, and 1926). The current OSHA standard for chloroprene is 25 ppm, based largely on results of 4-week inhalation toxicity studies in rats and hamsters (Clary *et al.*, 1978).

16-Day and 13-Week Studies in Rats and Mice

Exposure of F344/N rats to chloroprene for 16 days at chamber concentrations ranging from 32 to 500 ppm produced several toxic effects: 1) mortality at 500 ppm and reductions in body weight gain in males exposed to 200 or 500 ppm; 2) regenerative, normocytic, normochromic anemia in males exposed to 500 ppm and in females exposed to 200 or 500 ppm; 3) centrilobular hepatocellular necrosis in the 200 and 500 ppm groups and increases in alanine aminotransferase (ALT), glutamate dehydrogenase (GDH), and sorbitol dehydrogenase (SDH) activities in 200 ppm females and 500 ppm males and females; 4) olfactory epithelial degeneration in all exposed groups and respiratory metaplasia in the 500 ppm groups; and 5) thymic atrophy. Similar effects in the liver were reported in a 4-week inhalation study of chloroprene in Wistar rats (Clary *et al.*, 1978).

The hemorrhage observed clinically (epistaxis) in this study suggests that the rapidly developing normocytic, normochromic, responsive anemia that occurred on day 4 in the 500 ppm groups may have been related to acute blood loss. The thrombocytopenia seen in this study is also consistent with the clinically observed hemorrhage. 1,3-Butadiene has also been shown to cause an anemia in mice (Irons *et al.*, 1986; Melnick *et al.*, 1990b); however, in this species the anemia was macrocytic, normochromic, and nonresponsive and was suggested to involve altered bone marrow production of erythrocytes. No hematologic effects were observed in rats exposed to 1,3-butadiene or isoprene at concentrations as high as 8,000 ppm and 7,000 ppm, respectively (Crouch *et al.*, 1979; Melnick *et al.*, 1994).

Findings from the 13-week inhalation toxicity studies of chloroprene in F344/N rats and B6C3F$_1$ mice have been reported by Melnick *et al*. (1996a). Exposure of rats to 32 ppm chloroprene or greater concentrations caused olfactory epithelial degeneration, and 80 ppm or greater caused respiratory metaplasia; exposure to 200 ppm caused anemia (characterized as normocytic, normochromic, and nonresponsive), minimal to mild hepatocellular necrosis, and reduced sperm motility. These lesions had not been observed in rats exposed to 1,3-butadiene or isoprene even at exposure concentrations as high as 8,000 and 7,000 ppm, respectively (Crouch *et al.*, 1979; Melnick *et al.*, 1994). Neurobehavioral assessments showed an increase in motor activity in exposed males but not females with no effects on grip strength or startle response in either male or female rats (Tilson, 1990).

As in the 16-day rat study, rats in the 200 ppm groups demonstrated evidence of hemorrhage, which may, in part, explain the minimal normocytic, normochromic, and nonresponsive anemia that was observed at week 13. The increase in activated partial thromboplastin time and prothrombin time on day 2 of the 13-week study suggests that coagulopathy may have contributed to the hemorrhage and subsequent anemia. The lack of a bone marrow response at the end of the 13-week study may be because the changes in erythroid parameters were not severe enough to stimulate a demonstrable erythropoietic response.

Increases in serum ALT, GDH, and SDH activities indicative of hepatocellular pathology resulting in a loss of cell membrane integrity, or cellular necrosis with subsequent enzyme release, were observed in both the 16-day and 13-week studies. These changes were transient, however, and by week 13 the activities of these serum enzymes had returned to chamber control levels. Centrilobular necrosis was also observed in the liver of rats exposed to 200 ppm or greater concentrations of chloroprene, and this would account for the increases in the serum activities of these enzymes. However, while the biochemical effects appeared to be transient, liver injury (hepatocellular necrosis) was still evident at study termination.

In the 13-week study, proteinuria and alkaline phosphatase enzymeuria occurred in the 200 ppm animals as early as day 22; these findings suggest a renal tubule effect. There were no microscopic lesions to

support these biochemical alterations, suggesting that the renal injury was too mild to result in structural damage or that the biochemical effects may precede the eventual development of microscopic lesions. Exposure-related increases in kidney weights also suggest a renal effect and support the biochemical findings. These findings suggest that the kidney is a target tissue for the inhalation toxicity of chloroprene and that the renal effects would not have been identified by microscopic evaluation alone.

In the 16-day inhalation study of chloroprene in $B6C3F_1$ mice, exposure concentrations were slightly less than those in the rat study (from 12 to 200 ppm in mice versus 32 to 500 ppm in rats). In spite of the lower exposure concentration, all mice exposed to 200 ppm died during the first 3 days of the study. Chloroprene at exposure concentrations up to 80 ppm had no effect on survival, body weight gain, hematology, or clinical chemistry parameters. Histopathologic findings in the 200 ppm group included multifocal hepatic necrosis, thymic necrosis, and focal hemorrhage, erosions, or necrosis of the glandular stomach mucosa. Squamous epithelial hyperplasia of the forestomach was observed in a small number of mice exposed to 80 ppm.

In the 13-week inhalation study in $B6C3F_1$ mice, exposure to 80 ppm caused a marginal decrease in body weight gain in males and epithelial hyperplasia of the forestomach in males and females. This lesion had also been observed in mice exposed to isoprene or 1,3-butadiene. A mild, normocytic, normochromic, nonresponsive anemia was also detected in exposed female mice. Decreases in hepatic nonprotein sulfhydryl concentrations in mice exposed to 80 ppm were not associated with any histopathologic changes in the liver.

In conjunction with these toxicity studies on chloroprene, additional groups of mice were included for evaluations of cytogenetic effects after 12 exposures over a 16-day period. Unlike the effects seen in mice exposed to 1,3-butadiene or isoprene, chloroprene did not induce cytogenetic damage in bone marrow cells of mice exposed to concentrations up to 80 ppm (Tice *et al.*, 1988). For 1,3-butadiene, this exposure concentration produced increases in sister chromatid exchanges and in the frequency of micronuclei in peripheral blood. Isoprene also produced cytogenetic effects in mice but at exposure concentrations greater than those that could be achieved with chloroprene.

The 16-day and 13-week studies indicate that chloroprene is substantially more toxic to rats and mice than either 1,3-butadiene or isoprene. This difference is reflected in the maximum tolerated exposures that were selected for long-term studies of these chemicals: 1,3-butadiene, 8,000 ppm for rats (Owen *et al.*, 1987) and 1,250 ppm for mice (NTP, 1993; Huff *et al.*, 1985); isoprene, 7,000 ppm for rats and mice (Melnick *et al.*, 1994); and chloroprene, 200 ppm for rats and 80 ppm for mice. Table 31 shows that the profile of toxicologic effects of chloroprene, in terms of target sites and effective exposures, differs considerably from that of isoprene or 1,3-butadiene; this may be due in part to differences in exposure concentrations that were used in the toxicology studies of these compounds but is also likely due to the influence of the chlorine substitution on the toxicokinetics and biotransformation of this chemical and the reactivity of metabolic intermediates with tissue macromolecules.

TABLE 31
Toxicologic Effects (Lowest-Observable-Adverse-Effect Level in ppm) of Chloroprene, 1,3-Butadiene, and Isoprene in Rats and Mice[a]

	Rats			Mice		
Toxic Effect	**Chloroprene**	**Butadiene**	**Isoprene**	**Chloroprene**	**Butadiene**	**Isoprene**
Anemia	200[b]	neg(8,000)[c]	neg(7,000)[d]	neg(80)[b]	62.5[e]	220[d]
Liver, necrosis	200[b]	neg(8,000)[c]	neg(7,000)[d]	neg(80)[b]	625[f]	neg(7,000)[d]
Nose, olfactory epithelium degeneration	32[b]	neg(8,000)[c]	neg(7,000)[d]	neg(80)[b]	625[g]	220[d]
Forestomach, squamous epithelial hyperplasia	neg(200)[b]	neg(8,000)[c]	neg(7,000)[d]	80[b]	200[e]	438[h]
Testes, atrophy	neg(200)[b]	neg(8,000)[c]	neg(7,000)[d]	neg(80)[b]	625[e]	7,000[h]
Cytogenetic damage						
Chromosomal aberrations	NS	NS	NS	neg(80)[i]	625[j]	neg (7,000)[i]
Sister chromatid exchange	NS	neg(10,000)[k]	NS	neg(80)[i]	6.25[j]	220[l]
Micronuclei	NS	neg(10,000)[k]	NS	neg(80)[i]	6.25[l]	438[i]

[a] Taken from Melnick *et al.*, 1996a. Neg = no effect. NS = not studied. The highest concentration studied is given in parentheses.
[b] The current study
[c] Crouch *et al.*, 1979
[d] Melnick *et al.*, 1994
[e] Melnick *et al.*, 1990b
[f] NTP, 1984
[g] NTP, 1993
[h] Melnick *et al.*, 1990c
[i] Tice *et al.*, 1988
[j] Tice *et al.*, 1987
[k] Cunningham *et al.*, 1986
[l] Shelby, 1990

2-Year Study in Rats

In the 2-year study of chloroprene in rats, survival rates were less in all exposed groups of males and significantly reduced in 32 and 80 ppm males relative to the chamber controls. Males exposed to 80 ppm had decreased body weights compared to the chamber controls; a large part of this difference occurred during the last month of the study. There were no differences in survival or body weights among the female exposed and chamber control rats.

Exposure of rats to chloroprene produced a multiple-organ carcinogenic response. Some sites affected by chloroprene were not affected by 1,3-butadiene, whereas other sites were affected similarly even though the exposure concentrations used in the studies of these two chemicals differed substantially (Table 32). Exposure-related carcinogenic effects of chloroprene were seen in the lung, oral cavity, thyroid gland, mammary gland, and kidney. In addition, low incidences of rare neoplasms in the urinary bladder in males and females may have been exposure related.

TABLE 32
Sites of Increased Incidences of Neoplasms in the 2-Year Inhalation Studies of Chloroprene and 1,3-Butadiene in Rats and Mice

	Chloroprene[a]		1,3-Butadiene[b]	
	Male	**Female**	**Male**	**Female**
Rats				
			Pancreas	
				Uterus
	Oral Cavity	Oral Cavity		
	Thyroid gland	Thyroid gland		Thyroid gland
	Lung			
		Mammary gland		Mammary gland
	Kidney	Kidney		
			Testis	
				Zymbal's gland
			Brain	
Mice				
			Hematopoietic system	Hematopoietic system
	Lung	Lung	Lung	Lung
	Circulatory system	Circulatory system		
			Heart (hemangiosarcoma)	Heart (hemangiosarcoma)
	Harderian gland	Harderian gland	Harderian gland	Harderian gland
	Forestomach	Forestomach	Forestomach	Forestomach
	Kidney		Kidney	
		Mammary gland		Mammary gland
		Liver	Liver	Liver
		Skin		
		Mesentery		
		Zymbal's gland		
			Preputial gland	
				Ovary

[a] Current study in F344/N rats and B6C3F$_1$ mice
[b] Studies in Sprague-Dawley rats at exposure concentrations of 1,000 or 8,000 ppm (Owen *et al.*, 1987) and B6C3F$_1$ mice at exposure concentrations of 6.25, 20, 62.5, 200, or 625 ppm (Melnick *et al.*, 1990a; NTP, 1993)

In rats exposed to chloroprene, increased incidences of proliferative lesions of the oral cavity included squamous cell hyperplasia, squamous cell papilloma, and squamous cell carcinoma and involved the palate, pharynx, gingiva, cheek, and tongue. In addition to the positive exposure-related trends, the incidences of squamous cell papilloma and squamous cell carcinoma (combined) increased significantly in males and females and far exceeded the NTP historical control incidence. Oral cavity neoplasms have not been reported in rats or mice exposed to 1,3-butadiene or isoprene (NTP, 1993, 1995).

Exposure-related positive trends and increased incidences of follicular cell adenoma or carcinoma (combined) in rats were indicative of a carcinogenic effect of chloroprene in the thyroid gland. Thyroid gland follicular cell neoplasms have been reported to be induced in female Sprague-Dawley rats exposed to 1,000 or 8,000 ppm 1,3-butadiene (Owen *et al.*, 1987).

The incidences of alveolar epithelial hyperplasia were increased in all exposed groups of male and female rats relative to their respective chamber control groups, and there was also a slight increase in the incidence of alveolar/bronchiolar carcinomas (4 of 50) in 80 ppm males. The NTP historical control database recorded only 6 of 654 (0.9%) chamber control male rats with alveolar/bronchiolar carcinoma. Although exposure to 1,3-butadiene or isoprene induced lung neoplasms in mice, neither of these chemicals has been reported to cause lung neoplasms in rats (NTP, 1993, 1995).

The incidences of mammary gland fibroadenoma were increased in female rats exposed to 32 or 80 ppm; however, the incidence of mammary gland carcinoma was not increased. Increases in the incidences of multiple fibroadenoma of the mammary gland in female rats support the conclusion that this effect is exposure related. Exposure of female rats to 1,3-butadiene also caused increases in the incidence and multiplicity of mammary gland fibroadenoma (Owen *et al.*, 1987; Melnick and Huff, 1992).

Slight increases in the incidences of renal tubule adenoma and renal tubule hyperplasia were observed in male and female rats exposed to chloroprene compared to the chamber controls. Renal tubule hyperplasias are thought to represent an early stage in the morphologic continuum of proliferative kidney lesions leading to renal tubule adenoma and carcinoma. Even though the severity of nephropathy was increased slightly in exposed rats compared to the chamber controls, the renal tubule hyperplasias observed in this study were distinguishable from regenerative epithelial changes associated with renal nephropathy in this strain of rat. Because renal tubule neoplasms are uncommon in chamber control F344/N rats, additional kidney sections were examined from chamber control and exposed male and female rats to provide a clearer indication of the potential effects of chloroprene in this organ. Analyses of the step-section data indicated that the incidences of renal tubule hyperplasia were increased significantly in 32 and 80 ppm males and 80 ppm females. The incidences of renal tubule adenoma or carcinoma (combined) were increased in all exposed groups of males compared to the chamber controls. Particularly unusual was the finding of renal tubule adenomas in four 80 ppm females and a renal tubule carcinoma in one 12.8 ppm male. Thus, the results from the additional kidney step sections support the evidence from the original pathology review, which indicated that chloroprene induces proliferative renal tubule lesions, including neoplasms, in male and female rats.

A variety of exposure-related nasal lesions were induced in male and female rats including necrosis, chronic active inflammation, atrophy, respiratory metaplasia, adenomatous hyperplasia, basal cell hyperplasia, and fibrosis of the olfactory epithelium. Although the incidences of many of these lesions approached or reached 100% in the 80 ppm groups, there was no evidence of progression of these lesions to neoplasms. Similar nasal lesions without neoplastic effects were seen in several other NTP 2-year studies, including 2-chloroacetophenone, *o*-chlorobenzalmalononitrile, *l*-epinephrine hydrochloride, vinyl toluene, and tetranitromethane (NTP, 1990a,b,c,d,e). Although increased cell turnover may contribute to multistage carcinogenesis, a review of 19 NTP inhalation bioassays found that chronic toxicity and cell proliferation frequently were not associated with nasal carcinogenesis (Ward *et al.*, 1993). Olfactory epithelial degeneration and respiratory metaplasia in rats had been identified as a toxic effect of chloroprene in the 13-week studies; however, nasal lesions were not observed in rats exposed to 8,000 ppm 1,3-butadiene for 2 years (Owen *et al.*, 1987) or to 7,000 ppm isoprene for 26 weeks (Melnick *et al.*, 1994).

2-Year Study in Mice

In the 2-year study of chloroprene in mice, survival rates were less in 32 and 80 ppm males and in all exposed groups of females than in the chamber controls. Many early deaths and moribund kills were associated with chloroprene-induced neoplasms. Mean body weights of 80 ppm female mice were less than those of chamber controls after week 75.

Exposure of mice to chloroprene produced a potent multisite carcinogenic response. Several organs that were targets of 1,3-butadiene carcinogenicity in mice were similarly affected by chloroprene, including the lung, harderian gland, liver, forestomach, and mammary gland; however, some carcinogenic effects of 1,3-butadiene in mice were not seen in the chloroprene study (Table 32). Most notable was the lack of lymphomas in mice exposed to chloroprene compared to the early occurrence and extensive development of lymphocytic lymphomas in mice exposed to 625 ppm 1,3-butadiene. This may be related to differences in exposure to the parent compound and differences in target organ dosimetry and/or reactivity of metabolic intermediates. Exposure of mice to 1,3-butadiene was also associated with the development of rarely occurring hemangiosarcomas of the heart. Although exposure to chloroprene in the present study did not induce hemangiosarcomas of the heart, there were exposure-related increases in the incidences of hemangioma and hemangiosarcoma at multiple organ sites. In addition, 1,3-butadiene, but not chloroprene, induced granulosa cell tumors of the ovary; and chloroprene, but not 1,3-butadiene, induced skin and mesentery sarcomas in female mice. Small numbers of renal tubule adenomas were observed in male mice exposed to either 1,3-butadiene or chloroprene. The present studies included a step-section evaluation of the kidneys from chamber control and exposed male mice to more clearly ascertain the potential relationship between exposure to chloroprene and kidney neoplasms. The occurrence of Zymbal's gland carcinomas in three female mice exposed to 80 ppm chloroprene is also indicative of an exposure-related effect. The four organ sites where isoprene was reported to induce neoplasms in mice (lung, liver, harderian gland, and forestomach; Melnick *et al.*, 1994) were also affected by chloroprene.

The lung was a major target organ of chloroprene-induced neoplasms in male and female mice. In addition to producing increases in the incidences of bronchiolar epithelial hyperplasia and alveolar/bronchiolar adenoma or carcinoma (combined), chloroprene exposure caused significant increases in the incidences of alveolar/bronchiolar carcinoma, multiple adenoma, and multiple carcinoma. Qinan *et al.* (1989) also observed an increase in lung neoplasm incidence and multiplicity in mice exposed to chloroprene for 7 months. Lung neoplasms including alveolar/bronchiolar carcinoma were induced in female mice exposed to 1,3-butadiene at concentrations as low as 6.25 ppm (Melnick *et al.*, 1990a; NTP, 1993). Lung neoplasms were also induced by vinyl chloride in male and female mice (Maltoni *et al.*, 1981).

The livers of most chamber control and exposed male mice contained a spectrum of lesions consistent with *Helicobacter* infection; these included karyomegaly, regeneration, and bile duct hyperplasia. The liver lesions associated with *Helicobacter* infection were not present in female mice, and an exposure-related increase in the incidences of hepatocellular carcinoma was evident. Neoplasm responses in female mice or at other sites in male mice (including hemangiosarcoma) were not considered to be affected by the *Helicobacter* infection.

Based on retrospective analyses, *Helicobacter hepaticus* was determined to have infected mice in 12 recent NTP 2-year studies (Appendix O). Of the 12 studies, mice (primarily males) from nine studies (including this chloroprene study) had *H. hepaticus*-associated hepatitis. Qualitatively, the hepatitis and silver-staining organisms within the liver were similar among the nine studies. An organism compatible with *H. hepaticus* was identified by an assay based on polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) in studies from which adequately preserved (frozen) liver tissue was available, including livers from 5 animals in this chloroprene study. Generally, efforts to identify *H. hepaticus* from tissue fixed in formalin for over a week were not successful (Malarkey *et al.*, 1997). Because of the presence of the typical liver lesions, silver-positive helical organisms, and confirmation with PCR-RFLP-based assays, mice from the current study were determined to be infected with *H. hepaticus*.

Increased incidences of hepatocellular neoplasms in male mice have been shown to be associated with *H. hepaticus* infection when hepatitis is also present

(Ward *et al.*, 1994; Fox *et al.*, 1996; Appendix O). Additionally, in NTP studies with *H. hepaticus*-associated hepatitis, increased incidences of hemangiosarcoma were seen in the livers of male mice (Appendix O). In this study of chloroprene, hemangiosarcomas and hemangiomas, which are endothelial cell neoplasms derived from blood vessels, occurred primarily in the mesentery, subcutis of the skin, and liver; the bone and spleen were sometimes affected. Because of the association noted above, hemangiosarcomas of the liver were excluded from the analyses of circulatory (endothelial) neoplasms in males in this study. Hemangiomas did not occur in the liver of male mice in this study. Even with this exclusion, the incidences of the combined occurrence of hemangiosarcoma or hemangioma at other sites were significantly increased at all chloroprene exposure concentrations in males and in 32 ppm females. Incidences of neoplasms at other sites in this study of chloroprene were not considered to have been significantly impacted by the infection with *H. hepaticus* or its associated hepatitis (Appendix O).

As with 1,3-butadiene, mammary gland neoplasms induced by chloroprene included both carcinomas and adenoacanthomas. The detection of mammary gland adenoacanthomas provides an additional indicator of an exposure-related effect because the historical incidence of these neoplasms is much less than that of mammary gland carcinoma in control female mice (0.1% versus 3.1%).

The slight increases in incidences of squamous cell papilloma of the forestomach were considered to be exposure related because there were similar increases in the incidences of this uncommon neoplasm in exposed groups of male and female mice, and these responses were accompanied by increased incidences of hyperplasia of the forestomach epithelium. The latter lesion probably represents a proliferative preneoplastic change caused by chloroprene.

As in the study of chloroprene in rats, exposure-related increases in the incidences of renal tubule hyperplasia and renal tubule adenoma were observed in male mice. Because renal tubule adenomas are uncommon in historical control $B6C3F_1$ mice (0.2%), additional sections of kidney from chamber control and chloroprene-exposed male mice were examined to verify the proliferative effects of chloroprene in this organ. The step-section data confirmed the original findings that exposure to chloroprene increased the incidences of renal tubule hyperplasia and produced an exposure-related increase in the incidences of renal tubule hyperplasia and renal tubule adenoma in males. The incidence of renal tubule adenoma in the 80 ppm group was significantly greater than that in the chamber controls, and the incidences of renal tubule hyperplasia were increased in all exposed groups of males. No renal tubule neoplasms were seen in chamber control males even after step sectioning.

Several sites of neoplasm induction by chloroprene in mice have been mentioned as sites of increased risk of human cancer associated with occupational exposure to chloroprene, including the lung, skin, and liver (Infante *et al.*, 1977; Shouqi *et al.*, 1989).

Exposure of male and female mice to 80 ppm chloroprene produced high incidences of olfactory epithelial atrophy, metaplasia, and adenomatous hyperplasia in the nose of males and females. These changes were not associated with neoplastic effects, although an adenoma of the respiratory epithelium was detected in one 80 ppm male and one 32 ppm female. Olfactory epithelial degeneration has been observed in mice exposed to 1,3-butadiene or isoprene (Melnick *et al.*, 1988; NTP, 1993).

For neoplasms in mice showing exposure-related effects, the shapes of the dose-response curves and ED_{10} values were estimated by fitting a modified Weibull model (Portier *et al.*, 1986) to the Poly-3 survival-adjusted neoplasm rates. These values for chloroprene are shown along with those for 1,3-butadiene in Table 33. If the estimated shape parameter is greater than 1, the resulting dose response has more curvature than a linear model (shape parameter equal to 1) and exhibits "threshold-like behavior." If the estimated shape parameter is less than 1, then the dose-response curve is very steep (supralinear) in the low-dose region. The ED_{10} values represent the estimated exposure concentration associated with an excess cancer risk of 10% at each site. Small differences in mean body weights between the chamber control group and groups of mice exposed to chloroprene or 1,3-butadiene were not

TABLE 33
Comparison of Dose-Response Shape Parameter and ED_{10} Values (ppm) for Chloroprene (Chl) and 1,3-Butadiene (BD) in Mice[a]

	Males				Females			
	Shape Parameter		ED_{10}-Chl	ED_{10}-BD	Shape Parameter		ED_{10}-Chl	ED_{10}-BD
	Chl	BD	(LCL, UCL)	(LCL, UCL)	Chl	BD	(LCL, UCL)	(LCL, UCL)
Lung								
Alveolar/bronchiolar Carcinoma	0.743	0.576*	3.7 (0.1, 13.7)	8.1 (1.1, 30.7)	0.686	0.456**	1.9 (0.05, 6.7)	2.8 (0.3, 7.8)
Alveolar/bronchiolar Adenoma or Carcinoma	0.682	0.459**	0.9 (< 0.01, 4.8)	2.1 (0.01, 21.2)	0.597*	0.374**	0.3 (< 0.01, 1.6)	0.3 (< 0.01, 1.8)
All organs[b]								
Hemangioma or Hemangiosarcoma	0.292**	0.737	0.2 (< 0.01, 4.8)	14.0 (14.0, 28.4)	0.329*	0.982	1.4 (< 0.01, 17.4)	24.4 (11.4, 46.6)
Harderian Gland								
Adenoma or Carcinoma	0.661	0.649**	12.1 (< 0.01, 39.6)	5.8 (1.4, 16.2)	0.814	0.574*	22.5 (< 0.01, 79.2)	9.4 (1.0, 40.9)
Mammary Gland								
Adenoacanthoma or Carcinoma					0.844	0.706**	11.8 (0.5, 34.5)	13.1 (5.4, 24.1)
Liver								
Hepatocellular Carcinoma	0.414	0.399*	0.6 (< 0.01, 20.2)	2.33 (< 0.01, 29.0)	0.605	0.279*	2.7 (< 0.01, 13.3)	9.1 (< 0.01, 112.8)
Hepatocellular Adenoma or Carcinoma	1.330	0.362*	36.9 (11.7, 79.5)	0.7 (< 0.01, 22.8)	0.584	0.315	1.9 (< 0.01, 78.4)	7.2 (< 0.01, 625)
Forestomach								
Squamous Cell Papilloma or Carcinoma	1.83	1.412	70.0 (51.3, 79.9)	120.4 (87.5, 172.1)	> 10.0*	1.182	79.1 (76.9, 80[c])	63.9 (37.5, 185.4)
Kidney								
Renal Tubule Adenoma								
Single Section	0.773	0.247	80[c] (51, 80)	625[c] (241, 625)				
Single + Step Section	1.01		32.2 (14.2, 60.8)					

TABLE 33
Comparison of Dose-Response Shape Parameter and ED_{10} Values (ppm) for Chloroprene (Chl) and 1,3-Butadiene (BD) in Mice

	Males				Females			
	Shape Parameter		ED_{10}-Chl	ED_{10}-BD	Shape Parameter		ED_{10}-Chl	ED_{10}-BD
	Chl	BD	(LCL, UCL)	(LCL, UCL)	Chl	BD	(LCL, UCL)	(LCL, UCL)
Skin								
Sarcoma					0.459**	0.555	1.1 (< 0.01, 6.3)	70.4 (65.1, 237.9)
Mesentery								
Sarcoma					0.074**	> 10.0	0.02 (< 0.01, 17.5)	602 (577.6, 618.4)

* Shape is significantly different ($P < 0.05$) from 1 by a likelihood ratio test
** $P < 0.01$
[a] Shape parameter and ED_{10} values were estimated by fitting a modified Weibull model (Portier *et al.*, 1986) to the Poly-3 survival-adjusted neoplasm rates for chloroprene and for 1,3-butadiene. The 95% lower confidence limit (LCL) and 95% upper confidence limit (UCL) are given in parentheses.
[b] Liver hemangioma and hemangiosarcoma were excluded for chloroprene-exposed male mice.
[c] Estimates and upper limits of ED_{10} values were not allowed to exceed the maximum exposure concentration.

considered to have a substantial impact on the neoplasm dose-response evaluations.

For many of the chloroprene-induced neoplastic effects that were evaluated, the dose responses were consistent with a linear model. In most instances in which a departure from linearity was evident, the shape parameter indicated a dose-response curve that was supralinear (concave downward) in the low-dose region (hemangioma and hemangiosarcoma in male and female mice, alveolar/bronchiolar adenoma or carcinoma, skin and mesentery sarcomas in female mice). Only squamous cell papilloma or carcinoma of the forestomach in female mice had evidence of a sublinear (concave upward) dose response. For 1,3-butadiene, the shape parameter values indicated supralinear dose responses for lung, harderian gland, and liver neoplasms in male and female mice and for mammary gland neoplasms in female mice.

ED_{10} values, which are central tendency estimates within the region of experimental observation, have been used to compare cancer potency between carcinogens. The data in Table 33 indicate that chloroprene is more potent than 1,3-butadiene at inducing hemangiomas or hemangiosarcomas in male and female mice and skin and mesentery sarcomas in female mice. The two chemicals were nearly equivalent in their potency to induce lung and harderian gland neoplasms in male and female mice and mammary gland, liver, and forestomach neoplasms in female mice. ED_{10} values for neoplasms induced by 1,3-butadiene but not by chloroprene (e.g., malignant lymphoma and granulosa cell tumors of the ovary) were higher than those estimated for 1,3-butadiene-induced lung neoplasms, harderian gland neoplasms, or hemangioma and hemangiosarcoma. Hence, the carcinogenic potency of chloroprene in mice appears to be equivalent to or greater than that of 1,3-butadiene.

A similar type of analysis on the dose response and potency of vinyl chloride-induced neoplasms was not possible because of differences in study design (including different strains of rats and mice and different durations of exposure) and because individual animal data were not available. However, vinyl chloride (Maltoni *et al.*, 1981) and chloroprene have several common sites of induction of neoplasms, in particular hemangiosarcomas as well as mammary gland neoplasms in rats and neoplasms of the liver, lung, mammary gland, and forestomach in mice.

Bartsch *et al*. (1975, 1979) reported that chloroprene was mutagenic to *Salmonella typhimurium* with and without metabolic activation; however, others have found no evidence of mutagenicity for chloroprene in

S. typhimurium (Zeiger *et al.*, 1987; Westphal *et al.*, 1994). Westphal *et al.* (1994) observed mutagenic effects in *S. typhimurium* with aged samples of chloroprene but not with freshly distilled samples. These results indicate either that chloroprene is not mutagenic to *S. typhimurium* or that in the systems used to determine its mutagenicity, the reactive alkylating intermediate did not reach the target DNA. In addition, chloroprene did not induce sex-linked recessive lethal mutations in germ cells of male *Drosophila melanogaster*, nor did it induce chromosomal aberrations, sister chromatid exchanges, or micronucleated erythrocytes in bone marrow or peripheral blood of mice exposed to concentrations as high as 80 ppm. Using similar protocols, both 1,3-butadiene and isoprene induced cytogenetic changes in mice. Clearly, *in vivo* and *in vitro* genotoxicity data were not predictive of the potent multisite carcinogenic effects of chloroprene. These results reveal the in-adequacy of relying on oversimplified operational classification systems, such as genotoxic versus non-genotoxic, in regard to cancer risk rather than focusing on increasing the understanding of causal relationships between exposure and cancer outcome (Melnick *et al.*, 1996b). The finding of a higher frequency of unique K-*ras* mutations, predominantly A to T transversions at codon 61 in chloroprene-induced lung and harderian gland neoplasms (Appendix N), suggests the involvement of a mutagenic event in chloroprene-induced neoplasia. A similar high frequency of A to T transversions at codon 61 of K-*ras* were detected in lung and harderian gland neoplasms induced by isoprene.

The carcinogenic effects of 1,3-butadiene have been attributed to its mutagenic epoxide intermediates (Melnick and Kohn, 1995). Similarly, the mutagenic and carcinogenic effects of vinyl chloride have been attributed to its epoxide metabolite, chlorothyleneoxide, and the rearrangement product, chloroacetaldehyde, both of which can react with DNA to form a variety of adducts (Guengerich, 1992; Singer, 1996). Neither the metabolic fate of chloroprene nor the biological properties of its metabolic intermediates have been well studied. Oxidation of chloroprene to epoxide intermediates (2-chloro-1,2-epoxybutene-3 and 2-chloro-3,4-epoxybutene-1) was suggested to occur based on the detection of alkylated 4-(4-itrobenzyl)pyridine in incubations of chloroprene and mouse liver microsomes (Haley, 1978; Bartsch *et al.*, 1979). Analogous to the formation of chloroacetaldehyde subsequent to the oxidation of vinyl chloride to chloroethylene oxide, 2-chloro-1,2-epoxybutene-3 could undergo rearrangement to form an unsaturated chloroketone. These postulated oxidative intermediates of chloroprene metabolism may be protein and/or DNA reactive and may account for the cytotoxicity and carcinogenic effects of this compound. Differences in stability, distribution, and reactivity of these various intermediates may account for differences in dose-related carcinogenic effects of chloroprene and 1,3-butadiene. Further studies are needed to understand the processes involved in chloroprene carcinogenesis.

CONCLUSIONS

Under the conditions of these 2-year inhalation studies, there was *clear evidence of carcinogenic activity** of chloroprene in male F344/N rats based on increased incidences of neoplasms of the oral cavity; increased incidences of neoplasms of the thyroid gland, lung, and kidney were also attributed to chloroprene exposure. There was *clear evidence of carcinogenic activity* of chloroprene in female F344/N rats based on increased incidences of neoplasms of the oral cavity; increased incidences of neoplasms of the thyroid gland, mammary gland, and kidney were also attributed to exposure to chloroprene. Low incidences of urinary bladder neoplasms in male and female rats and lung neoplasms in female rats may also have been related to exposure to chloroprene.

There was *clear evidence of carcinogenic activity* of chloroprene in male B6C3F_1 mice based on increased incidences of neoplasms of the lung, circulatory system (hemangiomas and hemangiosarcomas), and harderian gland; increased incidences of neoplasms of the forestomach and kidney were also attributed to exposure to chloroprene. There was *clear evidence of carcinogenic activity* of chloroprene in female B6C3F_1 mice based on increased incidences of neoplasms of the lung, circulatory system (hemangiomas and hemangiosarcomas), harderian gland, mammary gland, liver, skin, and mesentery; increased incidences of neoplasms of the forestomach and Zymbal's gland were also attributed to exposure to chloroprene.

Exposure of male and female rats to chloroprene was associated with increased incidences of alveolar epithelial hyperplasia in the lung; nephropathy; and several nonneoplastic effects in the nose including olfactory epithelial atrophy, fibrosis, adenomatous hyperplasia, basal cell hyperplasia, chronic inflammation, respiratory metaplasia, and necrosis. Exposure of male and female mice to chloroprene was associated with increased incidences of bronchiolar hyperplasia and histiocytic cell infiltration in the lung; epithelial hyperplasia in the forestomach; renal tubule hyperplasia (males only); several effects in the nose including olfactory epithelial atrophy, respiratory metaplasia, and adenomatous hyperplasia; and hematopoietic cell proliferation in the spleen.

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* Explanation of Levels of Evidence of Carcinogenic Activity is on page 14. A summary of the Technical Reports Review Subcommittee comments and the public discussion on this Technical Report appears on page 16.

REFERENCES

American Conference of Governmental Industrial Hygienists (ACGIH) (1985). *Guidelines for the Selection of Chemical Protective Clothing*, 2nd ed., p. 46. ACGIH, Cincinnati, OH.

American Conference of Governmental Industrial Hygienists (ACGIH) (1986). *Documentation of the Threshold Limit Values and Biological Exposure Indices*, 5th ed., p. 135. ACGIH, Cincinnati, OH.

American Conference of Governmental Industrial Hygienists (ACGIH) (1996). *1996-1997 Threshold Limit Values for Chemical Substances and Physical Agents and Biological Exposure Indices*. ACGIH, Cincinnati, OH.

Arevshatyan, G.S. (1972). Prophylactic care of the oral cavities of workers engaged in chloroprene production [in Russian]. *Biol. Zh. Arm.* **25**, 115-117.

Armitage, P. (1971). *Statistical Methods in Medical Research*, pp. 362-365. John Wiley and Sons, New York.

Ashby, J., and Tennant, R.W. (1991). Definitive relationships among chemical structure, carcinogenicity and mutagenicity for 301 chemicals tested by the U.S. NTP. *Mutat. Res.* **257**, 229-306.

Asmangulian, T.A., and Badalian, S.O. (1971). Toxicity of chloroprene in an acute test during oral administration. *Tr. Erevan. Med. Inst.* **15**, 461-465.

Bagdinov, Y.M., (1973). Working conditions and the status of a number of the physiological functions in women employed in the manufacture of articles made from cholorprene latex [in Russian]. *Nauchni Tr. Akusher. Ginekol. Profpatol.*, 12-19.

Bailer, A.J., and Portier, C.J. (1988). Effects of treatment-induced mortality and tumor-induced mortality on tests for carcinogenicity in small samples. *Biometrics* **44**, 417-431.

Bartsch, H., Malaveille, C., Montesano, R., and Tomatis, L. (1975). Tissue-mediated mutagenicity of vinylidene chloride and 2-chlorobutadiene in *Salmonella typhimurium*. *Nature* **255**, 641-643.

Bartsch, H., Malaveille, C., Barbin, A., and Planche, G. (1979). Mutagenic and alkylating metabolites of haloethylenes, chlorobutadienes and dichlorobutenes produced by rodent or human liver tissues; evidence for oxirane formation by P450-linked microsomal mono-oxygenases. *Arch. Toxicol.* **41**, 249-277.

Boorman, G.A., Montgomery, C.A., Jr., Eustis, S.L., Wolfe, M.J., McConnell, E.E., and Hardisty, J.F. (1985). Quality assurance in pathology for rodent carcinogenicity studies. In *Handbook of Carcinogen Testing* (H.A. Milman and E.K. Weisburger, Eds.), pp. 345-357. Noyes Publications, Park Ridge, NJ.

Bothner-By, A.A., and Harris, R.K. (1953). *J. Am. Chem. Soc.* **87**, 3445-3450.

Clary, J.J., Feron, V.J., and Reuzel, P.G.J. (1978). Toxicity of β-chloroprene (2-chlorobutadiene-1,3): Acute and subacute toxicity. *Toxicol. Appl. Pharmacol.* **46**, 375-384.

Code of Federal Regulations (CFR) **21**, Part 58.

Code of Federal Regulations (CFR) **21**, §§175.105, 175.300, 177.2600.

Code of Federal Regulations (CFR) **29**, Parts 1910, 1915, and 1926.

Cox, D.R. (1972). Regression models and life-tables. *J. R. Stat. Soc.* **B34**, 187-220.

Crawford, B.D. (1985). Perspectives on the somatic mutation model of carcinogenesis. In *Advances in Modern Environmental Toxicology*. *Mechanisms and Toxicity of Chemical Carcinogens and Mutagens* (M.A. Mehlman, W.G. Flamm, and R.J. Lorentzen, Eds.), pp. 13-59. Princeton Scientific Publishing Co., Princeton, NJ.

CRC Handbook of Chemistry and Physics (1982). 62nd ed., p. C-184. CRC Press, Inc., Boca Raton, FL.

Crouch, C.N., Pullinger, D.H., and Gaunt, I.F. (1979). Inhalation toxicity studies with 1,3-butadiene —2. 3 month toxicity study in rats. *Am. Ind. Hyg. Assoc. J.* **40**, 796-802.

Culik, R., Kelly, D.P., and Clary, J.J. (1978). Inhalation studies to evaluate the teratogenic and embryotoxic potential of β-chloroprene (2-chloro-butadiene-1,3). *Toxicol. Appl. Pharmacol.* **44**, 81-88.

Cunningham, M.J., Choy, W.N., Arce, G.T., Rickard, L.B., Vlachos, D.A., Kinney, L.A., and Sarrif, A.M. (1986). *In vivo* sister chromatid exchange and micronucleus induction studies with 1,3-butadiene in B6C3F_1 mice and Sprague-Dawley rats. *Mutagenesis* **1**, 449-452.

Delzell, E., Sathiakumar, N., Hovinga, M., Macaluso, M., Julian, J., Larson, R., Cole, P., and Muir, D.C.F. (1996). A follow-up study of synthetic rubber workers. *Toxicology* **113**, 182-189.

Dinse, G.E., and Haseman, J.K. (1986). Logistic regression analysis of incidental-tumor data from animal carcinogenicity experiments. *Fundam. Appl. Toxicol.* **6**, 44-52.

Dinse, G.E., and Lagakos, S.W. (1983). Regression analysis of tumour prevalence data. *Appl. Statist.* **32**, 236-248.

Divine, B.J. (1990). An update on mortality among workers at a 1,3-butadiene facility—Preliminary results. *Environ. Health Perspect.* **86**, 119-128.

Dixon, W.J., and Massey, F.J., Jr. (1951). *Introduction to Statistical Analysis*, 1st ed., pp. 145-147. McGraw-Hill Book Company, New York.

Drevon, C., and Kuroki, T. (1979). Mutagenicity of vinyl chloride, vinylidene chloride and chloroprene in V79 Chinese hamster cells. *Mutat. Res.* **67**, 173-182.

Dunn, O.J. (1964). Multiple comparisons using rank sums. *Technometrics* **6**, 241-252.

Dunnett, C.W. (1955). A multiple comparison procedure for comparing several treatments with a control. *J. Am. Stat. Assoc.* **50**, 1096-1121.

Ellman, G.L. (1959). Tissue sulfhydryl groups. *Arch. Biochem. Biophys.* **82**, 70-77.

Fomenko, V.N. (1974). The possibility of extrapolating animal data to man when studying the mutagenic and gonadotropic effect of chemical factors [in Russian]. In *Vsesoyuznaya Nauchnaya Konferentsiya Laboratornie Zzivontnie v Medicinskikh Issledovaniyakh*, pp. 44-46, Moscow.

Foureman, P., Mason, J.M., Valencia, R., and Zimmering, S. (1994). Chemical mutagenesis testing in *Drosophila*. X. Results of 70 coded chemicals tested for the National Toxicology Program. *Environ. Mol. Mutagen.* **23**, 208-227.

Fox, J.G., Li, X., Yan, L., Cahill, R.J., Hurley, R., Lewis, R., and Murphy, J.C. (1996). Chronic proliferative hepatitis in A/JCr mice associated with persistent *Helicobacter hepaticus* infection: A model of *Helicobacter*-induced carcinogenesis. *Infect. Immun.* **64**, 1548-1558.

Gart, J.J., Chu, K.C., and Tarone, R.E. (1979). Statistical issues in interpretation of chronic bioassay tests for carcinogenicity. *JNCI* **62**, 957-974.

Gooch, J.J., and Hawn, W.F. (1981). Biochemical and hematological evaluation of chloroprene workers. *J. Occup. Med.* **23**, 268-272.

Guengerich, F.P. (1992). Roles of the vinyl chloride oxidation products 2-chlorooxirane and 2-chloroacetaldehyde in the in vitro formation of etheno adducts of nucleic acid bases. *Chem. Res. Toxicol.* **5**, 2-5.

Haley, T.J. (1978). Chloroprene (2-chloro-1,3-butadiene)—What is the evidence for its carcinogenicity? *Clin. Toxicol.* **13**, 153-170.

Haseman, J.K. (1984). Statistical issues in the design, analysis and interpretation of animal carcinogenicity studies. *Environ. Health Perspect.* **58**, 385-392.

Hawley's Condensed Chemical Dictionary (1987). 11th ed. (N.I. Sax and R.J. Lewis, Sr., Eds.), pp. 271-272. Van Nostrand Reinhold Company, New York.

Herbert, J.T. (1976). Angiosarcoma of the liver in a rubber worker. Angiosarcoma surveillance memorandum. Centers for Disease Control, Atlanta.

Hollander, M., and Wolfe, D.A. (1973). *Nonparametric Statistical Methods*, pp. 120-123. John Wiley and Sons, New York.

Huff, J.E., Melnick, R.L., Solleveld, H.A., Haseman, J.K., Powers, M., and Miller, R.A. (1985). Multiple organ carcinogenicity of 1,3-butadiene in B6C3F$_1$ mice after 60 weeks of inhalation exposure. *Science* **227**, 548-549.

Infante, P.F., Wagoner, J.K., and Young, R.J. (1977). Chloroprene: Observations of carcinogenesis and mutagenesis. In *Origins of Human Cancer* (H.H. Hiatt, J.D. Watson, and J.A. Winsten, Eds.), Vol. 4, pp. 205-217. Cold Spring Harbor Laboratory, Cold Spring Harbor, NY.

International Agency for Research on Cancer (IARC) (1979). *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans: Some Monomers, Plastics and Synthetic Elastomers, and Acrolein*, Vol. 19., pp. 131-156. IARC, Lyon, France.

International Technical Information Institute (ITII) (1981). *Toxic and Hazardous Industrial Chemicals Safety Manual: For Handling and Disposal with Toxic and Hazard Data*, p. 128.

Irish, P. (1963). Aliphatic halogenated hydrocarbons. In *Industrial Hygiene and Toxicology*, Vol. 2 (F.A. Patty, Ed.), pp. 1319-1321. Interscience, New York.

Irons, R.D., Smith, C.N., Stillman, W.S., Shah, R.S., Steinhagen, W.H., Leiderman, L.J. (1986). Macrocytic-megaloblastic anemia in male B6C3F$_1$ mice following chronic exposure to 1,3-butadiene. *Toxicol. Appl. Pharmacol.* **83**, 95-100.

Jaeger, R.J., Conolly, R.B., Reynolds, E.S., and Murphy, S.D. (1975a). Biochemical toxicology of unsaturated halogenated monomers. *Environ. Health Perspect.* **11**, 121-128.

Jaeger, R.J., Conolly, R.B., and Murphy, S.D. (1975b). Short-term inhalation toxicity of halogenated hydrocarbons. *Arch. Environ. Health* **30**, 26-31.

Jonckheere, A.R. (1954). A distribution-free *k*-sample test against ordered alternatives. *Biometrika* **41**, 133-145.

Kaplan, E.L., and Meier, P. (1958). Nonparametric estimation from incomplete observations. *J. Am. Stat. Assoc.* **53**, 457-481.

Khachatrian, E.A. (1972a). The occurrence of lung cancer among people working with chloroprene. *Vopr. Onkol.* **18**, 85-86.

Khachatrian, E.A. (1972b). Role of chloroprene compounds in the genesis of cutaneous neoformations. *Gig. Tr. Prof. Zabol.* **16**, 54-55.

McConnell, E.E., Solleveld, H.A., Swenberg, J.A., and Boorman, G.A. (1986). Guidelines for combining neoplasms for evaluation of rodent carcinogenesis studies. *JNCI* **76**, 283-289.

McFee, A.F., Lowe, K.W., and San Sebastian, J.R. (1983). Improved sister-chromatid differentiation using paraffin-coated bromodeoxyuridine tablets in mice. *Mutat. Res.* **119**, 83-88.

MacGregor, J.T., Wehr, C.M., and Langlois, R.G. (1983). A simple fluorescent staining procedure for micronuclei and RNA in erythrocytes using Hoescht 33258 and pyronin Y. *Mutat. Res.* **120**, 269-275.

MacGregor, J.T., Wehr, C.M., Henika, P.R., and Shelby, M.D. (1990). The *in vivo* erythrocyte micronucleus test: Measurement at steady state increases assay efficiency and permits integration with toxicity studies. *Fundam. Appl. Toxicol.* **14**, 513-522.

McKnight, B., and Crowley, J. (1984). Tests for differences in tumor incidence based on animal carcinogenesis experiments. *J. Am. Stat. Assoc.* **79**, 639-648.

Malarkey, D.E., Ton, T.-V., Hailey, J.R., and Devereux, T.R. (1997). A PCR-RFLP method for the detection of *Helicobacter hepaticus* in frozen or fixed liver from $B6C3F_1$ mice. *Toxicol. Pathol.* **25**, 606-612.

Maltoni, C., Lefemine, G., Ciliberti, A., Cotti, G., and Carretti, D. (1981). Carcinogenicity bioassays of vinyl chloride monomer: A model of risk assessment on an experimental basis. *Environ. Health Perspect.* **41**, 3-29.

Margolin, B.H., and Risko, K.J. (1988). The analysis of in vivo genotoxicity data: Case studies of the rat hepatocyte UDS and mouse bone marrow micronucleus assays. In *Evaluation of Short-Term Tests for Carcinogens, Report of the International Programme on Chemical Safety's Collaborative Study on In Vivo Assays* (J. Ashby, F.J. de Serres, M.D. Shelby, B.H. Margolin, M. Ishidate, Jr., and G.C. Becking, Eds.), University Press, Cambridge, UK.

Margolin, B.H., Collings, B.J., and Mason, J.M. (1983). Statistical analysis and sample-size determinations for mutagenicity experiments with binomial responses. *Environ. Mutagen.* **5**, 705-716.

Margolin, B.H., Resnick, M.A., Rimpo, J.Y., Archer, P., Galloway, S.M., Bloom, A.D., and Zeiger, E. (1986). Statistical analyses for in vitro cytogenetic assays using Chinese hamster ovary cells. *Environ. Mutagen.* **8**, 183-204.

Maronpot, R.R., and Boorman, G.A. (1982). Interpretation of rodent hepatocellular proliferative alterations and hepatocellular tumors in chemical safety assessment. *Toxicol. Pathol.* **10**, 71-80.

Mast, T.J., Evanoff, J.J., Westerberg, R.B., Rommerreim, R.L., and Weigel, R.J. (1994). Inhalation developmental toxicology studies: Developmental toxicity of chloroprene vapors in New Zealand white rabbits. Report No. NIH-Y01-70153. National Technical Information Service, Report No. DE94-12384.

Matanoski, G.M., Santos-Burgoa, C., and Schwartz, L. (1990). Mortality of a cohort of workers in the styrene-butadiene polymer manufacturing industry (1943-1982). *Environ. Health Perspect.* **86**, 107-117.

Melnick, R.L., and Huff, J. (1992). 1,3-Butadiene: Toxicity and carcinogenicity in laboratory animals and in humans. *Rev. Environ. Contam. Toxicol.* **124**, 111-144.

Melnick, R.L., and Kohn, M.C. (1995). Mechanistic data indicate that 1,3-butadiene is a human carcinogen. *Carcinogenesis* **16**, 157-163.

Melnick, R.L., Huff, J.E., Haseman, J.K., and McConnell, E.E. (1988). Chronic toxicity results and ongoing studies of 1,3-butadiene by the National Toxicology Program. *Ann. N. Y. Acad. Sci.* **534**, 648-662.

Melnick, R.L., Huff, J., Chou, B.J, and Miller, R.A. (1990a). Carcinogenicity of 1,3-butadiene in C57BL/6 × C3H F_1 mice at low exposure concentrations. *Cancer Res.* **50**, 6592-6599.

Melnick, R.L., Huff, J.E., Roycroft, J.H., Chou, B.J. and Miller, R.A. (1990b). Inhalation toxicology and carcinogenicity of 1,3-butadiene in $B6C3F_1$ mice following 65 weeks exposure. *Environ. Health Perspect.* **86**, 27-36.

Melnick, R.L., Roycroft, J.H., Chou, B.J., Ragan, H.A., and Miller, R.A. (1990c). Inhalation toxicology of isoprene in F344 rats and B6C3F1 mice following two-week exposures. *Environ. Health Perspect.* **86**, 93-98.

Melnick, R.L., Sills, R.C., Roycroft, J.H., Chou, B.J., Ragan, H.A., and Miller, R.A. (1994). Isoprene, an endogenous hydrocarbon and industrial chemical, induces multiple organ neoplasia in rodents after 26 weeks of inhalation exposure. *Cancer Res*. **54**, 5333-5339.

Melnick, R.L., Elwell, M.R., Roycroft, J.H., Chou, B.J., Ragan, H.A., and Miller, R.A. (1996a). Toxicity of inhaled chloroprene (2-chloro-1,3-butadiene) in F344 rats and B6C3F$_1$ mice. *Toxicology* **108**, 79-91.

Melnick, R.L., Kohn, M.C., and Portier, C.J. (1996b). Implications for risk assessment of suggested nongenotoxic mechanisms of chemical carcinogenesis. *Environ. Health Perspect*. **104**, 123-134.

Menezes, S., Padadopoulo, D., Levy, S., and Markovits, P. (1979). In vitro transformation of lung cells of young hamsters by chloro-2-butadiene. *C.R. Hebd. Seances Acad. Sci. D.* **288**, 926-929.

Miller, J.A., and Miller, E.C. (1977). Ultimate chemical carcinogens as reactive mutagenic electrophiles. In *Origins of Human Cancer* (H.H. Hiatt, J.D. Watson, and J.A. Winsten, Eds.), pp. 605-627. Cold Spring Harbor Laboratory, Cold Spring Harbor, NY.

Mnatsakanyan, A.V. (1965). *Sb. Tr. Inst. Epidemiol. Gig. Arm. S.S.R.* **4**, 133.

Mnatsakanyan, A.V. (1966). Effect of atmospheric traces of chloroprene on the function of the adrenal glands of kindergarten children [in Russian]. *Gig. Sanit*. **31**, 98-100.

Morrison, D.F. (1976). *Multivariate Statistical Methods*, 2nd ed., pp. 170-179. McGraw-Hill Book Company, New York.

National Cancer Institute (NCI) (1976). Guidelines for Carcinogen Bioassay in Small Rodents. Technical Report Series No. 1. NIH Publication No. 76-801. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, Bethesda, MD.

National Institute for Occupational Safety and Health (NIOSH) (1990a). National Occupational Exposure Survey (1981-1983), unpublished provisional data as of July 1, 1990. NIOSH, Cincinnati, OH.

National Institute for Occupational Safety and Health (NIOSH) (1990b). *NIOSH Pocket Guide to Chemical Hazards*. U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, Washington, DC.

National Institutes of Health (NIH) (1978). Open Formula Rat and Mouse Ration (NIH-07). Specification NIH-11-1335. U.S. Department of Health, Education, and Welfare, Public Health Service, NIH, Bethesda, MD.

National Toxicology Program (NTP) (1984). Toxicology and Carcinogenesis Studies of 1,3-Butadiene (CAS No. 106-99-0) in B6C3F$_1$ Mice (Inhalation Studies). Technical Report Series No. 288. NIH Publication No. 84-2544. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, Research Triangle Park, NC.

National Toxicology Program (NTP) (1985). Technical Protocol for Sperm Morphology and Vaginal Cytology Evaluations in Toxicity Testing for Rats and Mice, 10/31/82 version (updated March 1985). Research Triangle Park, NC.

National Toxicology Program (NTP) (1990a). Toxicology and Carcinogenesis Studies of 2-Chloroacetophenone (CAS No. 532-27-4) in F344/N Rats and B6C3F$_1$ Mice (Inhalation Studies). Technical Report Series No. 379. NIH Publication No. 90-2834. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, Research Triangle Park, NC.

National Toxicology Program (NTP) (1990b). Toxicology and Carcinogenesis Studies of CS2 (94% *o*-Chlorobenzalmalononitrile, CAS No. 2698-41-1) in F344/N Rats and B6C3F$_1$ Mice (Inhalation Studies). Technical Report Series No. 377. NIH Publication No. 90-2832. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, Research Triangle Park, NC.

National Toxicology Program (NTP) (1990c). Toxicology and Carcinogenesis Studies of *l*-Epinephrine Hydrochloride (CAS No. 55-31-2) in F344/N Rats and B6C3F$_1$ Mice (Inhalation Studies). Technical Report Series No. 380. NIH Publication No. 90-2835. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, Research Triangle Park, NC.

National Toxicology Program (NTP) (1990d). Toxicology and Carcinogenesis Studies of Vinyl Toluene (Mixed Isomers) (65%-71% *Meta*-Isomer and 32%-35% *Para*-Isomer) (CAS No. 25013-15-4) in F344/N Rats and B6C3F$_1$ Mice (Inhalation Studies). Technical Report Series No. 375. NIH Publication No. 90-2830. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, Research Triangle Park, NC.

National Toxicology Program (NTP) (1990e). Toxicology and Carcinogenesis Studies of Tetranitromethane (CAS No. 509-14-8) in F344/N Rats and B6C3F$_1$ Mice (Inhalation Studies). Technical Report Series No. 386. NIH Publication No. 90-2841. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, Research Triangle Park, NC.

National Toxicology Program (NTP) (1993). Toxicology and Carcinogenesis Studies of 1,3-Butadiene (CAS No. 106-99-0) in B6C3F$_1$ Mice (Inhalation Studies). Technical Report Series No. 434. NIH Publication No. 93-3165. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, Research Triangle Park, NC.

National Toxicology Program (NTP) (1995). Toxicity Studies of Isoprene (CAS No. 78-79-5) Administered by Inhalation in F344/N Rats and B63C3F$_1$ Mice. Toxicity Study Report Series No. 31. NIH Publication No. 95-3354. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, Research Triangle Park, NC.

Nyström, Å.E. (1948). Health hazards in the chloroprene rubber industry and their prevention. A clinical and experimental study with special reference to chloroprene as well as oxidation and polymerization products thereof. *Acta Med. Scand.* **132**, 1-125.

von Oettingen, W.F., Hueper, W.C., Deichmann-Gruebler, W., and Wiley, F.H. (1936). 2-chlorobutadiene (chloroprene): Its toxicity and pathology and the mechanism of its action. *J. Ind. Hyg. Toxicol.* **18**, 240-270.

Orlova, A.A., and Solovyova, E.A. (1962). Clinical studies of chronic effects of chemical substances used in manufacturing synthetic rubber. *Tr. Voronezhsk. Med. Inst.* **47**, 86-87.

Owen, P.E., Glaister, J.R., Gaunt, I.F., and Pullinger, D.H. (1987). Inhalation toxicity studies with 1,3-butadiene. 3 two year toxicity/carcinogenicity study in rats. *Am. Ind. Hyg. Assoc. J.* **48**, 407-413.

Patty's Industrial Hygiene and Toxicology (1981). 3rd revised ed. (G.D. Clayton and F.E. Clayton, Eds.), Vol. 2B, pp. 2895, 3577-3581, and 3586-3601. John Wiley and Sons, New York.

Pell, S. (1978). Mortality of workers exposed to chloroprene. *J. Occup. Med.* **20**, 21-29.

Plugge, H., and Jaeger, R.J. (1979). Acute inhalation toxicity of 2-chloro-1,3-butadiene (chloroprene): Effects on liver and lung. *Toxicol. Appl. Pharmacol.* **50**, 565-572.

Ponomarkov, V., and Tomatis, L. (1980). Long-term testing of vinylidene chloride and chloroprene for carcinogenicity in rats. *Oncology* **37**, 136-141.

Portier, C.J., and Bailer, A.J. (1989). Testing for increased carcinogenicity using a survival-adjusted quantal response test. *Fundam. Appl. Toxicol.* **12**, 731-737.

Portier, C.J., Hedges, J.C., and Hoel, D.G. (1986). Age-specific models of mortality and tumor onset for historical control animals in the National Toxicology Program's carcinogenicity experiments. *Cancer Res*. **46**, 4372-4378.

Qinan, D., Bangliang, X., Yuhua, H., and Shouqi, L. (1989). Short-term test for the induction of lung tumor in mouse by chloroprene. *Biomed. Environ. Sci*. **2**, 150-153.

Ritter, W.L., and Carter, A.S. (1948). Hair loss in neoprene manufacture. *J. Ind. Hyg. Toxicol*. **30**, 192-195.

Sal'nikova, L.S. (1968). Embryotropic effect of volatile substances given off by polychloroprene latices. *Toksikol. Nov. Prom. Khim. Veshchestv* **11**, 106-111.

Sal'nikova, L.S., and Fomenko, V.N. (1973). Experimental investigation of the influence produced by chloroprene on the embryogenesis [in Russian]. *Gig. Tr. Prof. Zabol*. **17**, 23-26.

Sanotskii, I.V. (1976). Aspects of the toxicology of chloroprene: Immediate and long-term effects. *Environ. Health Perspect*. **17**, 85-93.

Santos-Burgoa, C., Matanoski, G.M., Zeger, S., and Schwartz, L. (1992). Lymphohematopoietic cancer in styrene-butadiene polymerization workers. *Am. J. Epidemiol*. **136**, 843-854.

Schmid, W. (1976). The micronucleus test for cytogenetic analysis. In *Chemical Mutagens. Principles and Methods for their Detection* (A. Hollaender, Ed.), Vol. 4, pp. 31-53. Plenum Press, New York.

Schwartz, L. (1945). Skin hazards in the manufacture and processing of synthetic rubber. *JAMA* **127**, 389-391.

Sedlak, J., and Lindsay, R.H. (1968). Estimation of total, protein-bound, and nonprotein sulfhydryl groups in tissues with Ellman's Reagent. *Anal. Biochem*. **25**, 192-205.

Shelby, M.D. (1990). Results of NTP-sponsored mouse cytogenetic studies on 1,3-butadiene, isoprene, and chloroprene. *Environ. Health Perspect*. **86**, 71-73.

Shelby, M.D., and Witt, K.L. (1995). Comparison of results from mouse bone marrow chromosome aberration and micronucleus tests. *Environ. Mol. Mutagen*. **25**, 302-313.

Shelby, M.D., Erexson, G.L., Hook, G.J., and Tice, R.R. (1993). Evaluation of a three-exposure mouse bone marrow micronucleus protocol: Results with 49 chemicals. *Environ. Mol. Mutagen*. **21**, 160-179.

Shirley, E. (1977). A non-parametric equivalent of Williams' test for contrasting increasing dose levels of a treatment. *Biometrics* **33**, 386-389.

Shouqi, L., Qinan, D., Yuqing, L., and Yingfei, L. (1989). Epidemiologic study of cancer mortality among chloroprene workers. *Biomed. Environ. Sci*. **2**, 141-149.

Sills, R., Greenwell, A., Marsman, D., Wiseman, R., Devereux, T., and Boorman, G. (1993). Expression of P53 and PCNA in chemically-induced neoplasms of B6C3F1 mice. *Vet. Pathol*. **30**, 480 (Abstr.).

Singer, B. (1996). DNA damage: Chemistry, repair, and mutagenic potential. *Regul. Toxicol. Pharmacol*. **23**, 2-13.

Sittig, M. (1985). Chloroprene. In *Handbook of Toxic and Hazardous Chemicals and Carcinogens*, 2nd ed., pp. 239-241. Noyes Publications, Park Ridge, NJ.

Stewart, C.A., Jr. (1971). Dimerization of chloroprene and related dimers. *J. Am. Chem. Soc*. **93**, 4815.

Straus, D.S. (1981). Somatic mutation, cellular differentiation, and cancer causation. *JNCI* **67**, 233-241.

Summer, K.H., and Greim, H. (1980). Detoxification of chloroprene (2-chloro-1,3-butadiene) with glutathione in the rat. *Biochem. Biophys. Res. Commun.* **96**, 566-573.

Summer, K.H., Rozman, K., Coulston, F., and Greim, H. (1979). Urinary excretion of mercapturic acids in chimpanzees and rats. *Toxicol. Appl. Pharmacol.* **50**, 207-212.

Szasz, G.J. and Sheppard, N. (1953). *Trans. Faraday Soc.* **49**, 358-363.

Tarone, R.E. (1975). Tests for trend in life table analysis. *Biometrika* **62**, 679-682.

Tennant, R.W., Margolin, B.H., Shelby, M.D., Zeiger, E., Haseman, J.K., Spalding, J., Caspary, W., Resnick, M., Stasiewicz, S., Anderson, B., and Minor, R. (1987). Prediction of chemical carcinogenicity in rodents from *in vitro* genetic toxicity assays. *Science* **236**, 933-941.

Tice, R.R., Boucher, R., Luke, C.A., and Shelby, M.D. (1987). Comparative cytogenetic analysis of bone marrow damage induced in male B6C3F1 mice by multiple exposures to gaseous 1,3-butadiene. *Environ. Mutagen.* **9**, 235-250.

Tice, R.R., Boucher, R., Luke, C.A., Paquette, D.E., and Shelby, M.D. (1988). Chloroprene and isoprene: Cytogenetic studies in mice. *Mutagenesis* **3**, 141-146.

Tilson, H.A. (1990). Animal neurobehavioral test battery in NTP assessment. In *Advances in Neurobehavioral Toxicology: Applications in Environmental & Occupational Health* (B.L. Johnson, Ed.), pp. 403-418. Lewis Publishers.

Vogel, E. (1979). Mutagenicity of chloroprene, 1-chloro-1,3-*trans*-butadiene, 1,1-dichlorobutene-2 and 1,4-dichloro-2,3-epoxybutane in *Drosophila melanogaster*. *Mutat. Res.* **67**, 377-381.

Volkova, Z.A. (1971). Hygienic problems in the industrial use of chloroprene and divinylstryrene latexes [in Russian]. In *Problems of Synthesis and Properties of Latex*, pp. 23-25.

Volkova, Z.A. (1976). Establishing the value of the MPEL of chloroprene in the air of a working area [in Russian]. *Gig. Tr. Profzabol.* **20**, 31.

Ward, E.M., Fajen, J.M., Ruder, A.M., Rinsky, R.A., Halperin, W.E., and Fessler-Flesch, C.A. (1995). Mortality study of workers in 1,3-butadiene production units identified from a chemical workers cohort. *Environ. Health Perspect.* **103**, 598-603.

Ward, J.M., Uno, H., Kurata, Y., Weghorst, C.M., and Jang, J.-J. (1993). Cell proliferation not associated with carcinogenesis in rodents and humans. *Environ. Health Perspect.* **101** (Suppl. 5), 125-136.

Ward, J.M., Fox, J.G., Anver, M.R., Haines, D.C., George, C.V., Collins, M.J., Jr., Gorelick, P.L., Nagashima, K., Gonda, M.A., Gilden, R.V., Tully, J.G., Russell, R.J., Benveniste, R.E., Paster, B.J., Dewhirst, F.E., Donovan, J.C., Anderson, L.M., and Rice, J.M. (1994). Chronic active hepatitis and associated liver tumors in mice caused by a persistent bacterial infection with a novel *Helicobacter* species. *J. Natl. Cancer Inst.* **86**, 1222-1227.

Weissermel, K., and Arpe, H.J. (1990). Chloropren. In *Industrielle Organische Chemie*, pp. 127-130. VCH, Weinheim.

Westphal, G.A., Blaszkewicz, M., Leutbecher, M., Müller, A., Hallier, E., and Bolt, H.M. (1994). Bacterial mutagenicity of 2-chloro-1,3-butadiene (chloroprene) caused by decomposition products. *Arch. Toxicol.* **68**, 79-84.

Williams, D.A. (1971). A test for differences between treatment means when several dose levels are compared with a zero dose control. *Biometrics* **27**, 103-117.

Williams, D.A. (1972). The comparison of several dose levels with a zero dose control. *Biometrics* **28**, 519-531.

Zeiger, E., Anderson, B., Haworth, S., Lawlor, T., Mortelmans, K., and Speck, W. (1987). *Salmonella* mutagenicity tests: III. Results from the testing of 255 chemicals. *Environ. Mutagen.* **9** (Suppl. 9), 1-110.

Zeiger, E., Haseman, J.K., Shelby, M.D., Margolin, B.H., and Tennant, R.W. (1990). Evaluation of four in vitro genetic toxicity tests for predicting rodent carcinogenicity: Confirmation of earlier results with 41 additional chemicals. *Environ. Mol. Mutagen.***16** (Suppl. 18), 1-14.

Zil'fian, V.N., and Fichidzhyan, B.S. (1972). Effect of chloroprene on development of Crocker's murine sarcoma. In *Proceedings of a Scientific Conference Devoted to the 50 Years of the Universities of U.S.S.R. and to the 25 Years of the Armenian Institute of Roentgenology and Oncology*, pp. 105-106. Armenian Institute of Roentgenology and Oncology. Yerevan, U.S.S.R.

Zil'fian, V.N., Fichidzhyan, B.S., and Pogosova, A.M. (1975). Results of testing on chloroprene for carcinogenicity [in Russian]. *Zh. Eksp. Klin. Med.* **15**, 54-57.

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

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

	Chamber Control	12.8 ppm	32 ppm	80 ppm
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Moribund	34	40	41	41
Natural deaths	3	1	4	5
Survivors				
Terminal sacrifice	13	9	5	4
Animals examined microscopically	50	50	50	50
Alimentary System				
Intestine large, colon	(50)	(49)	(48)	(49)
Intestine large, cecum	(48)	(49)	(46)	(48)
Polyp adenomatous				1 (2%)
Intestine small, duodenum	(50)	(49)	(49)	(50)
Polyp adenomatous	1 (2%)	1 (2%)		
Intestine small, jejunum	(48)	(49)	(46)	(47)
Carcinoma				1 (2%)
Intestine small, ileum	(49)	(49)	(46)	(46)
Liver	(50)	(50)	(49)	(50)
Histiocytic sarcoma				2 (4%)
Schwannoma malignant, metastatic, heart			1 (2%)	
Mesentery	(16)	(13)	(18)	(13)
Hemangioma		1 (8%)		
Sarcoma			1 (6%)	
Schwannoma malignant			1 (6%)	
Fat, lipoma				1 (8%)
Oral mucosa		(2)	(1)	(7)
Buccal, squamous cell papilloma				1 (14%)
Gingival, squamous cell papilloma				1 (14%)
Pharyngeal, squamous cell papilloma		2 (100%)	1 (100%)	2 (29%)
Pancreas	(50)	(50)	(49)	(50)
Adenoma	1 (2%)		1 (2%)	1 (2%)
Histiocytic sarcoma				1 (2%)
Salivary glands	(50)	(50)	(50)	(50)
Stomach, forestomach	(50)	(50)	(50)	(50)
Histiocytic sarcoma				1 (2%)
Stomach, glandular	(49)	(50)	(49)	(50)
Histiocytic sarcoma				1 (2%)
Tongue			(4)	(8)
Squamous cell carcinoma			1 (25%)	2 (25%)
Squamous cell papilloma			3 (75%)	6 (75%)
Cardiovascular System				
Blood vessel			(3)	(1)
Aorta, schwannoma malignant, metastatic, heart			1 (33%)	
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 Inhalation Study of Chloroprene

	Chamber Control	12.8 ppm	32 ppm	80 ppm
Endocrine System				
Adrenal cortex	(50)	(50)	(49)	(50)
Adenoma	2 (4%)		1 (2%)	
Adrenal medulla	(50)	(50)	(49)	(50)
Pheochromocytoma malignant	1 (2%)	1 (2%)		
Pheochromocytoma benign	14 (28%)	13 (26%)	11 (22%)	9 (18%)
Bilateral, pheochromocytoma benign	5 (10%)	7 (14%)	10 (20%)	9 (18%)
Islets, pancreatic	(50)	(50)	(49)	(50)
Adenoma	3 (6%)	3 (6%)	2 (4%)	2 (4%)
Carcinoma	3 (6%)	5 (10%)	3 (6%)	1 (2%)
Parathyroid gland	(48)	(49)	(50)	(50)
Adenoma	1 (2%)			
Pituitary gland	(50)	(49)	(50)	(49)
Pars distalis, adenoma	40 (80%)	40 (82%)	43 (86%)	39 (80%)
Pars intermedia, adenoma				1 (2%)
Thyroid gland	(50)	(50)	(49)	(50)
C-cell, adenoma	3 (6%)	6 (12%)	4 (8%)	7 (14%)
C-cell, carcinoma	2 (4%)	2 (4%)	2 (4%)	
Follicular cell, adenoma		2 (4%)	2 (4%)	4 (8%)
Follicular cell, carcinoma			2 (4%)	1 (2%)
General Body System				
Peritoneum			(3)	
Genital System				
Epididymis	(50)	(50)	(50)	(50)
Preputial gland	(50)	(50)	(48)	(50)
Adenoma	3 (6%)	3 (6%)	4 (8%)	1 (2%)
Carcinoma	3 (6%)	3 (6%)	4 (8%)	1 (2%)
Histiocytic sarcoma				1 (2%)
Prostate	(50)	(50)	(50)	(50)
Adenoma		1 (2%)	3 (6%)	1 (2%)
Seminal vesicle	(50)	(50)	(50)	(49)
Histiocytic sarcoma				1 (2%)
Testes	(50)	(50)	(50)	(50)
Bilateral, interstitial cell, adenoma	23 (46%)	21 (42%)	15 (30%)	17 (34%)
Interstitial cell, adenoma	11 (22%)	13 (26%)	13 (26%)	12 (24%)
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(50)
Histiocytic sarcoma				1 (2%)
Lymph node	(12)	(18)	(11)	(15)
Iliac, histiocytic sarcoma				1 (7%)
Lymph node, bronchial	(45)	(31)	(44)	(43)
Alveolar/bronchiolar carcinoma, metastatic, lung			1 (2%)	
Histiocytic sarcoma				2 (5%)
Lymph node, mandibular	(47)	(45)	(44)	(49)
Lymph node, mesenteric	(50)	(50)	(48)	(50)
Histiocytic sarcoma				1 (2%)
Lymph node, mediastinal	(46)	(47)	(48)	(47)
Alveolar/bronchiolar carcinoma, metastatic, lung			1 (2%)	
Histiocytic sarcoma				2 (4%)

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Inhalation Study of Chloroprene

	Chamber Control	12.8 ppm	32 ppm	80 ppm
Hematopoietic System (continued)				
Spleen	(50)	(50)	(49)	(50)
Hemangiosarcoma			1 (2%)	
Histiocytic sarcoma				1 (2%)
Sarcoma	1 (2%)	1 (2%)		
Thymus	(42)	(42)	(46)	(48)
Histiocytic sarcoma				1 (2%)
Thymoma benign	1 (2%)			2 (4%)
Integumentary System				
Mammary gland	(30)	(23)	(30)	(28)
Adenoma			1 (3%)	
Carcinoma		1 (4%)	1 (3%)	
Fibroadenoma	2 (7%)	1 (4%)		1 (4%)
Skin	(50)	(50)	(50)	(50)
Basal cell adenoma	1 (2%)			
Basal cell carcinoma		2 (4%)		
Histiocytic sarcoma				1 (2%)
Keratoacanthoma	2 (4%)	4 (8%)	2 (4%)	4 (8%)
Squamous cell papilloma			1 (2%)	1 (2%)
Sebaceous gland, adenoma	1 (2%)	2 (4%)		
Subcutaneous tissue, fibroma		2 (4%)		1 (2%)
Subcutaneous tissue, fibrosarcoma	1 (2%)			
Subcutaneous tissue, lipoma	2 (4%)			
Subcutaneous tissue, melanoma malignant		1 (2%)	1 (2%)	
Subcutaneous tissue, sarcoma	1 (2%)		1 (2%)	1 (2%)
Subcutaneous tissue, schwannoma malignant		1 (2%)		
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Osteosarcoma	1 (2%)			1 (2%)
Skeletal muscle		(1)		
Sarcoma		1 (100%)		
Nervous System				
Brain	(50)	(50)	(50)	(50)
Glioma malignant, mixed cell				1 (2%)
Glioma malignant, mixed	1 (2%)			
Meninges, granular cell tumor benign				1 (2%)
Respiratory System				
Larynx	(50)	(50)	(50)	(50)
Lung	(50)	(50)	(49)	(50)
Alveolar/bronchiolar adenoma	2 (4%)		3 (6%)	3 (6%)
Alveolar/bronchiolar carcinoma		2 (4%)	1 (2%)	3 (6%)
Alveolar/bronchiolar carcinoma, multiple				1 (2%)
Histiocytic sarcoma				2 (4%)
Melanoma malignant, metastatic, skin		1 (2%)		
Osteosarcoma, metastatic, bone				1 (2%)
Mediastinum, alveolar/bronchiolar carcinoma, metastatic, lung				1 (2%)
Mediastinum, schwannoma malignant, metastatic, heart			1 (2%)	

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Inhalation Study of Chloroprene

	Chamber Control	12.8 ppm	32 ppm	80 ppm
Respiratory System (continued)				
Nose	(50)	(50)	(49)	(49)
Respiratory epithelium, adenoma				1 (2%)
Trachea	(50)	(50)	(50)	(50)
Special Senses System				
Zymbal's gland	(1)	(1)		(2)
Adenoma				1 (50%)
Carcinoma	1 (100%)	1 (100%)		1 (50%)
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Histiocytic sarcoma				1 (2%)
Mesenchymal tumor NOS				1 (2%)
Bilateral, renal tubule, adenoma		1 (2%)		
Renal tubule, adenoma			1 (2%)	2 (4%)
Transitional epithelium, carcinoma		1 (2%)		
Urinary bladder	(50)	(50)	(50)	(49)
Histiocytic sarcoma				1 (2%)
Transitional epithelium, carcinoma			1 (2%)	
Transitional epithelium, papilloma				1 (2%)
Systemic Lesions				
Multiple organs[b]	(50)	(50)	(50)	(50)
Histiocytic sarcoma				2 (4%)
Leukemia mononuclear	33 (66%)	34 (68%)	29 (58%)	27 (54%)
Mesothelioma malignant		1 (2%)	5 (10%)	3 (6%)
Neoplasm Summary				
Total animals with primary neoplasms[c]	50	50	50	50
Total primary neoplasms	166	181	176	180
Total animals with benign neoplasms	50	50	50	48
Total benign neoplasms	118	123	121	133
Total animals with malignant neoplasms	40	37	37	36
Total malignant neoplasms	47	58	55	46
Total animals with metastatic neoplasms		1	2	2
Total metastatic neoplasms		1	5	2
Total animals with uncertain neoplasms—benign or malignant	1			1
Total uncertain neoplasms	1			1

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

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

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

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

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

Number of Days on Study	6 4 6	6 4 9	6 5 7	6 5 8	6 9 3	6 9 5	6 9 5	6 9 5	7 0 2	7 1 6	7 1 6	7 2 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	0 4 7	0 5 0	0 0 5	0 4 2	0 1 3	0 1 4	0 3 6	0 4 0	0 2 2	0 0 8	0 4 8	0 0 4	0 1 0	0 1 7	0 1 8	0 2 1	0 2 5	0 2 6	0 2 8	0 3 0	0 3 2	0 3 5	0 3 7	0 4 1	0 4 3	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp adenomatous																										1
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery											+	+						+		+	+					16
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																					X					2
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant																			X							1
Pheochromocytoma benign	X	X	X				X			X	X					X	X		X	X				X	X	14
Bilateral, pheochromocytoma benign								X													X	X				5
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																						X	X			3
Carcinoma				X								X														3
Parathyroid gland	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma																										1
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma		X	X	X	X	X	X	X	X	X	X			X	X	X		X		X	X	X	X	X	X	40
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma														X									X			3
C-cell, carcinoma																									X	2
General Body System																										
None																										
Genital System																										
Coagulating gland																										1
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Penis																										1
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																			X							3
Carcinoma															X						X					3
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

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

Number of Days on Study	4 6 9	4 8 9	5 2 5	5 3 3	5 3 4	5 3 6	5 4 1	5 6 9	5 6 9	5 7 1	5 7 5	5 7 6	5 8 0	5 8 9	6 0 0	6 0 4	6 1 3	6 1 3	6 1 6	6 1 6	6 3 4	6 3 4	6 3 7	6 3 7	6 4 2
Carcass ID Number	0 3 9	0 2 3	0 4 4	0 2 7	0 0 2	0 2 0	0 3 8	0 4 5	0 4 6	0 3 4	0 0 1	0 1 1	0 3 1	0 1 6	0 0 9	0 0 3	0 1 5	0 2 4	0 0 6	0 2 9	0 1 9	0 3 3	0 0 7	0 1 2	0 4 9
Genital System (continued)																									
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma					X		X						X	X	X		X					X			X
Interstitial cell, adenoma	X							X	X			X						X		X	X		X	X	
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node		+													+	+									
Lymph node, bronchial	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	M	+	+	+
Lymph node, mandibular	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma					X																				
Thymus	+	+	M	M	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymoma benign																									
Integumentary System																									
Mammary gland	+	+	M	+	+	+	+	M	M	M	+	+	+	+	M	+	+	+	M	+	M	M	+	+	M
Fibroadenoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell adenoma																								X	
Keratoacanthoma																									
Sebaceous gland, adenoma																									
Subcutaneous tissue, fibrosarcoma																									
Subcutaneous tissue, lipoma																		X							
Subcutaneous tissue, sarcoma												X													
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma																									
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Glioma malignant, mixed																					X				
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																				X					X
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Zymbal's gland			+																						
Carcinoma			X																						
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear		X							X			X	X	X	X	X		X	X	X	X	X	X		

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

Number of Days on Study	6 4 6	6 4 9	6 5 7	6 5 8	6 9 3	6 9 5	6 9 5	6 9 5	7 0 2	7 1 6	7 1 6	7 2 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	0 4 7	0 5 0	0 0 5	0 4 2	0 1 3	0 1 4	0 3 6	0 4 0	0 2 2	0 0 8	0 4 8	0 0 4	0 1 0	0 1 7	0 1 8	0 2 1	0 2 5	0 2 6	0 2 8	0 3 0	0 3 2	0 3 5	0 3 7	0 4 1	0 4 3	Total Tissues/ Tumors
Genital System (continued)																										
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, interstitial cell, adenoma	X								X	X	X	X	X	X		X	X	X	X	X			X	X	X	23
Interstitial cell, adenoma							X	X																		11
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+				+			+			+	+						+	+		+	+				12
Lymph node, bronchial	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	45
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	M	46
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma																										1
Thymus	+	+	+	+	+	+	+	+	M	+	+	+	M	+	M	+	+	+	+	M	+	+	+	+	+	42
Thymoma benign																	X									1
Integumentary System																										
Mammary gland	M	+	+	+	+	M	+	+	+	M	+	M	M	M	M	+	+	M	+	+	+	M	M	M	+	30
Fibroadenoma				X					X																	2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basal cell adenoma																										1
Keratoacanthoma			X																		X					2
Sebaceous gland, adenoma																X										1
Subcutaneous tissue, fibrosarcoma															X											1
Subcutaneous tissue, lipoma															X											2
Subcutaneous tissue, sarcoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma													X													1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Glioma malignant, mixed																										1
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																										2
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
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	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X		X		33

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Chloroprene: 12.8 ppm

Number of Days on Study	3 5 7	4 3 7	4 9 7	5 2 5	5 3 0	5 3 4	5 4 1	5 4 1	5 4 4	5 5 6	5 7 5	5 8 1	5 8 1	5 9 7	6 0 0	6 0 3	6 0 8	6 0 9	6 1 3	6 1 8	6 3 7	6 3 8	6 4 5	6 5 0	6 5 1
Carcass ID Number	2 4 0	2 3 1	2 2 3	2 2 0	2 1 2	2 0 4	2 2 8	2 3 2	2 1 5	2 3 4	2 4 7	2 2 9	2 4 5	2 4 8	2 3 5	2 4 9	2 4 3	2 3 8	2 0 8	2 1 1	2 2 7	2 0 1	2 2 1	2 2 6	2 5 0
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp adenomatous										X															
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery											+						+	+		+					+
Hemangioma																									
Oral mucosa																									
Pharyngeal, squamous cell papilloma																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth			+									+													
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Schwannoma malignant																									
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant																									
Pheochromocytoma benign						X	X									X					X			X	X
Bilateral, pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma				X												X									
Carcinoma																X									
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma	X	X	X		X	X	X	X	X		X	X	X	X	X	X			X			X	X	X	X
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma							X								X										
C-cell, carcinoma																									
Follicular cell, adenoma														X											
General Body System																									
None																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Penis																						+			
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																			X						
Carcinoma																					X				
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Chloroprene: 12.8 ppm

Number of Days on Study	6 6 3	6 6 5	6 6 5	6 6 5	6 7 0	6 7 7	6 7 9	6 8 9	7 0 0	7 0 0	7 0 1	7 0 1	7 0 2	7 0 6	7 0 7	7 3 0	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	
Carcass ID Number	2 1 3	2 0 9	2 2 4	2 3 6	2 1 7	2 1 9	2 3 7	2 0 6	2 0 3	2 4 1	2 1 4	2 1 6	2 1 0	2 3 3	2 3 9	2 4 4	2 0 2	2 0 5	2 0 7	2 1 8	2 2 2	2 2 5	2 3 0	2 4 2	2 4 6	Total Tissues/ Tumors
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	A	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, cecum	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Polyp adenomatous																									1
Intestine small, jejunum	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, ileum	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery			+		+								+		+		+			+				+	13
Hemangioma															X										1
Oral mucosa											+		+												2
Pharyngeal, squamous cell papilloma											X		X												2
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tooth																									2
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Schwannoma malignant																					X				1
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant																					X				1
Pheochromocytoma benign					X		X			X	X		X			X	X								13
Bilateral, pheochromocytoma benign									X			X		X	X			X					X		X	7
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma										X													X		3
Carcinoma				X	X											X	X								5
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma	X	X	X	X	X	X	X	X	X	X			X		X	X	X	X	X	X		X	X	X	X	40
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma	X		X		X					X															6
C-cell, carcinoma							X			X															2
Follicular cell, adenoma																								X	2
General Body System																									
None																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Penis														+	+										3
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																				X	X				3
Carcinoma																		X					X		3
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																								X	1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Chloroprene: 12.8 ppm

Number of Days on Study	3 5 7	4 3 7	4 9 7	5 2 5	5 3 0	5 3 4	5 4 1	5 4 1	5 4 4	5 5 6	5 7 5	5 8 1	5 8 1	5 9 7	6 0 0	6 0 3	6 0 8	6 0 9	6 1 3	6 1 8	6 3 7	6 3 8	6 4 5	6 5 0	6 5 1
Carcass ID Number	2 4 0	2 3 1	2 2 3	2 2 0	2 1 2	2 0 4	2 2 8	2 3 2	2 1 5	2 3 4	2 4 7	2 2 9	2 4 5	2 4 8	2 3 5	2 4 9	2 4 3	2 3 8	2 0 8	2 1 1	2 2 7	2 0 1	2 2 1	2 2 6	2 5 0
Genital System (continued)																									
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma										X		X	X	X			X		X	X	X				
Interstitial cell, adenoma				X			X											X				X			
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node							+	+			+	+	+	+		+						+			
Lymph node, bronchial	+	M	+	M	M	+	M	+	M	+	M	M	M	+	+	+	M	+	M	+	+	+	M	M	M
Lymph node, mandibular	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma																									
Thymus	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	M	M	+	M	+	M	M	M	+	+	M	+	+	M	M	M	+	+	M	M	+	M	M	+	+
Carcinoma																									
Fibroadenoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell carcinoma																		X							
Keratoacanthoma																		X				X			
Sebaceous gland, adenoma								X																	
Subcutaneous tissue, fibroma																									
Subcutaneous tissue, melanoma malignant																									
Subcutaneous tissue, schwannoma malignant																							X		
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																									
Sarcoma																									
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma																									
Melanoma malignant, metastatic, skin																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye																									
Zymbal's gland																									
Carcinoma																									

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Chloroprene: 12.8 ppm

Number of Days on Study	6 6 3	6 6 5	6 6 5	6 6 5	6 7 0	6 7 7	6 7 9	6 8 9	7 0 0	7 0 0	7 0 1	7 0 1	7 0 2	7 0 6	7 0 7	7 3 0	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	
Carcass ID Number	2 1 3	2 0 9	2 2 4	2 3 6	2 1 7	2 1 9	2 3 7	2 0 6	2 0 3	2 4 1	2 1 4	2 1 6	2 1 0	2 3 3	2 3 9	2 4 4	2 0 2	2 0 5	2 0 7	2 1 8	2 2 2	2 2 5	2 3 0	2 4 2	2 4 6	Total Tissues/ Tumors
Genital System (continued)																									
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, interstitial cell, adenoma							X	X	X	X	X	X	X	X	X		X				X			X	X	21
Interstitial cell, adenoma		X	X	X												X		X	X	X		X	X			13
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node					+			+	+	+			+	+	+			+	+		+				18
Lymph node, bronchial	+	+	+	+	+	M	M	+	+	+	+	+	+	+	M	+	+	+	M	+	M	M	+	+	+	31
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	M	+	M	45
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mediastinal	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	47
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma				X																						1
Thymus	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	M	+	+	M	+	+	42
Integumentary System																									
Mammary gland	M	M	+	+	M	+	M	+	M	M	M	M	+	+	+	M	M	+	M	+	M	+	M	+	+	23
Carcinoma																		X								1
Fibroadenoma				X																						1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basal cell carcinoma										X																2
Keratoacanthoma		X							X																	4
Sebaceous gland, adenoma																					X					2
Subcutaneous tissue, fibroma										X						X										2
Subcutaneous tissue, melanoma malignant		X																								1
Subcutaneous tissue, schwannoma malignant																										1
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle											+															1
Sarcoma											X															1
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma													X										X			2
Melanoma malignant, metastatic, skin		X																								1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																									
Eye																+										1
Zymbal's gland																+										1
Carcinoma																X										1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Chloroprene: 12.8 ppm

Number of Days on Study	3 5 7	4 3 7	4 9 7	5 2 5	5 3 0	5 3 4	5 4 1	5 4 1	5 4 4	5 5 6	5 7 5	5 8 1	5 8 1	5 9 7	6 0 0	6 0 3	6 0 8	6 0 9	6 1 3	6 1 8	6 3 7	6 3 8	6 4 5	6 5 0	6 5 1
Carcass ID Number	2 4 0	2 3 1	2 2 3	2 2 0	2 1 2	2 0 4	2 2 8	2 3 2	2 1 5	2 3 4	2 4 7	2 2 9	2 4 5	2 4 8	2 3 5	2 4 9	2 4 3	2 3 8	2 0 8	2 1 1	2 2 7	2 0 1	2 2 1	2 2 6	2 5 0
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, renal tubule, adenoma																									
Transitional epithelium, carcinoma																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear				X			X	X		X	X		X	X		X	X	X	X	X	X	X			X
Mesothelioma malignant																									

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Chloroprene: 12.8 ppm

Number of Days on Study	6 6 3	6 6 5	6 6 5	6 6 5	6 7 0	6 7 7	6 7 9	6 8 9	7 0 0	7 0 0	7 0 1	7 0 1	7 0 2	7 0 6	7 0 7	7 3 0	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	
Carcass ID Number	2 1 3	2 0 9	2 2 4	2 3 6	2 1 7	2 1 9	2 3 7	2 0 6	2 0 3	2 4 1	2 1 4	2 1 6	2 1 0	2 3 3	2 3 9	2 4 4	2 0 2	2 0 5	2 0 7	2 1 8	2 2 2	2 2 5	2 3 0	2 4 2	2 4 6	Total Tissues/ Tumors
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, renal tubule, adenoma										X																1
Transitional epithelium, carcinoma								X																		1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X			X	X	X	X	X	X	X	X		X	X	X	X	X	X	X			X	X	X		34
Mesothelioma malignant					X																					1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Chloroprene: 32 ppm

Number of Days on Study	460	460	497	497	505	516	512	523	524	528	534	534	540	549	561	565	567	568	569	569	569	584	585	590	595
Carcass ID Number	425	450	430	448	431	427	439	404	444	417	408	412	419	423	438	411	416	403	405	413	421	442	447	407	437
Alimentary System																									
Esophagus	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+
Intestine small, jejunum	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+
Intestine small, ileum	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+
Schwannoma malignant, metastatic, heart																									
Mesentery							+	+					+	+			+	+				+			+
Sarcoma																									
Schwannoma malignant													X												
Oral mucosa																									
Pharyngeal, squamous cell papilloma																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+
Adenoma																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+
Tongue																									
Squamous cell carcinoma																									
Squamous cell papilloma																									
Cardiovascular System																									
Blood vessel																									
Aorta, schwannoma malignant, metastatic, heart																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Schwannoma malignant																									
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+
Adenoma																									
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+
Pheochromocytoma benign			X								X			X									X		
Bilateral, pheochromocytoma benign									X	X														X	
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+
Adenoma																									
Carcinoma																									
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
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
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+
C-cell, adenoma																									
C-cell, carcinoma																									
Follicular cell, adenoma																				X					
Follicular cell, carcinoma																									
General Body System																									
Peritoneum			+																				+		

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Chloroprene: 32 ppm

Number of Days on Study	6 0 9	6 0 9	6 2 0	6 2 2	6 2 2	6 2 2	6 3 7	6 4 2	6 5 2	6 6 5	6 6 7	6 7 9	6 8 1	6 8 1	7 0 2	7 0 5	7 0 7	7 2 1	7 2 1	7 2 5	7 3 3	7 3 3	7 3 3	7 3 3	
Carcass ID Number	4 2 4	4 4 5	4 0 1	4 1 4	4 3 5	4 4 6	4 0 2	4 0 6	4 3 6	4 2 0	4 4 9	4 2 6	4 3 4	4 4 3	4 2 2	4 1 0	4 3 2	4 1 8	4 2 9	4 2 8	4 0 9	4 1 5	4 3 3	4 4 0	4 4 1	Total Tissues/ Tumors
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	46
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	46
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	46
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Schwannoma malignant, metastatic, heart																			X						1
Mesentery	+		+	+				+	+	+	+						+			+	+				18
Sarcoma																					X				1
Schwannoma malignant																									1
Oral mucosa			+																						1
Pharyngeal, squamous cell papilloma			X																						1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma												X													1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Tongue	+			+							+								+						4
Squamous cell carcinoma	X																								1
Squamous cell papilloma				X							X								X						3
Cardiovascular System																									
Blood vessel																+	+		+						3
Aorta, schwannoma malignant, metastatic, heart																			X						1
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Schwannoma malignant																			X						1
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma																X									1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma benign	X													X	X	X	X			X	X				11
Bilateral, pheochromocytoma benign			X	X	X			X		X									X			X			10
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma		X																X							2
Carcinoma	X					X						X													3
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X		X	X	X	X	X	X	X	43
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
C-cell, adenoma		X																X		X			X		4
C-cell, carcinoma									X	X															2
Follicular cell, adenoma																					X				2
Follicular cell, carcinoma				X	X																				2
General Body System																									
Peritoneum									+																3

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Chloroprene: 32 ppm

Number of Days on Study	460	460	497	497	505	506	512	523	524	528	534	534	540	549	561	565	567	568	569	569	584	585	590	595
Carcass ID Number	425	450	530	448	531	527	539	504	444	517	508	512	519	523	538	511	516	503	505	513	521	542	547	537
Genital System																								
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	A	+	+	+	+	+	+
Adenoma			X	X																				
Carcinoma			X																					
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																								
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma	X		X				X				X						X				X	X	X	
Interstitial cell, adenoma									X	X			X	X					X					
Hematopoietic System																								
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node									+	+	+					+			+					
Lymph node, bronchial	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung																								
Lymph node, mandibular	+	+	+	M	+	+	M	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Alveolar/bronchiolar carcinoma, metastatic, lung																								
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+
Hemangiosarcoma						X																		
Thymus	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M
Integumentary System																								
Mammary gland	+	M	+	+	+	M	+	+	M	+	M	M	M	+	+	+	+	M	+	+	+	+	M	M
Adenoma																								
Carcinoma																								
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma													X											
Squamous cell papilloma																		X						
Subcutaneous tissue, melanoma malignant															X									
Subcutaneous tissue, sarcoma																								
Musculoskeletal System																								
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																								
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																								
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+
Alveolar/bronchiolar adenoma					X							X												
Alveolar/bronchiolar carcinoma																								
Mediastinum, schwannoma malignant, metastatic, heart																								
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Chloroprene: 32 ppm

Number of Days on Study	6 0 9	6 0 9	6 2 0	6 2 2	6 2 2	6 2 2	6 3 7	6 4 2	6 5 2	6 6 5	6 6 7	6 7 9	6 8 1	6 8 1	7 0 2	7 0 5	7 0 7	7 2 1	7 2 1	7 2 5	7 3 3	7 3 3	7 3 3	7 3 3	
Carcass ID Number	4 2 4	4 4 5	4 0 1	4 1 4	4 3 5	4 4 6	4 0 2	4 0 6	4 3 6	4 2 0	4 4 9	4 2 6	4 3 4	4 3 4	4 2 2	4 1 0	4 3 2	4 1 8	4 2 9	4 2 8	4 0 9	4 1 5	4 3 3	4 4 0	4 4 1	Total Tissues/ Tumors
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma															X	X									4
Carcinoma				X			X															X			4
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma												X							X		X				3
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, interstitial cell, adenoma			X			X			X												X		X	X	X	15
Interstitial cell, adenoma	X	X					X				X		X			X	X		X						13
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node		+							+	+				+		+		+							11
Lymph node, bronchial	M	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	44
Alveolar/bronchiolar carcinoma, metastatic, lung											X														1
Lymph node, mandibular	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	48
Lymph node, mediastinal	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Alveolar/bronchiolar carcinoma, metastatic, lung											X														1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma																									1
Thymus	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Integumentary System																									
Mammary gland	+	+	+	M	+	M	+	M	+	M	M	M	M	M	M	+	+	+	+	+	+	+	M	M	30
Adenoma																			X						1
Carcinoma																			X						1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Keratoacanthoma													X												2
Squamous cell papilloma																									1
Subcutaneous tissue, melanoma malignant																									1
Subcutaneous tissue, sarcoma																			X						1
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar adenoma																X									3
Alveolar/bronchiolar carcinoma											X														1
Mediastinum, schwannoma malignant, metastatic, heart																			X						1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Chloroprene: 32 ppm

Number of Days on Study	460	460	497	497	505	506	512	523	524	528	534	534	540	549	561	561	567	568	569	569	584	585	590	595
Carcass ID Number	425	450	300	488	311	727	939	044	444	717	088	412	919	123	381	115	166	033	055	133	121	422	477	737
Special Senses System																								
Eye																								
Urinary System																								
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Renal tubule, adenoma																								
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Transitional epithelium, carcinoma																								
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 Inhalation Study of Chloroprene: 32 ppm

Number of Days on Study	6 0 9	6 0 9	6 2 0	6 2 2	6 2 2	6 2 2	6 3 7	6 4 2	6 5 2	6 6 5	6 6 7	6 7 9	6 8 1	6 8 1	7 0 2	7 0 5	7 0 7	7 2 1	7 2 1	7 2 5	7 3 3	7 3 3	7 3 3	7 3 3	
Carcass ID Number	4 2 4	4 4 5	4 0 1	4 1 4	4 3 5	4 4 6	4 0 2	4 0 6	4 3 6	4 2 0	4 4 9	4 2 6	4 3 4	4 4 3	4 2 2	4 1 0	4 3 2	4 1 8	4 2 9	4 2 8	4 0 9	4 1 5	4 3 3	4 4 0	4 4 1	Total Tissues/ Tumors
Special Senses System																									
Eye							+																		1
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Renal tubule, adenoma																		X							1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Transitional epithelium, carcinoma																		X							1
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X	X		X		X	X	X			X	X	X	X		X		X			X	X	X	X	29
Mesothelioma malignant									X					X			X								5

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Chloroprene: 80 ppm

Number of Days on Study	3 0 5	3 0 7	4 6 3	4 7 0	4 9 7	5 2 2	5 3 0	5 3 2	5 3 3	5 3 9	5 4 0	5 4 9	5 5 8	5 6 7	5 7 6	5 7 8	5 8 3	5 9 7	6 0 1	6 0 3	6 0 8	6 0 9	6 1 1	6 1 3	6 1 7
Carcass ID Number	6 3 1	6 1 7	6 2 3	6 4 3	6 4 8	6 0 1	6 2 2	6 4 4	6 4 0	6 2 9	6 4 2	6 1 0	6 0 2	6 1 1	6 4 1	6 3 4	6 2 5	6 0 9	6 1 9	6 1 8	6 3 2	6 0 4	6 2 4	6 3 3	6 2 6
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp adenomatous													X												
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	A	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma								X																	
Intestine small, ileum	A	+	+	+	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma							X																		X
Mesentery												+						+	+		+	+			
Fat, lipoma																									
Oral mucosa											+					+							+		
Buccal, squamous cell papilloma																									
Gingival, squamous cell papilloma																									
Pharyngeal, squamous cell papilloma											X														
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Histiocytic sarcoma																									X
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									X
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									X
Tongue										+															
Squamous cell carcinoma																									
Squamous cell papilloma										X															
Cardiovascular System																									
Blood vessel																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign											X										X		X		X
Bilateral, pheochromocytoma benign																						X			
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Carcinoma																									
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma				X	X	X		X	X	X		X	X	X	X	X	X	X	X		X	X			X
Pars intermedia, adenoma											X														
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma												X					X								
Follicular cell, adenoma		X																							X
Follicular cell, carcinoma																									
General Body System																									
None																									

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Chloroprene: 80 ppm

Number of Days on Study	6 2 5	6 2 5	6 2 5	6 2 8	6 4 6	6 4 9	6 5 1	6 5 1	6 6 0	6 6 0	6 6 3	6 6 3	6 6 7	6 7 2	6 7 3	6 9 1	6 9 3	7 0 2	7 0 2	7 1 5	7 2 8	7 3 3	7 3 3	7 3 3	
Carcass ID Number	6 1 2	6 1 6	6 3 8	6 2 7	6 0 8	6 0 7	6 3 0	6 4 5	6 3 5	6 4 9	6 0 5	6 2 8	6 2 0	6 3 7	6 0 6	6 4 6	6 1 4	6 3 6	6 3 9	6 5 0	6 4 7	6 0 3	6 1 3	6 1 5	6 2 1	Total Tissues/ Tumors
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	48
Polyp adenomatous																									1
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	47
Carcinoma																									1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	46
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																									2
Mesentery		+									+			+		+	+	+	+	+					13
Fat, lipoma											X														1
Oral mucosa	+				+			+										+							7
Buccal, squamous cell papilloma								X																	1
Gingival, squamous cell papilloma					X																				1
Pharyngeal, squamous cell papilloma	X																								2
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																	X								1
Histiocytic sarcoma																									1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																									1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																									1
Tongue						+	+					+			+						+	+	+		8
Squamous cell carcinoma						X						X													2
Squamous cell papilloma							X								X						X	X	X		6
Cardiovascular System																									
Blood vessel																								+	1
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign									X		X			X			X							X	9
Bilateral, pheochromocytoma benign																X		X	X	X	X	X	X		9
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																X	X								2
Carcinoma								X																	1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	49
Pars distalis, adenoma	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			X		X	39
Pars intermedia, adenoma																									1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma	X															X		X		X		X			7
Follicular cell, adenoma								X																	4
Follicular cell, carcinoma					X																				1
General Body System																									
None																									

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Chloroprene: 80 ppm

Number of Days on Study	305	307	463	470	497	522	530	532	533	539	540	549	558	567	576	578	583	597	601	603	608	609	611	613	617
Carcass ID Number	631	617	623	643	648	601	622	644	640	629	642	610	602	611	641	634	625	609	619	618	632	604	624	633	626
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																			X						
Carcinoma																									
Histiocytic sarcoma																									X
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Seminal vesicle	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									X
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma																		X		X		X		X	X
Interstitial cell, adenoma			X					X			X					X						X		
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma							X																		
Lymph node		+							+	+	+	+		+	+					+					+
Iliac, histiocytic sarcoma																									X
Lymph node, bronchial	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma							X																		X
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									X
Lymph node, mediastinal	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma							X																		X
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									X
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									X
Thymoma benign																									
Integumentary System																									
Mammary gland	+	M	+	+	+	+	+	M	M	+	M	+	M	M	+	M	+	M	M	M	+	M	M	M	+
Fibroadenoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									X
Keratoacanthoma																									
Squamous cell papilloma																									
Subcutaneous tissue, fibroma																				X					
Subcutaneous tissue, sarcoma		X																							
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma	X																								
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Glioma malignant, mixed cell																									
Meninges, granular cell tumor benign																						X			

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Chloroprene: 80 ppm

Number of Days on Study	6 2 5	6 2 5	6 2 5	6 2 8	6 4 6	6 4 9	6 5 1	6 5 1	6 6 0	6 6 0	6 6 3	6 6 3	6 6 7	6 7 2	6 7 3	6 9 1	6 9 3	7 0 2	7 0 2	7 1 5	7 2 8	7 3 3	7 3 3	7 3 3	
Carcass ID Number	6 1 2	6 1 6	6 3 8	6 2 7	6 0 8	6 0 7	6 3 0	6 4 5	6 3 5	6 4 9	6 0 5	6 2 8	6 2 0	6 3 7	6 0 6	6 4 6	6 1 4	6 3 6	6 3 9	6 5 0	6 4 7	6 0 3	6 1 3	6 1 5	6 2 1	Total Tissues/ Tumors
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Carcinoma																								X		1
Histiocytic sarcoma																										1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma									X																	1
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma																										1
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, interstitial cell, adenoma		X			X		X			X			X					X	X	X	X	X	X	X		17
Interstitial cell, adenoma			X	X				X	X					X			X								X	12
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Lymph node	+							+		+						+		+		+						15
Iliac, histiocytic sarcoma																										1
Lymph node, bronchial	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	M	43
Histiocytic sarcoma																										2
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	49
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Lymph node, mediastinal	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Histiocytic sarcoma																										2
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Thymus	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	48
Histiocytic sarcoma																										1
Thymoma benign						X							X													2
Integumentary System																										
Mammary gland	M	+	M	+	M	+	+	+	+	+	M	M	+	+	M	+	M	M	M	+	+	+	+	+	+	28
Fibroadenoma																							X			1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Keratoacanthoma			X						X										X	X						4
Squamous cell papilloma																		X								1
Subcutaneous tissue, fibroma																										1
Subcutaneous tissue, sarcoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Glioma malignant, mixed cell				X																						1
Meninges, granular cell tumor benign																										1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Chloroprene: 80 ppm

Number of Days on Study	3 0 5	3 0 7	4 6 3	4 7 0	4 9 7	5 2 2	5 3 0	5 3 2	5 3 3	5 3 9	5 4 0	5 4 9	5 5 8	5 6 7	5 7 6	5 7 8	5 8 3	5 9 7	6 0 1	6 0 3	6 0 8	6 0 9	6 1 1	6 1 3	6 1 7
Carcass ID Number	6 3 1	6 1 7	6 2 3	6 4 3	6 4 8	6 0 1	6 2 2	6 4 4	6 4 0	6 2 9	6 4 2	6 1 0	6 0 2	6 1 1	6 4 1	6 3 4	6 2 5	6 0 9	6 1 9	6 1 8	6 3 2	6 0 4	6 2 4	6 3 3	6 2 6
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar carcinoma											X														X
Alveolar/bronchiolar carcinoma, multiple																									
Histiocytic sarcoma							X																		X
Osteosarcoma, metastatic, bone	X																								
Mediastinum, alveolar/bronchiolar carcinoma, metastatic, lung																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory epithelium, adenoma																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear											+														
Zymbal's gland											+								+						
Adenoma											X														
Carcinoma																			X						
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									X
Mesenchymal tumor NOS			X																						
Renal tubule, adenoma																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									X
Transitional epithelium, papilloma																					X				
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma							X																		X
Leukemia mononuclear											X	X	X	X					X		X	X	X	X	
Mesothelioma malignant																						X			

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Chloroprene: 80 ppm

Number of Days on Study	6 2 5	6 2 5	6 2 5	6 2 8	6 4 6	6 4 9	6 5 1	6 5 1	6 6 0	6 6 0	6 6 3	6 6 3	6 6 7	6 7 2	6 7 3	6 9 1	6 9 3	7 0 2	7 0 2	7 1 5	7 2 8	7 3 3	7 3 3	7 3 3	7 3 3	
Carcass ID Number	6 1 2	6 1 6	6 3 8	6 2 7	6 0 8	6 0 7	6 3 0	6 4 5	6 3 5	6 4 9	6 0 5	6 2 8	6 2 0	6 3 7	6 0 6	6 4 6	6 1 4	6 3 6	6 3 9	6 5 0	6 4 7	6 0 3	6 1 3	6 1 5	6 2 1	Total Tissues/ Tumors
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma									X													X			X	3
Alveolar/bronchiolar carcinoma																						X				3
Alveolar/bronchiolar carcinoma, multiple													X													1
Histiocytic sarcoma																										2
Osteosarcoma, metastatic, bone																										1
Mediastinum, alveolar/bronchiolar carcinoma, metastatic, lung													X													1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	49
Respiratory epithelium, adenoma													X													1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Ear																										1
Zymbal's gland																										2
Adenoma																										1
Carcinoma																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Mesenchymal tumor NOS																										1
Renal tubule, adenoma	X																	X								2
Urinary bladder	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma																										1
Transitional epithelium, papilloma																										1
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										2
Leukemia mononuclear	X	X	X					X	X	X	X	X			X	X	X	X	X	X	X	X	X	X		27
Mesothelioma malignant												X							X							3

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

	Chamber Control	12.8 ppm	32 ppm	80 ppm
Adrenal Medulla: Benign Pheochromocytoma				
Overall rate[a]	19/50 (38%)	20/50 (40%)	21/49 (43%)	18/50 (36%)
Adjusted rate[b]	76.2%	78.0%	82.2%	100.0%
Terminal rate[c]	8/13 (62%)	4/9 (44%)	2/5 (40%)	4/4 (100%)
First incidence (days)	576	534	497	540
Life table test[d]	P = 0.029	P = 0.280	P = 0.027	P = 0.022
Logistic regression test[d]	P = 0.312	P = 0.444	P = 0.150	P = 0.237
Cochran-Armitage test[d]	P = 0.422N			
Fisher exact test[d]		P = 0.500	P = 0.387	P = 0.500N
Adrenal Medulla: Benign or Malignant Pheochromocytoma				
Overall rate	19/50 (38%)	21/50 (42%)	21/49 (43%)	18/50 (36%)
Adjusted rate	76.2%	82.4%	82.2%	100.0%
Terminal rate	8/13 (62%)	5/9 (56%)	2/5 (40%)	4/4 (100%)
First incidence (days)	576	534	497	540
Life table test	P = 0.031	P = 0.214	P = 0.027	P = 0.022
Logistic regression test	P = 0.336	P = 0.356	P = 0.150	P = 0.237
Cochran-Armitage test	P = 0.388N			
Fisher exact test		P = 0.419	P = 0.387	P = 0.500N
Kidney (Renal Tubule): Adenoma (Step Section)				
Overall rate	1/50 (2%)	6/50 (12%)	6/50 (12%)	7/50 (14%)
Adjusted rate	7.7%	37.0%	52.5%	65.9%
Terminal rate	1/13 (8%)	2/9 (22%)	0/5 (0%)	2/4 (50%)
First incidence (days)	733 (T)	600	679	625
Life table test	P = 0.002	P = 0.036	P = 0.008	P = 0.002
Logistic regression test	P = 0.010	P = 0.047	P = 0.007	P = 0.005
Cochran-Armitage test	P = 0.080			
Fisher exact test		P = 0.056	P = 0.056	P = 0.030
Kidney (Renal Tubule): Adenoma (Single and Step Sections)				
Overall rate	1/50 (2%)	7/50 (14%)	6/50 (12%)	8/50 (16%)
Adjusted rate	7.7%	40.7%	52.5%	70.7%
Terminal rate	1/13 (8%)	2/9 (22%)	0/5 (0%)	2/4 (50%)
First incidence (days)	733 (T)	600	679	625
Life table test	P < 0.001	P = 0.021	P = 0.008	P < 0.001
Logistic regression test	P = 0.005	P = 0.024	P = 0.007	P = 0.002
Cochran-Armitage test	P = 0.058			
Fisher exact test		P = 0.030	P = 0.056	P = 0.015
Kidney (Renal Tubule): Adenoma or Carcinoma (Step Section)				
Overall rate	1/50 (2%)	7/50 (14%)	6/50 (12%)	7/50 (14%)
Adjusted rate	7.7%	39.8%	52.5%	65.9%
Terminal rate	1/13 (8%)	2/9 (22%)	0/5 (0%)	2/4 (50%)
First incidence (days)	733 (T)	600	679	625
Life table test	P = 0.004	P = 0.021	P = 0.008	P = 0.002
Logistic regression test	P = 0.016	P = 0.025	P = 0.007	P = 0.005
Cochran-Armitage test	P = 0.109			
Fisher exact test		P = 0.030	P = 0.056	P = 0.030

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

	Chamber Control	12.8 ppm	32 ppm	80 ppm
Kidney (Renal Tubule): Adenoma or Carcinoma (Single and Step Sections)				
Overall rate	1/50 (2%)	8/50 (16%)	6/50 (12%)	8/50 (16%)
Adjusted rate	7.7%	43.4%	52.5%	70.7%
Terminal rate	1/13 (8%)	2/9 (22%)	0/5 (0%)	2/4 (50%)
First incidence (days)	733 (T)	600	679	625
Life table test	P = 0.002	P = 0.012	P = 0.008	P < 0.001
Logistic regression test	P = 0.008	P = 0.013	P = 0.007	P = 0.002
Cochran-Armitage test	P = 0.080			
Fisher exact test		P = 0.015	P = 0.056	P = 0.015
Lung: Alveolar/bronchiolar Adenoma				
Overall rate	2/50 (4%)	0/50 (0%)	3/49 (6%)	3/50 (6%)
Adjusted rate	6.9%	0.0%	14.2%	52.9%
Terminal rate	0/13 (0%)	0/9 (0%)	0/5 (0%)	2/4 (50%)
First incidence (days)	616	—[e]	505	660
Life table test	P = 0.092	P = 0.235N	P = 0.381	P = 0.254
Logistic regression test	P = 0.200	P = 0.233N	P = 0.563	P = 0.370
Cochran-Armitage test	P = 0.230			
Fisher exact test		P = 0.247N	P = 0.490	P = 0.500
Lung: Alveolar/bronchiolar Carcinoma				
Overall rate	0/50 (0%)	2/50 (4%)	1/49 (2%)	4/50 (8%)
Adjusted rate	0.0%	17.9%	6.7%	35.1%
Terminal rate	0/13 (0%)	1/9 (11%)	0/5 (0%)	1/4 (25%)
First incidence (days)	—	702	667	540
Life table test	P = 0.007	P = 0.173	P = 0.433	P = 0.021
Logistic regression test	P = 0.023	P = 0.200	P = 0.452	P = 0.052
Cochran-Armitage test	P = 0.044			
Fisher exact test		P = 0.247	P = 0.495	P = 0.059
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rate	2/50 (4%)	2/50 (4%)	4/49 (8%)	6/50 (12%)
Adjusted rate	6.9%	17.9%	19.9%	59.3%
Terminal rate	0/13 (0%)	1/9 (11%)	0/5 (0%)	2/4 (50%)
First incidence (days)	616	702	505	540
Life table test	P = 0.009	P = 0.639	P = 0.224	P = 0.040
Logistic regression test	P = 0.039	P = 0.684	P = 0.366	P = 0.094
Cochran-Armitage test	P = 0.058			
Fisher exact test		P = 0.691N	P = 0.329	P = 0.134
Oral Cavity (Oral Mucosa, Tongue, Pharynx, Gingiva): Squamous Cell Papilloma				
Overall rate	0/50 (0%)	2/50 (4%)	4/50 (8%)	10/50 (20%)
Adjusted rate	0.0%	13.8%	25.4%	71.7%
Terminal rate	0/13 (0%)	0/9 (0%)	0/5 (0%)	2/4 (50%)
First incidence (days)	—	701	620	539
Life table test	P < 0.001	P = 0.198	P = 0.029	P < 0.001
Logistic regression test	P < 0.001	P = 0.217	P = 0.040	P < 0.001
Cochran-Armitage test	P < 0.001			
Fisher exact test		P = 0.247	P = 0.059	P < 0.001

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

	Chamber Control	12.8 ppm	32 ppm	80 ppm
Oral Cavity (Oral Mucosa, Tongue, Pharynx, Gingiva): Squamous Cell Papilloma or Squamous Cell Carcinoma				
Overall rate	0/50 (0%)	2/50 (4%)	5/50 (10%)	12/50 (24%)
Adjusted rate	0.0%	13.8%	28.4%	74.9%
Terminal rate	0/13 (0%)	0/9 (0%)	0/5 (0%)	2/4 (50%)
First incidence (days)	—	701	609	539
Life table test	P < 0.001	P = 0.198	P = 0.013	P < 0.001
Logistic regression test	P < 0.001	P = 0.217	P = 0.022	P < 0.001
Cochran-Armitage test	P < 0.001			
Fisher exact test		P = 0.247	P = 0.028	P < 0.001
Oral Mucosa: Squamous Cell Papilloma				
Overall rate	0/50 (0%)	2/50 (4%)	1/50 (2%)	4/50 (8%)
Adjusted rate	0.0%	13.8%	4.3%	15.5%
Terminal rate	0/13 (0%)	0/9 (0%)	0/5 (0%)	0/4 (0%)
First incidence (days)	—	701	620	540
Life table test	P = 0.019	P = 0.198	P = 0.447	P = 0.048
Logistic regression test	P = 0.034	P = 0.217	P = 0.508	P = 0.065
Cochran-Armitage test	P = 0.043			
Fisher exact test		P = 0.247	P = 0.500	P = 0.059
Pancreatic Islets: Adenoma				
Overall rate	3/50 (6%)	3/50 (6%)	2/49 (4%)	2/50 (4%)
Adjusted rate	17.6%	18.1%	16.0%	20.0%
Terminal rate	2/13 (15%)	1/9 (11%)	0/5 (0%)	0/4 (0%)
First incidence (days)	576	525	609	691
Life table test	P = 0.492	P = 0.574	P = 0.601	P = 0.529
Logistic regression test	P = 0.515N	P = 0.651	P = 0.627N	P = 0.659N
Cochran-Armitage test	P = 0.393N			
Fisher exact test		P = 0.661N	P = 0.510N	P = 0.500N
Pancreatic Islets: Carcinoma				
Overall rate	3/50 (6%)	5/50 (10%)	3/49 (6%)	1/50 (2%)
Adjusted rate	13.2%	29.1%	14.9%	5.3%
Terminal rate	0/13 (0%)	1/9 (11%)	0/5 (0%)	0/4 (0%)
First incidence (days)	489	603	609	651
Life table test	P = 0.337N	P = 0.315	P = 0.488	P = 0.444N
Logistic regression test	P = 0.181N	P = 0.346	P = 0.652	P = 0.306N
Cochran-Armitage test	P = 0.140N			
Fisher exact test		P = 0.357	P = 0.651	P = 0.309N
Pancreatic Islets: Adenoma or Carcinoma				
Overall rate	6/50 (12%)	8/50 (16%)	5/49 (10%)	3/50 (6%)
Adjusted rate	28.4%	42.8%	28.6%	24.2%
Terminal rate	2/13 (15%)	2/9 (22%)	0/5 (0%)	0/4 (0%)
First incidence (days)	489	525	609	651
Life table test	P = 0.452N	P = 0.300	P = 0.433	P = 0.583N
Logistic regression test	P = 0.194N	P = 0.369	P = 0.601N	P = 0.331N
Cochran-Armitage test	P = 0.118N			
Fisher exact test		P = 0.387	P = 0.514N	P = 0.243N

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

	Chamber Control	12.8 ppm	32 ppm	80 ppm
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	40/50 (80%)	40/49 (82%)	43/50 (86%)	39/49 (80%)
Adjusted rate	92.2%	97.0%	100.0%	96.3%
Terminal rate	10/13 (77%)	8/9 (89%)	5/5 (100%)	3/4 (75%)
First incidence (days)	469	357	460	470
Life table test	P = 0.018	P = 0.340	P = 0.009	P = 0.036
Logistic regression test	P = 0.508	P = 0.526	P = 0.263	P = 0.466
Cochran-Armitage test	P = 0.506N			
Fisher exact test		P = 0.520	P = 0.298	P = 0.579N
Preputial Gland: Adenoma				
Overall rate	3/50 (6%)	3/50 (6%)	4/48 (8%)	1/50 (2%)
Adjusted rate	12.3%	24.7%	21.6%	3.1%
Terminal rate	1/13 (8%)	2/9 (22%)	0/5 (0%)	0/4 (0%)
First incidence (days)	534	613	497	601
Life table test	P = 0.451N	P = 0.567	P = 0.331	P = 0.440N
Logistic regression test	P = 0.239N	P = 0.655	P = 0.533	P = 0.285N
Cochran-Armitage test	P = 0.230N			
Fisher exact test		P = 0.661N	P = 0.477	P = 0.309N
Preputial Gland: Carcinoma				
Overall rate	3/50 (6%)	3/50 (6%)	4/48 (8%)	1/50 (2%)
Adjusted rate	17.3%	24.8%	29.2%	25.0%
Terminal rate	2/13 (15%)	2/9 (22%)	1/5 (20%)	1/4 (25%)
First incidence (days)	541	637	497	733 (T)
Life table test	P = 0.551N	P = 0.553	P = 0.237	P = 0.649N
Logistic regression test	P = 0.318N	P = 0.642	P = 0.438	P = 0.431N
Cochran-Armitage test	P = 0.230N			
Fisher exact test		P = 0.661N	P = 0.477	P = 0.309N
Preputial Gland: Adenoma or Carcinoma				
Overall rate	6/50 (12%)	6/50 (12%)	7/48 (15%)	2/50 (4%)
Adjusted rate	28.6%	48.0%	43.3%	27.3%
Terminal rate	3/13 (23%)	4/9 (44%)	1/5 (20%)	1/4 (25%)
First incidence (days)	534	613	497	601
Life table test	P = 0.418N	P = 0.463	P = 0.196	P = 0.399N
Logistic regression test	P = 0.153N	P = 0.600	P = 0.437	P = 0.172N
Cochran-Armitage test	P = 0.099N			
Fisher exact test		P = 0.620N	P = 0.468	P = 0.134N
Prostate Gland: Adenoma				
Overall rate	0/50 (0%)	1/50 (2%)	3/50 (6%)	1/50 (2%)
Adjusted rate	0.0%	11.1%	35.0%	5.9%
Terminal rate	0/13 (0%)	1/9 (11%)	1/5 (20%)	0/4 (0%)
First incidence (days)	—	733 (T)	679	660
Life table test	P = 0.182	P = 0.427	P = 0.038	P = 0.458
Logistic regression test	P = 0.263	P = 0.427	P = 0.045	P = 0.465
Cochran-Armitage test	P = 0.448			
Fisher exact test		P = 0.500	P = 0.121	P = 0.500

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

	Chamber Control	12.8 ppm	32 ppm	80 ppm
Skin: Keratoacanthoma				
Overall rate	2/50 (4%)	4/50 (8%)	2/50 (4%)	4/50 (8%)
Adjusted rate	11.7%	15.6%	10.1%	34.1%
Terminal rate	1/13 (8%)	0/9 (0%)	0/5 (0%)	0/4 (0%)
First incidence (days)	657	609	540	625
Life table test	P = 0.145	P = 0.336	P = 0.514	P = 0.122
Logistic regression test	P = 0.265	P = 0.324	P = 0.646	P = 0.195
Cochran-Armitage test	P = 0.359			
Fisher exact test		P = 0.339	P = 0.691N	P = 0.339
Skin: Squamous Cell Papilloma or Keratoacanthoma				
Overall rate	2/50 (4%)	4/50 (8%)	3/50 (6%)	5/50 (10%)
Adjusted rate	11.7%	15.6%	12.8%	43.5%
Terminal rate	1/13 (8%)	0/9 (0%)	0/5 (0%)	0/4 (0%)
First incidence (days)	657	609	540	625
Life table test	P = 0.063	P = 0.336	P = 0.312	P = 0.051
Logistic regression test	P = 0.145	P = 0.324	P = 0.477	P = 0.094
Cochran-Armitage test	P = 0.215			
Fisher exact test		P = 0.339	P = 0.500	P = 0.218
Skin: Squamous Cell Papilloma, Keratoacanthoma, Basal Cell Adenoma, or Basal Cell Carcinoma				
Overall rate	3/50 (6%)	5/50 (10%)	3/50 (6%)	5/50 (10%)
Adjusted rate	14.9%	20.8%	12.8%	43.5%
Terminal rate	1/13 (8%)	0/9 (0%)	0/5 (0%)	0/4 (0%)
First incidence (days)	637	609	540	625
Life table test	P = 0.134	P = 0.361	P = 0.457	P = 0.116
Logistic regression test	P = 0.273	P = 0.341	P = 0.644	P = 0.201
Cochran-Armitage test	P = 0.376			
Fisher exact test		P = 0.357	P = 0.661N	P = 0.357
Testes: Adenoma				
Overall rate	34/50 (68%)	34/50 (68%)	28/50 (56%)	29/50 (58%)
Adjusted rate	90.7%	100.0%	93.7%	100.0%
Terminal rate	10/13 (77%)	9/9 (100%)	4/5 (80%)	4/4 (100%)
First incidence (days)	469	525	460	463
Life table test	P = 0.061	P = 0.289	P = 0.154	P = 0.077
Logistic regression test	P = 0.348N	P = 0.529	P = 0.238N	P = 0.448N
Cochran-Armitage test	P = 0.140N			
Fisher exact test		P = 0.585N	P = 0.151N	P = 0.204N
Thyroid Gland (C-cell): Adenoma				
Overall rate	3/50 (6%)	6/50 (12%)	4/49 (8%)	7/50 (14%)
Adjusted rate	18.0%	21.6%	44.0%	55.3%
Terminal rate	2/13 (15%)	0/9 (0%)	1/5 (20%)	1/4 (25%)
First incidence (days)	616	541	609	549
Life table test	P = 0.024	P = 0.227	P = 0.172	P = 0.019
Logistic regression test	P = 0.092	P = 0.233	P = 0.287	P = 0.078
Cochran-Armitage test	P = 0.183			
Fisher exact test		P = 0.243	P = 0.489	P = 0.159

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

	Chamber Control	12.8 ppm	32 ppm	80 ppm
Thyroid Gland (C-cell): Adenoma or Carcinoma				
Overall rate	5/50 (10%)	7/50 (14%)	6/49 (12%)	7/50 (14%)
Adjusted rate	27.3%	25.8%	50.6%	55.3%
Terminal rate	3/13 (23%)	0/9 (0%)	1/5 (20%)	1/4 (25%)
First incidence (days)	571	541	609	549
Life table test	P = 0.076	P = 0.333	P = 0.148	P = 0.070
Logistic regression test	P = 0.240	P = 0.366	P = 0.285	P = 0.240
Cochran-Armitage test	P = 0.396			
Fisher exact test		P = 0.380	P = 0.486	P = 0.380
Thyroid Gland (Follicular Cell): Adenoma				
Overall rate	0/50 (0%)	2/50 (4%)	2/49 (4%)	4/50 (8%)
Adjusted rate	0.0%	13.5%	22.5%	33.1%
Terminal rate	0/13 (0%)	1/9 (11%)	1/5 (20%)	1/4 (25%)
First incidence (days)	—	597	569	307
Life table test	P = 0.013	P = 0.202	P = 0.117	P = 0.027
Logistic regression test	P = 0.063	P = 0.232	P = 0.201	P = 0.089
Cochran-Armitage test	P = 0.054			
Fisher exact test		P = 0.247	P = 0.242	P = 0.059
Thyroid Gland (Follicular Cell): Adenoma or Carcinoma				
Overall rate	0/50 (0%)	2/50 (4%)	4/49 (8%)	5/50 (10%)
Adjusted rate	0.0%	13.5%	29.5%	36.3%
Terminal rate	0/13 (0%)	1/9 (11%)	1/5 (20%)	1/4 (25%)
First incidence (days)	—	597	569	307
Life table test	P = 0.007	P = 0.202	P = 0.021	P = 0.014
Logistic regression test	P = 0.029	P = 0.232	P = 0.050	P = 0.044
Cochran-Armitage test	P = 0.029			
Fisher exact test		P = 0.247	P = 0.056	P = 0.028
Tongue: Squamous Cell Papilloma				
Overall rate	0/50 (0%)	0/50 (0%)	3/50 (6%)	6/50 (12%)
Adjusted rate	0.0%	0.0%	22.0%	66.4%
Terminal rate	0/13 (0%)	0/9 (0%)	0/5 (0%)	2/4 (50%)
First incidence (days)	—	—[f]	622	539
Life table test	P < 0.001		P = 0.063	P < 0.001
Logistic regression test	P < 0.001	—	P = 0.077	P = 0.005
Cochran-Armitage test	P = 0.001			
Fisher exact test		—	P = 0.121	P = 0.013
Tongue: Squamous Cell Papilloma or Squamous Cell Carcinoma				
Overall rate	0/50 (0%)	0/50 (0%)	4/50 (8%)	8/50 (16%)
Adjusted rate	0.0%	0.0%	25.2%	70.2%
Terminal rate	0/13 (0%)	0/9 (0%)	0/5 (0%)	2/4 (50%)
First incidence (days)	—	—	609	539
Life table test	P < 0.001	—	P = 0.028	P < 0.001
Logistic regression test	P < 0.001	—	P = 0.041	P = 0.001
Cochran-Armitage test	P < 0.001			
Fisher exact test		—	P = 0.059	P = 0.003

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

	Chamber Control	12.8 ppm	32 ppm	80 ppm
All Organs: Mononuclear Cell Leukemia				
Overall rate	33/50 (66%)	34/50 (68%)	29/50 (58%)	27/50 (54%)
Adjusted rate	86.3%	90.8%	94.1%	95.6%
Terminal rate	8/13 (62%)	6/9 (67%)	4/5 (80%)	3/4 (75%)
First incidence (days)	489	525	506	540
Life table test	P = 0.121	P = 0.296	P = 0.099	P = 0.116
Logistic regression test	P = 0.169N	P = 0.461	P = 0.470N	P = 0.408N
Cochran-Armitage test	P = 0.082N			
Fisher exact test		P = 0.500	P = 0.268N	P = 0.154N
All Organs: Malignant Mesothelioma				
Overall rate	0/50 (0%)	1/50 (2%)	5/50 (10%)	3/50 (6%)
Adjusted rate	0.0%	4.8%	27.1%	21.1%
Terminal rate	0/13 (0%)	0/9 (0%)	0/5 (0%)	0/4 (0%)
First incidence (days)	—	670	497	609
Life table test	P = 0.039	P = 0.500	P = 0.014	P = 0.061
Logistic regression test	P = 0.092	P = 0.494	P = 0.031	P = 0.089
Cochran-Armitage test	P = 0.113			
Fisher exact test		P = 0.500	P = 0.028	P = 0.121
All Organs: Benign Neoplasms				
Overall rate	50/50 (100%)	50/50 (100%)	50/50 (100%)	48/50 (96%)
Adjusted rate	100.0%	100.0%	100.0%	100.0%
Terminal rate	13/13 (100%)	9/9 (100%)	5/5 (100%)	4/4 (100%)
First incidence (days)	469	357	460	307
Life table test	P = 0.013	P = 0.308	P = 0.013	P = 0.021
Logistic regression test	P = 0.170N	—	—	P = 0.576N
Cochran-Armitage test	P = 0.043N			
Fisher exact test		P = 1.000N	P = 1.000N	P = 0.247N
All Organs: Malignant Neoplasms				
Overall rate	40/50 (80%)	37/50 (74%)	37/50 (74%)	36/50 (72%)
Adjusted rate	95.0%	94.4%	96.5%	96.9%
Terminal rate	11/13 (85%)	7/9 (78%)	4/5 (80%)	3/4 (75%)
First incidence (days)	489	525	497	305
Life table test	P = 0.026	P = 0.465	P = 0.047	P = 0.048
Logistic regression test	P = 0.496N	P = 0.370N	P = 0.547N	P = 0.434N
Cochran-Armitage test	P = 0.262N			
Fisher exact test		P = 0.318N	P = 0.318N	P = 0.241N

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

	Chamber Control	12.8 ppm	32 ppm	80 ppm
All Organs: Benign or Malignant Neoplasms				
Overall rate	50/50 (100%)	50/50 (100%)	50/50 (100%)	50/50 (100%)
Adjusted rate	100.0%	100.0%	100.0%	100.0%
Terminal rate	13/13 (100%)	9/9 (100%)	5/5 (100%)	4/4 (100%)
First incidence (days)	469	357	460	305
Life table test	P = 0.007	P = 0.308	P = 0.013	P = 0.013
Logistic regression test	—	—	—	—
Cochran-Armitage test	—			
Fisher exact test		P = 1.000N	P = 1.000N	P = 1.000N

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

TABLE A4a
Historical Incidence of Oral Cavity Neoplasms in Chamber Control Male F344/N Rats[a]

Study	Incidence in Controls		
	Squamous Cell Papilloma	Squamous Cell Carcinoma	Squamous Cell Papilloma or Carcinoma
Historical Incidence at Battelle Pacific Northwest Laboratories			
o-Chlorobenzalmalononitrile	0/50	0/50	0/50
Acetonitrile	0/48	0/48	0/48
2-Chloroacetophenone	3/50	0/50	3/50
l-Epinephrine Hydrochloride	1/50	0/50	1/50
Chloroethane	0/50	0/50	0/50
Hexachlorocyclopentadiene	0/50	0/50	0/50
Ozone	1/50	0/50	1/50
Overall Historical Incidence			
Total	8/655 (1.2%)	1/655 (0.2%)	9/655 (1.4%)
Standard deviation	1.9%	0.6%	1.9%
Range	0%-6%	0%-2%	0%-6%

[a] Data as of 12 May 1995. Includes oral mucosa, tongue, pharynx, tooth, and gingiva

TABLE A4b
Historical Incidence of Thyroid Gland Follicular Cell Neoplasms in Chamber Control Male F344/N Rats[a]

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Battelle Pacific Northwest Laboratories			
o-Chlorobenzalmalononitrile	0/48	0/48	0/48
Acetonitrile	0/48	0/48	0/48
2-Chloroacetophenone	1/45	0/45	1/45
l-Epinephrine Hydrochloride	0/50	2/50	2/50
Chloroethane	0/49	2/49	2/49
Hexachlorocyclopentadiene	0/49	0/49	0/49
Ozone	0/49	1/49	1/49
Overall Historical Incidence			
Total	3/641 (0.5%)	8/641 (1.3%)	11/641 (1.7%)
Standard deviation	0.9%	1.5%	1.6%
Range	0%-2%	0%-4%	0%-4%

[a] Data as of 12 May 1995

TABLE A4c
Historical Incidence of Alveolar/bronchiolar Neoplasms in Chamber Control Male F344/N Rats[a]

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Battelle Pacific Northwest Laboratories			
o-Chlorobenzalmalononitrile	4/50	0/50	4/50
Acetonitrile	1/48	1/48	2/48
2-Chloroacetophenone	1/49	1/49	2/49
l-Epinephrine Hydrochloride	4/50	1/50	5/50
Chloroethane	0/50	0/50	0/50
Hexachlorocyclopentadiene	5/50	0/50	5/50
Ozone	1/50	1/50	2/50
Overall Historical Incidence			
Total	17/654 (2.6%)	6/654 (0.9%)	23/654 (3.5%)
Standard deviation	3.6%	1.0%	3.7%
Range	0%-10%	0%-2%	0%-10%

[a] Data as of 12 May 1995

TABLE A4d
Historical Incidence of Renal Tubule Neoplasms in Chamber Control Male F344/N Rats[a]

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Battelle Pacific Northwest Laboratories			
o-Chlorobenzalmalononitrile	1/50	0/50	1/50
Acetonitrile	1/48	0/48	1/48
2-Chloroacetophenone	1/49	0/49	1/49
l-Epinephrine Hydrochloride	0/50	0/50	0/50
Chloroethane	0/50	0/50	0/50
Hexachlorocyclopentadiene	0/50	0/50	0/50
Ozone	2/50	0/50	2/50
Overall Historical Incidence			
Total	6/652 (0.9%)	0/652	6/652 (0.9%)
Standard deviation	1.3%		1.3%
Range	0%-4%		0%-4%

[a] Data as of 12 May 1995

TABLE A4e
Historical Incidence of Urinary Bladder Neoplasms in Chamber Control Male F344/N Rats[a]

Study	Incidence in Controls	
	Carcinoma	Papilloma
Historical Incidence at Battelle Pacific Northwest Laboratories		
o-Chlorobenzalmalononitrile	0/49	0/49
Acetonitrile	0/48	0/48
2-Chloroacetophenone	0/49	0/49
l-Epinephrine Hydrochloride	0/50	0/50
Chloroethane	0/50	0/50
Hexachlorocyclopentadiene	0/50	0/50
Ozone	0/50	0/50
Overall Historical Incidence		
Total	1/652 (0.2%)	0/652
Standard deviation	0.6%	
Range	0%-2%	

[a] Data as of 12 May 1995

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

	Chamber Control	12.8 ppm	32 ppm	80 ppm
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Moribund	34	40	41	41
Natural deaths	3	1	4	5
Survivors				
Terminal sacrifice	13	9	5	4
Animals examined microscopically	50	50	50	50
Alimentary System				
Intestine large, colon	(50)	(49)	(48)	(49)
Mineralization	1 (2%)			
Parasite metazoan	4 (8%)	7 (14%)		3 (6%)
Intestine large, rectum	(50)	(47)	(50)	(49)
Mineralization		1 (2%)	1 (2%)	
Parasite metazoan	2 (4%)	1 (2%)	2 (4%)	
Intestine large, cecum	(48)	(49)	(46)	(48)
Necrosis	1 (2%)			
Parasite metazoan	10 (21%)	7 (14%)	7 (15%)	6 (13%)
Intestine small, duodenum	(50)	(49)	(49)	(50)
Necrosis			1 (2%)	
Liver	(50)	(50)	(49)	(50)
Angiectasis	2 (4%)	5 (10%)	6 (12%)	5 (10%)
Basophilic focus	16 (32%)	17 (34%)	21 (43%)	13 (26%)
Clear cell focus	8 (16%)	6 (12%)	3 (6%)	2 (4%)
Degeneration, cystic	13 (26%)	18 (36%)	20 (41%)	21 (42%)
Degeneration, fatty	3 (6%)	4 (8%)	4 (8%)	3 (6%)
Eosinophilic focus			3 (6%)	4 (8%)
Hepatodiaphragmatic nodule	2 (4%)	1 (2%)	4 (8%)	3 (6%)
Inflammation, chronic		1 (2%)		
Mixed cell focus		1 (2%)	2 (4%)	1 (2%)
Necrosis		2 (4%)	1 (2%)	1 (2%)
Regeneration	2 (4%)	3 (6%)	3 (6%)	
Thrombosis			1 (2%)	
Bile duct, hyperplasia	36 (72%)	40 (80%)	35 (71%)	34 (68%)
Centrilobular, necrosis	13 (26%)	13 (26%)	13 (27%)	8 (16%)
Mesentery	(16)	(13)	(18)	(13)
Inflammation, chronic active	1 (6%)	1 (8%)		1 (8%)
Artery, mineralization			1 (6%)	
Fat, hemorrhage	1 (6%)			
Fat, necrosis	15 (94%)	13 (100%)	14 (78%)	11 (85%)
Oral mucosa		(2)	(1)	(7)
Pharyngeal, hyperplasia, squamous				3 (43%)
Pancreas	(50)	(50)	(49)	(50)
Atrophy	27 (54%)	27 (54%)	30 (61%)	23 (46%)
Basophilic focus	2 (4%)	2 (4%)	2 (4%)	1 (2%)
Hyperplasia	7 (14%)	3 (6%)	5 (10%)	1 (2%)
Artery, inflammation			2 (4%)	
Salivary glands	(50)	(50)	(50)	(50)
Atrophy				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 Inhalation Study of Chloroprene

	Chamber Control	12.8 ppm	32 ppm	80 ppm
Alimentary System (continued)				
Stomach, forestomach	(50)	(50)	(50)	(50)
Hyperplasia, squamous	2 (4%)	1 (2%)	2 (4%)	1 (2%)
Inflammation, chronic active				5 (10%)
Mineralization	1 (2%)	1 (2%)	1 (2%)	
Necrosis	2 (4%)	5 (10%)	2 (4%)	3 (6%)
Ulcer	1 (2%)	1 (2%)	6 (12%)	11 (22%)
Stomach, glandular	(49)	(50)	(49)	(50)
Mineralization	5 (10%)	5 (10%)	3 (6%)	5 (10%)
Necrosis	2 (4%)	2 (4%)	6 (12%)	2 (4%)
Tooth		(2)		
Developmental malformation		1 (50%)		
Inflammation, chronic active		2 (100%)		
Cardiovascular System				
Blood vessel			(3)	(1)
Aorta, mineralization			2 (67%)	1 (100%
Heart	(50)	(50)	(50)	(50)
Cardiomyopathy	43 (86%)	46 (92%)	39 (78%)	45 (90%)
Artery, mineralization			2 (4%)	
Atrium, thrombosis	1 (2%)	1 (2%)	4 (8%)	2 (4%)
Endocrine System				
Adrenal cortex	(50)	(50)	(49)	(50)
Atrophy		1 (2%)		
Hyperplasia	23 (46%)	25 (50%)	26 (53%)	23 (46%)
Hypertrophy	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Necrosis		2 (4%)	1 (2%)	2 (4%)
Vacuolization cytoplasmic	1 (2%)	4 (8%)	3 (6%)	2 (4%)
Adrenal medulla	(50)	(50)	(49)	(50)
Hyperplasia	23 (46%)	19 (38%)	19 (39%)	17 (34%)
Necrosis		1 (2%)		
Islets, pancreatic	(50)	(50)	(49)	(50)
Hyperplasia	3 (6%)	2 (4%)	3 (6%)	3 (6%)
Parathyroid gland	(48)	(49)	(50)	(50)
Hyperplasia	5 (10%)	10 (20%)	19 (38%)	24 (48%)
Pituitary gland	(50)	(49)	(50)	(49)
Pars distalis, cyst		1 (2%)		
Pars distalis, hyperplasia	7 (14%)	4 (8%)	5 (10%)	2 (4%)
Pars intermedia, hyperplasia		1 (2%)		
Thyroid gland	(50)	(50)	(49)	(50)
C-cell, hyperplasia	34 (68%)	24 (48%)	23 (47%)	28 (56%)
Follicular cell, hyperplasia		2 (4%)	4 (8%)	1 (2%)
General Body System				
None				
Genital System				
Coagulating gland	(1)			
Hyperplasia	1 (100%)			
Epididymis	(50)	(50)	(50)	(50)
Granuloma sperm	2 (4%)	3 (6%)	1 (2%)	
Hyperplasia		2 (4%)	6 (12%)	1 (2%)
Necrosis, fatty			1 (2%)	

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Inhalation Study of Chloroprene

	Chamber Control	12.8 ppm	32 ppm	80 ppm
Genital System (continued)				
Penis	(1)	(3)		
Vein, fibrosis		1 (33%)		
Preputial gland	(50)	(50)	(48)	(50)
Hyperplasia	4 (8%)	3 (6%)	1 (2%)	1 (2%)
Inflammation, chronic active	9 (18%)	6 (12%)	3 (6%)	4 (8%)
Prostate	(50)	(50)	(50)	(50)
Hyperplasia	7 (14%)	7 (14%)	5 (10%)	4 (8%)
Inflammation, chronic active	2 (4%)	4 (8%)	4 (8%)	5 (10%)
Mineralization	1 (2%)			
Seminal vesicle	(50)	(50)	(50)	(49)
Amyloid deposition			1 (2%)	
Inflammation, chronic active				1 (2%)
Mineralization			1 (2%)	
Testes	(50)	(50)	(50)	(50)
Atrophy	1 (2%)	4 (8%)	4 (8%)	1 (2%)
Hyperplasia		1 (2%)		
Artery, inflammation, chronic active	2 (4%)	2 (4%)	4 (8%)	3 (6%)
Interstitial cell, hyperplasia	10 (20%)	4 (8%)	9 (18%)	7 (14%)
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(50)
Necrosis	1 (2%)			
Lymph node	(12)	(18)	(11)	(15)
Iliac, ectasia		1 (6%)		
Pancreatic, hemorrhage			1 (9%)	
Renal, ectasia				1 (7%)
Renal, hemorrhage	1 (8%)	2 (11%)	3 (27%)	5 (33%)
Renal, infiltration cellular, plasma cell			1 (9%)	
Renal, pigmentation				1 (7%)
Lymph node, mandibular	(47)	(45)	(44)	(49)
Ectasia	1 (2%)			
Hemorrhage			1 (2%)	
Infiltration cellular, plasma cell		2 (4%)		1 (2%)
Lymph node, mesenteric	(50)	(50)	(48)	(50)
Hemorrhage			1 (2%)	
Infiltration cellular, plasma cell				1 (2%)
Lymph node, mediastinal	(46)	(47)	(48)	(47)
Hemorrhage			1 (2%)	
Spleen	(50)	(50)	(49)	(50)
Accessory spleen	2 (4%)	1 (2%)	1 (2%)	
Fibrosis	17 (34%)	19 (38%)	17 (35%)	20 (40%)
Hematopoietic cell proliferation	2 (4%)	2 (4%)	3 (6%)	6 (12%)
Hemorrhage	1 (2%)	1 (2%)		
Metaplasia, lipocyte		1 (2%)		
Necrosis	1 (2%)	2 (4%)	3 (6%)	
Thrombosis			1 (2%)	
Integumentary System				
Mammary gland	(30)	(23)	(30)	(28)
Galactocele	4 (13%)	3 (13%)	3 (10%)	1 (4%)
Inflammation, chronic	1 (3%)			
Skin	(50)	(50)	(50)	(50)
Cyst epithelial inclusion	1 (2%)			
Hyperkeratosis		2 (4%)		1 (2%)
Inflammation, chronic active	3 (6%)	4 (8%)	8 (16%)	5 (10%)

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Inhalation Study of Chloroprene

	Chamber Control	12.8 ppm	32 ppm	80 ppm
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Fibrous osteodystrophy		4 (8%)	7 (14%)	11 (22%)
Hyperplasia		1 (2%)		
Nervous System				
Brain	(50)	(50)	(50)	(50)
Hemorrhage		1 (2%)		
Hydrocephalus				1 (2%)
Mineralization				1 (2%)
Necrosis		1 (2%)	2 (4%)	
Respiratory System				
Larynx	(50)	(50)	(50)	(50)
Inflammation, acute	1 (2%)			1 (2%)
Lung	(50)	(50)	(49)	(50)
Foreign body				1 (2%)
Hemorrhage	1 (2%)	2 (4%)	1 (2%)	1 (2%)
Infiltration cellular	1 (2%)			
Inflammation, chronic active			1 (2%)	1 (2%)
Metaplasia, cartilagenous	1 (2%)			
Metaplasia, osseous		1 (2%)		
Mineralization		1 (2%)	1 (2%)	1 (2%)
Thrombosis	1 (2%)			
Alveolar epithelium, hyperplasia	5 (10%)	16 (32%)	14 (29%)	25 (50%)
Artery, mediastinum, mineralization			1 (2%)	2 (4%)
Nose	(50)	(50)	(49)	(49)
Cyst				1 (2%)
Inflammation, suppurative	1 (2%)	1 (2%)	4 (8%)	
Thrombosis	10 (20%)	9 (18%)	3 (6%)	2 (4%)
Olfactory epithelium, atrophy	3 (6%)	12 (24%)	46 (94%)	48 (98%)
Olfactory epithelium, fibrosis				47 (96%)
Olfactory epithelium, hyperplasia, basal cell			38 (78%)	46 (94%)
Olfactory epithelium, hyperplasia, adenomatous	2 (4%)		1 (2%)	42 (86%)
Olfactory epithelium, inflammation, chronic active		5 (10%)	9 (18%)	49 (100%)
Olfactory epithelium, metaplasia	6 (12%)	5 (10%)	45 (92%)	48 (98%)
Olfactory epithelium, necrosis		11 (22%)	26 (53%)	19 (39%)
Respiratory epithelium, hyperplasia				1 (2%)
Turbinate, fibrosis, focal			5 (10%)	
Trachea	(50)	(50)	(50)	(50)
Mineralization			1 (2%)	
Special Senses System				
Ear				(1)
External ear, inflammation, chronic active				1 (100%)
Eye		(1)	(1)	
Cataract			1 (100%)	
Retina, atrophy		1 (100%)	1 (100%)	

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Inhalation Study of Chloroprene

	Chamber Control	12.8 ppm	32 ppm	80 ppm
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Cyst	3 (6%)	3 (6%)	3 (6%)	5 (10%)
Hyperplasia, oncocytic				2 (4%)
Infarct		2 (4%)	2 (4%)	
Mineralization	1 (2%)		2 (4%)	1 (2%)
Nephropathy	50 (100%)	50 (100%)	50 (100%)	50 (100%)
Pelvis, inflammation, acute				1 (2%)
Renal tubule, hyperplasia	2 (4%)	3 (6%)	6 (12%)	6 (12%)
Transitional epithelium, hyperplasia				1 (2%)
Urinary bladder	(50)	(50)	(50)	(49)
Hemorrhage		1 (2%)		1 (2%)
Infiltration cellular	1 (2%)			
Inflammation, chronic active		2 (4%)	1 (2%)	1 (2%)
Transitional epithelium, hyperplasia		1 (2%)		

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

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

	Chamber Control	12.8 ppm	32 ppm	80 ppm
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Moribund	19	21	23	27
Natural deaths	1	1	1	2
Survivors				
Terminal sacrifice	29	28	26	21
Pregnant	1			
Animals examined microscopically	49	50	50	50
Alimentary System				
Esophagus	(49)	(50)	(50)	(50)
Squamous cell papilloma				1 (2%)
Intestine large, colon	(49)	(49)	(50)	(49)
Intestine large, cecum	(48)	(49)	(50)	(49)
Intestine small, duodenum	(49)	(49)	(50)	(50)
Intestine small, jejunum	(49)	(49)	(49)	(48)
Intestine small, ileum	(48)	(49)	(49)	(48)
Liver	(49)	(50)	(50)	(50)
Hemangiosarcoma				1 (2%)
Histiocytic sarcoma				1 (2%)
Mesentery	(5)	(6)	(8)	(11)
Lipoma			1 (13%)	
Oral mucosa	(1)	(1)	(2)	(1)
Buccal, squamous cell papilloma				1 (100%)
Gingival, squamous cell papilloma			1 (50%)	
Pharyngeal, squamous cell carcinoma			1 (50%)	
Pharyngeal, squamous cell papilloma	1 (100%)	1 (100%)		
Pancreas	(49)	(50)	(50)	(50)
Salivary glands	(49)	(50)	(50)	(50)
Stomach, forestomach	(49)	(50)	(50)	(50)
Stomach, glandular	(49)	(50)	(50)	(50)
Tongue	(1)	(4)	(5)	(12)
Squamous cell carcinoma		1 (25%)	2 (40%)	4 (33%)
Squamous cell papilloma		2 (50%)	1 (20%)	6 (50%)
Squamous cell papilloma, multiple				1 (8%)
Cardiovascular System				
Heart	(49)	(50)	(50)	(50)
Endocrine System				
Adrenal cortex	(49)	(50)	(50)	(50)
Adenoma	2 (4%)	4 (8%)	2 (4%)	1 (2%)
Adrenal medulla	(49)	(50)	(50)	(50)
Pheochromocytoma complex		1 (2%)		
Pheochromocytoma benign	3 (6%)	3 (6%)	3 (6%)	2 (4%)
Bilateral, pheochromocytoma benign				1 (2%)

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Inhalation Study of Chloroprene

	Chamber Control	12.8 ppm	32 ppm	80 ppm
Endocrine System (continued)				
Islets, pancreatic	(49)	(50)	(50)	(50)
Adenoma	2 (4%)	1 (2%)	1 (2%)	
Carcinoma	1 (2%)	1 (2%)	1 (2%)	
Pituitary gland	(48)	(50)	(50)	(50)
Pars distalis, adenoma	36 (75%)	44 (88%)	44 (88%)	36 (72%)
Thyroid gland	(49)	(50)	(50)	(50)
Bilateral, C-cell, adenoma		1 (2%)		
C-cell, adenoma	7 (14%)	2 (4%)	5 (10%)	5 (10%)
C-cell, carcinoma	1 (2%)	2 (4%)	1 (2%)	
Follicular cell, adenoma	1 (2%)	1 (2%)		3 (6%)
Follicular cell, carcinoma			1 (2%)	2 (4%)
General Body System				
None				
Genital System				
Clitoral gland	(46)	(48)	(46)	(46)
Adenoma	2 (4%)	5 (10%)	2 (4%)	2 (4%)
Carcinoma		5 (10%)	4 (9%)	2 (4%)
Bilateral, adenoma		1 (2%)		
Bilateral, carcinoma		1 (2%)		
Ovary	(49)	(50)	(50)	(50)
Uterus	(49)	(50)	(50)	(50)
Deciduoma malignant			1 (2%)	
Granular cell tumor malignant	1 (2%)			
Leiomyosarcoma	1 (2%)			
Polyp stromal	6 (12%)	4 (8%)	5 (10%)	8 (16%)
Polyp stromal, multiple			1 (2%)	2 (4%)
Schwannoma malignant	1 (2%)			
Vagina	(1)			
Schwannoma malignant, metastatic, uterus	1 (100%)			
Hematopoietic System				
Bone marrow	(49)	(50)	(50)	(50)
Lymph node	(1)	(4)	(4)	(5)
Lymph node, bronchial	(35)	(34)	(30)	(36)
Lymph node, mandibular	(44)	(48)	(37)	(50)
Lymph node, mesenteric	(49)	(50)	(49)	(49)
Lymph node, mediastinal	(44)	(43)	(43)	(45)
Spleen	(48)	(50)	(50)	(50)
Histiocytic sarcoma				1 (2%)
Thymus	(43)	(41)	(48)	(46)
Thymoma malignant			1 (2%)	
Integumentary System				
Mammary gland	(49)	(50)	(50)	(50)
Carcinoma	4 (8%)	5 (10%)	4 (8%)	4 (8%)
Fibroadenoma	19 (39%)	20 (40%)	21 (42%)	17 (34%)
Fibroadenoma, multiple	5 (10%)	12 (24%)	15 (30%)	19 (38%)

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Inhalation Study of Chloroprene

	Chamber Control	12.8 ppm	32 ppm	80 ppm
Integumentary System (continued)				
Skin	(49)	(50)	(50)	(50)
Basal cell carcinoma			1 (2%)	
Keratoacanthoma				1 (2%)
Subcutaneous tissue, fibroma			1 (2%)	
Subcutaneous tissue, fibrosarcoma	2 (4%)		1 (2%)	
Subcutaneous tissue, lipoma				1 (2%)
Subcutaneous tissue, melanoma malignant	1 (2%)		1 (2%)	
Musculoskeletal System				
Bone	(49)	(50)	(50)	(50)
Chordoma			1 (2%)	
Hemangiosarcoma				1 (2%)
Osteosarcoma	1 (2%)			
Nervous System				
Brain	(49)	(50)	(50)	(50)
Astrocytoma benign	1 (2%)			
Glioma benign		1 (2%)		
Respiratory System				
Larynx	(49)	(50)	(50)	(50)
Lung	(49)	(50)	(50)	(50)
Alveolar/bronchiolar adenoma	1 (2%)			2 (4%)
Alveolar/bronchiolar adenoma, multiple				1 (2%)
Carcinoma, metastatic, thyroid gland			1 (2%)	
Chordoma, metastatic, bone			1 (2%)	
Hemangiosarcoma, metastatic, liver				1 (2%)
Nose	(49)	(50)	(50)	(50)
Trachea	(49)	(50)	(50)	(50)
Special Senses System				
None				
Urinary System				
Kidney	(49)	(50)	(50)	(50)
Mesenchymal tumor NOS				1 (2%)
Renal tubule, adenoma				2 (4%)
Transitional epithelium, carcinoma		1 (2%)		
Urinary bladder	(49)	(50)	(50)	(50)
Leiomyosarcoma			1 (2%)	
Schwannoma malignant, metastatic, uterus	1 (2%)			
Transitional epithelium, carcinoma				2 (4%)

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Inhalation Study of Chloroprene

	Chamber Control	12.8 ppm	32 ppm	80 ppm
Systemic Lesions				
Multiple organs[b]	(49)	(50)	(50)	(50)
Histiocytic sarcoma				1 (2%)
Leukemia mononuclear	18 (37%)	18 (36%)	20 (40%)	26 (52%)
Mesothelioma benign	1 (2%)			
Mesothelioma NOS	1 (2%)			
Neoplasm Summary				
Total animals with primary neoplasms[c]	47	50	50	49
Total primary neoplasms	119	137	144	156
Total animals with benign neoplasms	44	48	49	46
Total benign neoplasms	87	102	103	112
Total animals with malignant neoplasms	26	26	31	37
Total malignant neoplasms	31	35	41	43
Total animals with metastatic neoplasms	1		2	1
Total metastatic neoplasms	2		2	1
Total animals with uncertain neoplasms—benign or malignant	1			1
Total uncertain neoplasms	1			1

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

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

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

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

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

Number of Days on Study	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	
Carcass ID Number	1 0 9	1 1 1	1 1 5	1 1 6	1 1 7	1 1 8	1 2 0	1 2 6	1 3 2	1 3 3	1 3 4	1 4 3	1 4 9	1 0 4	1 0 7	1 1 3	1 1 4	1 1 9	1 2 3	1 2 4	1 2 7	1 2 9	1 4 5	1 4 7	1 4 8	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Mesentery										+																5
Oral mucosa																										1
Pharyngeal, squamous cell papilloma																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Tongue			+																							1
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma															X											2
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma benign									X											X			X			3
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma																			X							2
Carcinoma															X											1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pituitary gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pars distalis, adenoma	X		X		X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X		X	X	X	36
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
C-cell, adenoma		X										X														7
C-cell, carcinoma														X												1
Follicular cell, adenoma											X															1
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	46
Adenoma																										2
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Granular cell tumor malignant										X																1
Leiomyosarcoma									X																	1
Polyp stromal						X				X	X	X		X												6
Schwannoma malignant																										1
Vagina																										1
Schwannoma malignant, metastatic, uterus																										1

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

Number of Days on Study	3 6 6	4 3 2	5 5 3	5 7 3	5 8 1	5 8 9	6 0 0	6 0 1	6 2 2	6 4 4	6 5 1	6 5 1	6 6 1	6 6 5	6 6 5	6 7 0	6 8 7	6 9 7	7 0 2	7 2 1	7 3 3	7 3 3	7 3 3	7 3 4
Carcass ID Number	1 0 3	1 3 8	1 3 0	1 2 2	1 3 7	1 3 1	1 2 5	1 1 0	1 0 8	1 0 2	1 1 2	1 5 0	1 4 0	1 3 6	1 4 4	1 4 6	1 4 1	1 4 0	1 6 6	1 2 8	1 0 1	1 2 1	1 3 9	1 4 2	1 0 5
Hematopoietic System																								
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node										+														
Lymph node, bronchial	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+
Lymph node, mandibular	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+
Thymus	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+
Integumentary System																								
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma													X			X								X
Fibroadenoma				X		X				X		X			X				X			X		
Fibroadenoma, multiple	X																							
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibrosarcoma																								X
Subcutaneous tissue, melanoma malignant																				X				
Musculoskeletal System																								
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma								X																
Nervous System																								
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma benign																						X		
Spinal cord																								
Respiratory System																								
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																								
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																								
Eye																		+						
Urinary System																								
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Schwannoma malignant, metastatic, uterus						X																		
Systemic Lesions																								
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear	X	X		X	X		X	X	X	X				X						X		X		X
Mesothelioma benign							X																	
Mesothelioma NOS							X																	

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

Number of Days on Study	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	
Carcass ID Number	1 0 9	1 1 1	1 1 5	1 1 6	1 1 7	1 1 8	1 2 0	1 2 6	1 3 2	1 3 3	1 3 4	1 4 3	1 4 9	1 0 4	1 0 7	1 1 3	1 1 4	1 1 9	1 2 3	1 2 4	1 2 7	1 2 9	1 4 5	1 4 7	1 4 8	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node																										1
Lymph node, bronchial	+	M	M	+	M	+	+	+	+	+	M	M	M	M	M	M	+	+	+	+	M	+	+	+	+	35
Lymph node, mandibular	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	M	+	44
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mediastinal	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	44
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Thymus	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	43
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma																					X					4
Fibroadenoma					X	X		X	X	X		X			X	X		X	X			X	X			19
Fibroadenoma, multiple	X												X	X										X		5
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Subcutaneous tissue, fibrosarcoma																									X	2
Subcutaneous tissue, melanoma malignant																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Osteosarcoma																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Astrocytoma benign																										1
Spinal cord														+												1
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar adenoma																								X		1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Special Senses System																										
Eye																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Schwannoma malignant, metastatic, uterus																										1
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia mononuclear			X				X	X				X			X								X			18
Mesothelioma benign																										1
Mesothelioma NOS																										1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Chloroprene: 12.8 ppm

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

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Chloroprene: 12.8 ppm

Number of Days on Study	7 3 3	7 3 3	7 3 3	7 3 3	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	
Carcass ID Number	3 4 1	3 4 3	3 4 4	3 5 0	3 0 3	3 1 1	3 1 5	3 1 7	3 1 9	3 2 0	3 2 6	3 2 8	3 3 3	3 3 4	3 3 5	3 4 9	3 0 4	3 1 4	3 1 6	3 2 1	3 2 5	3 2 7	3 2 9	3 3 0	3 4 5	Total Tissues/ Tumors
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery									+			+							+						6
Oral mucosa																									1
Pharyngeal, squamous cell papilloma																									1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tongue			+																						4
Squamous cell carcinoma																									1
Squamous cell papilloma																									2
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma			X												X										4
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma complex																									1
Pheochromocytoma benign																						X			3
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																									1
Carcinoma																									1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	44
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, C-cell, adenoma			X																						1
C-cell, adenoma																				X				X	2
C-cell, carcinoma					X														X						2
Follicular cell, adenoma																									1
General Body System																									
None																									
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma					X						X														5
Carcinoma																		X							5
Bilateral, adenoma												X													1
Bilateral, carcinoma													X												1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp stromal																		X				X			4

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Chloroprene: 12.8 ppm

Number of Days on Study	3 0 2	3 5 2	4 8 5	5 2 5	5 6 5	5 7 6	6 0 8	6 3 0	6 5 7	6 6 5	6 6 7	6 7 1	6 7 9	6 8 1	6 8 1	6 9 1	6 9 4	7 0 7	7 0 7	7 2 1	7 2 1	7 2 6	7 3 3	7 3 3	7 3 3
Carcass ID Number	3 1 8	3 3 1	3 4 7	3 0 1	3 1 3	3 2 4	3 4 8	3 1 0	3 3 9	3 0 5	3 0 9	3 0 2	3 3 2	3 0 8	3 3 8	3 3 7	3 0 7	3 2 2	4 2 2	3 1 2	4 4 0	4 4 6	3 0 6	2 3 3	3 3 6
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node							+															+			+
Lymph node, bronchial	+	M	+	+	M	M	+	+	+	M	M	M	+	M	+	+	+	M	M	+	+	M	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal	M	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	M
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma												X						X		X					
Fibroadenoma	X			X					X		X			X	X		X						X		X
Fibroadenoma, multiple																		X		X					
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Glioma benign																									
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye																						+			
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Transitional epithelium, carcinoma																							X		
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear			X				X	X		X		X	X		X	X	X	X	X			X			X

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Chloroprene: 12.8 ppm

Number of Days on Study	7 3 3	7 3 3	7 3 3	7 3 3	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	
Carcass ID Number	3 4 1	3 4 3	3 4 4	3 5 0	3 0 3	3 1 1	3 1 5	3 1 7	3 1 9	3 2 0	3 2 6	3 2 8	3 3 3	3 3 4	3 3 5	3 4 9	3 0 4	3 1 4	3 1 6	3 2 1	3 2 5	3 2 7	3 2 9	3 3 0	3 4 5	Total Tissues/ Tumors
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node										+															4
Lymph node, bronchial	M	M	+	+	+	+	+	+	+	+	+	M	+	M	+	M	+	M	+	+	+	+	+	+	34
Lymph node, mandibular	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mediastinal	+	M	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	43
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	M	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	M	+	+	M	41
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma									X													X			5
Fibroadenoma			X		X		X	X				X			X	X				X			X	X	X	20
Fibroadenoma, multiple	X	X				X				X	X			X			X		X		X	X				12
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Glioma benign													X												1
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																									
Eye																									1
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Transitional epithelium, carcinoma																									1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear					X				X	X	X			X											18

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Chloroprene: 32 ppm

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

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Chloroprene: 32 ppm

Number of Days on Study	7 3 3	7 3 3	7 3 3	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	
Carcass ID Number	5 1 8	5 3 4	5 3 6	5 0 2	5 1 1	5 1 9	5 2 0	5 2 8	5 3 3	5 4 0	5 4 2	5 4 3	5 4 8	5 5 0	5 0 4	5 0 6	5 1 3	5 2 1	5 2 9	5 3 2	5 3 5	5 3 7	5 4 1	5 4 5	5 4 9	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery				+													+				+					8
Lipoma																										1
Oral mucosa															+								+			2
Gingival, squamous cell papilloma																							X			1
Pharyngeal, squamous cell carcinoma															X											1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tongue	+	+																				+				5
Squamous cell carcinoma		X																								2
Squamous cell papilloma																						X				1
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma						X				X																2
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign					X				X																	3
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma	X																									1
Carcinoma																										1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma	X	X	X	X	X	X	X	X	X		X	X	X		X	X	X	X	X	X	X	X	X	X	X	44
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma			X															X							X	5
C-cell, carcinoma																										1
Follicular cell, carcinoma																	X									1
General Body System																										
None																										
Genital System																										
Clitoral gland	M	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	46
Adenoma														X												2
Carcinoma												X											X			4
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Deciduoma malignant																										1
Polyp stromal				X	X														X							5
Polyp stromal, multiple																X										1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Chloroprene: 32 ppm

Number of Days on Study	4 5 0	4 7 0	5 3 4	5 4 0	5 4 4	5 6 7	5 8 5	5 8 8	5 9 0	5 9 7	5 9 7	6 0 1	6 0 4	6 0 8	6 1 8	6 3 4	6 4 6	6 5 1	6 5 1	6 7 9	6 9 1	6 9 3	6 9 3	7 2 1	7 3 3
Carcass ID Number	5 2 5	5 1 2	5 3 0	5 2 7	5 2 6	5 0 7	5 0 5	5 1 4	5 4 4	5 0 3	5 1 7	5 2 3	5 4 7	5 4 6	5 1 6	5 3 9	5 0 8	5 2 2	5 3 1	5 3 8	5 1 0	5 0 9	5 2 4	5 1 5	5 0 1
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node				+								+	+												
Lymph node, bronchial	M	+	+	M	M	+	M	+	M	M	+	+	M	+	+	M	+	M	M	+	+	M	+	M	+
Lymph node, mandibular	+	M	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	M	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Thymoma malignant							X																		
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																X						X			
Fibroadenoma		X		X	X			X	X		X				X	X	X				X			X	X
Fibroadenoma, multiple										X								X	X			X	X		
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell carcinoma																									
Subcutaneous tissue, fibroma																									X
Subcutaneous tissue, fibrosarcoma																									
Subcutaneous tissue, melanoma malignant		X																							
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Chordoma																									
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, thyroid gland																									
Chordoma, metastatic, bone																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye				+			+																	+	
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma											X														
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear				X		X	X			X			X		X			X		X	X	X	X	X	

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Chloroprene: 32 ppm

Number of Days on Study	7 3 3	7 3 3	7 3 3	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	
Carcass ID Number	5 1 8	5 3 4	5 3 6	5 0 2	5 1 1	5 1 9	5 2 0	5 2 8	5 3 3	5 4 0	5 4 2	5 4 3	5 4 8	5 5 0	5 0 4	5 0 6	5 1 3	5 2 1	5 2 9	5 3 2	5 3 5	5 3 7	5 4 1	5 4 5	5 4 9	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node																	+									4
Lymph node, bronchial	+	+	+	+	M	+	+	+	+	M	+	+	M	+	M	+	+	+	M	+	+	M	+	M	M	30
Lymph node, mandibular	M	+	+	M	M	+	M	+	M	M	+	+	M	M	+	+	+	+	+	M	+	+	+	+	+	37
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mediastinal	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	43
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	48
Thymoma malignant																										1
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																	X						X			4
Fibroadenoma			X	X								X		X			X	X				X	X	X		21
Fibroadenoma, multiple	X	X			X	X		X							X	X			X		X				X	15
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basal cell carcinoma												X														1
Subcutaneous tissue, fibroma																										1
Subcutaneous tissue, fibrosarcoma				X																						1
Subcutaneous tissue, melanoma malignant																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Chordoma																								X		1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, thyroid gland																	X									1
Chordoma, metastatic, bone																								X		1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye																										3
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyosarcoma																										1
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X			X				X				X	X				X				X	X				20

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Chloroprene: 80 ppm

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

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Chloroprene: 80 ppm

Number of Days on Study	7 1 6	7 2 0	7 2 1	7 2 9	7 3 3	7 3 3	7 3 3	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	
Carcass ID Number	7 4 5	7 1 0	7 1 9	7 2 7	7 2 0	7 3 2	7 4 0	7 0 2	7 0 4	7 0 9	7 1 3	7 1 7	7 2 2	7 2 3	7 2 9	7 3 3	7 4 1	7 4 8	7 4 9	7 0 3	7 0 6	7 1 2	7 3 6	7 3 8	7 4 2	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma																		X								1
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, ileum	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Histiocytic sarcoma																										1
Mesentery										+									+		+		+			11
Oral mucosa														+												1
Buccal, squamous cell papilloma														X												1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tongue			+	+			+		+		+	+		+				+								12
Squamous cell carcinoma							X																			4
Squamous cell papilloma				X					X			X		X				X								6
Squamous cell papilloma, multiple											X															1
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																				X						1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign				X												X										2
Bilateral, pheochromocytoma benign									X																	1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	48
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma	X	X	X	X	X		X		X	X		X		X	X	X	X	X		X	X		X	X		36
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma							X								X			X								5
Follicular cell, adenoma	X																								X	3
Follicular cell, carcinoma																										2
General Body System																										
None																										
Genital System																										
Clitoral gland	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	46
Adenoma																										2
Carcinoma																										2
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp stromal	X	X									X											X	X			8
Polyp stromal, multiple																										2

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Chloroprene: 80 ppm

Number of Days on Study	4 3 3	4 6 3	5 2 5	5 5 3	5 7 2	5 7 6	5 8 9	5 9 1	6 0 9	6 1 1	6 1 3	6 1 7	6 2 4	6 2 4	6 3 7	6 4 8	6 4 9	6 6 0	6 6 6	6 6 7	6 7 1	7 7 3	7 7 9	7 0 5	7 0 5
Carcass ID Number	7 3 5	7 1 8	7 2 6	7 1 6	7 0 5	7 3 7	7 0 7	7 3 1	7 2 1	7 2 4	7 4 4	7 3 4	7 0 8	7 1 1	7 0 1	7 2 5	7 1 4	7 4 6	7 4 3	7 3 9	7 3 0	7 1 5	7 5 0	7 2 8	7 4 7
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node			+		+																				
Lymph node, bronchial	+	+	+	+	+	+	+	+	+	+	+	+	M	M	M	M	+	M	+	+	M	M	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																				X					
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma									X						X										
Fibroadenoma	X					X				X	X	X						X			X	X	X		X
Fibroadenoma, multiple									X				X		X					X				X	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma																									
Subcutaneous tissue, lipoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma											X			X											
Alveolar/bronchiolar adenoma, multiple																									
Hemangiosarcoma, metastatic, liver																X									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye													+												
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesenchymal tumor NOS																									
Renal tubule, adenoma									X		X														
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Transitional epithelium, carcinoma								X						X											
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																				X					
Leukemia mononuclear			X				X				X						X		X		X			X	

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Chloroprene: 80 ppm

Number of Days on Study	7 1 6	7 2 0	7 2 1	7 2 9	7 3 3	7 3 3	7 3 3	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	
Carcass ID Number	7 4 5	7 1 0	7 1 9	7 2 7	7 2 0	7 3 2	7 4 0	7 0 2	7 0 4	7 0 9	7 1 3	7 1 7	7 2 2	7 2 3	7 2 9	7 3 3	7 4 1	7 4 8	7 4 9	7 0 3	7 0 6	7 1 2	7 3 6	7 3 8	7 4 2	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node														+				+						+		5
Lymph node, bronchial	M	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	M	M	+	M	+	+	M	+	36
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mediastinal	M	+	M	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Thymus	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	46
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma												X												X		4
Fibroadenoma		X									X			X				X		X		X		X		17
Fibroadenoma, multiple	X		X	X			X	X	X			X	X		X	X	X				X		X		X	19
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Keratoacanthoma								X																		1
Subcutaneous tissue, lipoma					X																					1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma			X																							1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																										2
Alveolar/bronchiolar adenoma, multiple											X															1
Hemangiosarcoma, metastatic, liver																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye				+																						2
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesenchymal tumor NOS																		X								1
Renal tubule, adenoma																										2
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Transitional epithelium, carcinoma																										2
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Leukemia mononuclear		X	X	X	X	X		X		X	X	X		X	X	X	X	X		X	X	X	X	X		26

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

	Chamber Control	12.8 ppm	32 ppm	80 ppm
Adrenal Cortex: Adenoma				
Overall rate[a]	2/49 (4%)	4/50 (8%)	2/50 (4%)	1/50 (2%)
Adjusted rate[b]	6.5%	12.1%	7.7%	4.8%
Terminal rate[c]	1/29 (3%)	2/28 (7%)	2/26 (8%)	1/21 (5%)
First incidence (days)	697	630	733 (T)	733 (T)
Life table test[d]	P = 0.348N	P = 0.347	P = 0.649	P = 0.594N
Logistic regression test[d]	P = 0.287N	P = 0.349	P = 0.659	P = 0.549N
Cochran-Armitage test[d]	P = 0.240N			
Fisher exact test[d]		P = 0.349	P = 0.684N	P = 0.492N
Adrenal Medulla: Benign Pheochromocytoma				
Overall rate	3/49 (6%)	3/50 (6%)	3/50 (6%)	3/50 (6%)
Adjusted rate	10.3%	9.4%	10.9%	13.6%
Terminal rate	3/29 (10%)	1/28 (4%)	2/26 (8%)	2/21 (10%)
First incidence (days)	733 (T)	681	693	729
Life table test	P = 0.434	P = 0.659	P = 0.613	P = 0.511
Logistic regression test	P = 0.494	P = 0.641N	P = 0.614	P = 0.543
Cochran-Armitage test	P = 0.586N			
Fisher exact test		P = 0.651N	P = 0.651N	P = 0.651N
Adrenal Medulla: Benign or Complex Pheochromocytoma				
Overall rate	3/49 (6%)	4/50 (8%)	3/50 (6%)	3/50 (6%)
Adjusted rate	10.3%	12.8%	10.9%	13.6%
Terminal rate	3/29 (10%)	2/28 (7%)	2/26 (8%)	2/21 (10%)
First incidence (days)	733 (T)	681	693	729
Life table test	P = 0.494	P = 0.495	P = 0.613	P = 0.511
Logistic regression test	P = 0.555	P = 0.528	P = 0.614	P = 0.543
Cochran-Armitage test	P = 0.513N			
Fisher exact test		P = 0.511	P = 0.651N	P = 0.651N
Clitoral Gland: Adenoma				
Overall rate	2/46 (4%)	6/48 (13%)	2/46 (4%)	2/46 (4%)
Adjusted rate	6.8%	18.1%	7.0%	5.3%
Terminal rate	1/28 (4%)	3/27 (11%)	1/22 (5%)	0/19 (0%)
First incidence (days)	721	525	601	609
Life table test	P = 0.433N	P = 0.143	P = 0.632	P = 0.623
Logistic regression test	P = 0.324N	P = 0.145	P = 0.667	P = 0.693N
Cochran-Armitage test	P = 0.321N			
Fisher exact test		P = 0.148	P = 0.692N	P = 0.692N
Clitoral Gland: Carcinoma				
Overall rate	0/46 (0%)	6/48 (13%)	4/46 (9%)	2/46 (4%)
Adjusted rate	0.0%	18.1%	13.3%	5.1%
Terminal rate	0/28 (0%)	3/27 (11%)	2/22 (9%)	0/19 (0%)
First incidence (days)	—[e]	630	544	572
Life table test	P = 0.508	P = 0.021	P = 0.049	P = 0.225
Logistic regression test	P = 0.555N	P = 0.019	P = 0.074	P = 0.290
Cochran-Armitage test	P = 0.566N			
Fisher exact test		P = 0.015	P = 0.058	P = 0.247

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

	Chamber Control	12.8 ppm	32 ppm	80 ppm
Clitoral Gland: Adenoma or Carcinoma				
Overall rate	2/46 (4%)	12/48 (25%)	5/46 (11%)	3/46 (7%)
Adjusted rate	6.8%	34.0%	17.7%	7.3%
Terminal rate	1/28 (4%)	6/27 (22%)	3/22 (14%)	0/19 (0%)
First incidence (days)	721	525	544	572
Life table test	P = 0.364N	P = 0.007	P = 0.159	P = 0.432
Logistic regression test	P = 0.220N	P = 0.005	P = 0.202	P = 0.545
Cochran-Armitage test	P = 0.217N			
Fisher exact test		P = 0.005	P = 0.217	P = 0.500
Kidney (Renal Tubule): Adenoma (Single and Step Sections)				
Overall rate	0/49 (0%)	0/50 (0%)	0/50 (0%)	4/50 (8%)
Adjusted rate	0.0%	0.0%	0.0%	9.7%
Terminal rate	0/29 (0%)	0/28 (0%)	0/26 (0%)	1/21 (5%)
First incidence (days)	—	—[f]	—	609
Life table test	P = 0.002	—	—	P = 0.053
Logistic regression test	P = 0.002	—	—	P = 0.070
Cochran-Armitage test	P = 0.002			
Fisher exact test		—	—	P = 0.061
Kidney (Renal Tubule): Adenoma or Carcinoma (Single and Step Sections)				
Overall rate	0/49 (0%)	0/50 (0%)	0/50 (0%)	4/50 (8%)
Adjusted rate	0.0%	0.0%	0.0%	9.7%
Terminal rate	0/29 (0%)	0/28 (0%)	0/26 (0%)	1/21 (5%)
First incidence (days)	—	—	—	609
Life table test	P = 0.002	—	—	P = 0.053
Logistic regression test	P = 0.002	—	—	P = 0.070
Cochran-Armitage test	P = 0.002			
Fisher exact test		—	—	P = 0.061
Lung: Alveolar/bronchiolar Adenoma				
Overall rate	1/49 (2%)	0/50 (0%)	0/50 (0%)	3/50 (6%)
Adjusted rate	3.4%	0.0%	0.0%	9.6%
Terminal rate	1/29 (3%)	0/28 (0%)	0/26 (0%)	1/21 (5%)
First incidence (days)	733 (T)	—	—	613
Life table test	P = 0.046	P = 0.507N	P = 0.522N	P = 0.246
Logistic regression test	P = 0.066	P = 0.507N	P = 0.522N	P = 0.314
Cochran-Armitage test	P = 0.066			
Fisher exact test		P = 0.495N	P = 0.495N	P = 0.316
Mammary Gland: Fibroadenoma				
Overall rate	24/49 (49%)	32/50 (64%)	36/50 (72%)	36/50 (72%)
Adjusted rate	65.4%	86.0%	85.3%	89.7%
Terminal rate	17/29 (59%)	23/28 (82%)	20/26 (77%)	17/21 (81%)
First incidence (days)	366	302	470	433
Life table test	P < 0.001	P = 0.087	P = 0.009	P = 0.002
Logistic regression test	P = 0.005	P = 0.130	P = 0.011	P = 0.009
Cochran-Armitage test	P = 0.025			
Fisher exact test		P = 0.096	P = 0.016	P = 0.016

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

	Chamber Control	12.8 ppm	32 ppm	80 ppm
Mammary Gland: Carcinoma				
Overall rate	4/49 (8%)	5/50 (10%)	4/50 (8%)	4/50 (8%)
Adjusted rate	12.1%	15.1%	13.4%	14.1%
Terminal rate	2/29 (7%)	2/28 (7%)	2/26 (8%)	2/21 (10%)
First incidence (days)	661	671	634	609
Life table test	P = 0.486	P = 0.527	P = 0.576	P = 0.527
Logistic regression test	P = 0.546N	P = 0.518	P = 0.628	P = 0.643
Cochran-Armitage test	P = 0.510N			
Fisher exact test		P = 0.513	P = 0.631N	P = 0.631N
Mammary Gland: Fibroadenoma or Carcinoma				
Overall rate	28/49 (57%)	34/50 (68%)	36/50 (72%)	36/50 (72%)
Adjusted rate	72.7%	89.1%	85.3%	89.7%
Terminal rate	19/29 (66%)	24/28 (86%)	20/26 (77%)	17/21 (81%)
First incidence (days)	366	302	470	433
Life table test	P = 0.006	P = 0.177	P = 0.045	P = 0.011
Logistic regression test	P = 0.039	P = 0.235	P = 0.068	P = 0.059
Cochran-Armitage test	P = 0.115			
Fisher exact test		P = 0.182	P = 0.091	P = 0.091
Oral Cavity (Oral Mucosa, Tongue, Pharynx, Gingiva): Squamous Cell Papilloma				
Overall rate	1/49 (2%)	2/50 (4%)	2/50 (4%)	7/50 (14%)
Adjusted rate	3.0%	6.2%	7.7%	29.5%
Terminal rate	0/29 (0%)	1/28 (4%)	2/26 (8%)	5/21 (24%)
First incidence (days)	687	681	733 (T)	660
Life table test	P = 0.002	P = 0.516	P = 0.464	P = 0.013
Logistic regression test	P = 0.003	P = 0.508	P = 0.469	P = 0.020
Cochran-Armitage test	P = 0.007			
Fisher exact test		P = 0.508	P = 0.508	P = 0.032
Oral Cavity (Oral Mucosa, Tongue, Pharynx, Gingiva): Squamous Cell Carcinoma				
Overall rate	0/49 (0%)	1/50 (2%)	3/50 (6%)	4/50 (8%)
Adjusted rate	0.0%	3.2%	9.8%	14.8%
Terminal rate	0/29 (0%)	0/28 (0%)	2/26 (8%)	1/21 (5%)
First incidence (days)	—	721	588	671
Life table test	P = 0.017	P = 0.507	P = 0.109	P = 0.047
Logistic regression test	P = 0.028	P = 0.510	P = 0.121	P = 0.055
Cochran-Armitage test	P = 0.034			
Fisher exact test		P = 0.505	P = 0.125	P = 0.061
Oral Cavity (Oral Mucosa, Tongue, Pharynx, Gingiva): Squamous Cell Papilloma or Squamous Cell Carcinoma				
Overall rate	1/49 (2%)	3/50 (6%)	5/50 (10%)	11/50 (22%)
Adjusted rate	3.0%	9.2%	17.4%	40.8%
Terminal rate	0/29 (0%)	1/28 (4%)	4/26 (15%)	6/21 (29%)
First incidence (days)	687	681	588	660
Life table test	P < 0.001	P = 0.324	P = 0.086	P < 0.001
Logistic regression test	P < 0.001	P = 0.315	P = 0.093	P = 0.001
Cochran-Armitage test	P < 0.001			
Fisher exact test		P = 0.316	P = 0.107	P = 0.002

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

	Chamber Control	12.8 ppm	32 ppm	80 ppm
Pancreatic Islets: Adenoma or Carcinoma				
Overall rate	3/49 (6%)	2/50 (4%)	2/50 (4%)	0/50 (0%)
Adjusted rate	9.9%	6.1%	6.3%	0.0%
Terminal rate	2/29 (7%)	1/28 (4%)	1/26 (4%)	0/21 (0%)
First incidence (days)	702	679	601	—
Life table test	P = 0.133N	P = 0.491N	P = 0.549N	P = 0.172N
Logistic regression test	P = 0.100N	P = 0.481N	P = 0.516N	P = 0.146N
Cochran-Armitage test	P = 0.090N			
Fisher exact test		P = 0.490N	P = 0.490N	P = 0.117N
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	36/48 (75%)	44/50 (88%)	44/50 (88%)	36/50 (72%)
Adjusted rate	89.8%	97.7%	93.6%	83.3%
Terminal rate	24/28 (86%)	27/28 (96%)	23/26 (88%)	14/21 (67%)
First incidence (days)	553	352	450	463
Life table test	P = 0.198	P = 0.150	P = 0.051	P = 0.171
Logistic regression test	P = 0.193N	P = 0.061	P = 0.043	P = 0.549N
Cochran-Armitage test	P = 0.160N			
Fisher exact test		P = 0.080	P = 0.080	P = 0.458N
Thyroid Gland (C-cell): Adenoma				
Overall rate	7/49 (14%)	3/50 (6%)	5/50 (10%)	5/50 (10%)
Adjusted rate	20.3%	10.7%	16.2%	19.1%
Terminal rate	3/29 (10%)	3/28 (11%)	3/26 (12%)	3/21 (14%)
First incidence (days)	622	733 (T)	590	463
Life table test	P = 0.481	P = 0.162N	P = 0.460N	P = 0.538N
Logistic regression test	P = 0.516N	P = 0.145N	P = 0.391N	P = 0.380N
Cochran-Armitage test	P = 0.485N			
Fisher exact test		P = 0.151N	P = 0.365N	P = 0.365N
Thyroid Gland (C-cell): Adenoma or Carcinoma				
Overall rate	8/49 (16%)	5/50 (10%)	6/50 (12%)	5/50 (10%)
Adjusted rate	23.4%	17.9%	18.4%	19.1%
Terminal rate	4/29 (14%)	5/28 (18%)	3/26 (12%)	3/21 (14%)
First incidence (days)	622	733 (T)	590	463
Life table test	P = 0.493N	P = 0.282N	P = 0.474N	P = 0.440N
Logistic regression test	P = 0.333N	P = 0.249N	P = 0.392N	P = 0.282N
Cochran-Armitage test	P = 0.302N			
Fisher exact test		P = 0.264N	P = 0.371N	P = 0.264N
Thyroid Gland (Follicular Cell): Adenoma				
Overall rate	1/49 (2%)	1/50 (2%)	0/50 (0%)	3/50 (6%)
Adjusted rate	3.4%	3.2%	0.0%	12.0%
Terminal rate	1/29 (3%)	0/28 (0%)	0/26 (0%)	1/21 (5%)
First incidence (days)	733 (T)	721	—	705
Life table test	P = 0.090	P = 0.760	P = 0.522N	P = 0.229
Logistic regression test	P = 0.104	P = 0.753N	P = 0.522N	P = 0.252
Cochran-Armitage test	P = 0.142			
Fisher exact test		P = 0.747N	P = 0.495N	P = 0.316

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

	Chamber Control	12.8 ppm	32 ppm	80 ppm
Thyroid Gland (Follicular Cell): Adenoma or Carcinoma				
Overall rate	1/49 (2%)	1/50 (2%)	1/50 (2%)	5/50 (10%)
Adjusted rate	3.4%	3.2%	3.8%	16.8%
Terminal rate	1/29 (3%)	0/28 (0%)	1/26 (4%)	1/21 (5%)
First incidence (days)	733 (T)	721	733 (T)	617
Life table test	P = 0.010	P = 0.760	P = 0.738	P = 0.072
Logistic regression test	P = 0.017	P = 0.753N	P = 0.738	P = 0.098
Cochran-Armitage test	P = 0.022			
Fisher exact test		P = 0.747N	P = 0.747N	P = 0.107
Tongue: Squamous Cell Papilloma				
Overall rate	0/49 (0%)	2/50 (4%)	1/50 (2%)	7/50 (14%)
Adjusted rate	0.0%	6.2%	3.8%	29.5%
Terminal rate	0/29 (0%)	1/28 (4%)	1/26 (4%)	5/21 (24%)
First incidence (days)	—	681	733 (T)	660
Life table test	P < 0.001	P = 0.248	P = 0.478	P = 0.003
Logistic regression test	P < 0.001	P = 0.244	P = 0.478	P = 0.005
Cochran-Armitage test	P = 0.001			
Fisher exact test		P = 0.253	P = 0.505	P = 0.007
Tongue: Squamous Cell Carcinoma				
Overall rate	0/49 (0%)	1/50 (2%)	2/50 (4%)	4/50 (8%)
Adjusted rate	0.0%	3.2%	6.1%	14.8%
Terminal rate	0/29 (0%)	0/28 (0%)	1/26 (4%)	1/21 (5%)
First incidence (days)	—	721	588	671
Life table test	P = 0.014	P = 0.507	P = 0.225	P = 0.047
Logistic regression test	P = 0.023	P = 0.510	P = 0.248	P = 0.055
Cochran-Armitage test	P = 0.026			
Fisher exact test		P = 0.505	P = 0.253	P = 0.061
Tongue: Squamous Cell Papilloma or Squamous Cell Carcinoma				
Overall rate	0/49 (0%)	3/50 (6%)	3/50 (6%)	11/50 (22%)
Adjusted rate	0.0%	9.2%	9.8%	40.8%
Terminal rate	0/29 (0%)	1/28 (4%)	2/26 (8%)	6/21 (29%)
First incidence (days)	—	681	588	660
Life table test	P < 0.001	P = 0.131	P = 0.109	P < 0.001
Logistic regression test	P < 0.001	P = 0.126	P = 0.121	P < 0.001
Cochran-Armitage test	P < 0.001			
Fisher exact test		P = 0.125	P = 0.125	P < 0.001
Uterus: Stromal Polyp				
Overall rate	6/49 (12%)	4/50 (8%)	6/50 (12%)	10/50 (20%)
Adjusted rate	19.3%	11.9%	20.5%	31.2%
Terminal rate	5/29 (17%)	2/28 (7%)	4/26 (15%)	3/21 (14%)
First incidence (days)	644	565	608	572
Life table test	P = 0.029	P = 0.377N	P = 0.540	P = 0.112
Logistic regression test	P = 0.067	P = 0.352N	P = 0.571	P = 0.199
Cochran-Armitage test	P = 0.079			
Fisher exact test		P = 0.357N	P = 0.606N	P = 0.220

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

	Chamber Control	12.8 ppm	32 ppm	80 ppm
All Organs: Mononuclear Cell Leukemia				
Overall rate	18/49 (37%)	18/50 (36%)	20/50 (40%)	26/50 (52%)
Adjusted rate	43.4%	43.4%	51.4%	83.0%
Terminal rate	8/29 (28%)	6/28 (21%)	8/26 (31%)	16/21 (76%)
First incidence (days)	366	485	540	525
Life table test	P = 0.010	P = 0.541N	P = 0.321	P = 0.020
Logistic regression test	P = 0.044	P = 0.536	P = 0.504	P = 0.088
Cochran-Armitage test	P = 0.046			
Fisher exact test		P = 0.553N	P = 0.449	P = 0.092
All Organs: Benign Neoplasms				
Overall rate	44/49 (90%)	48/50 (96%)	49/50 (98%)	46/50 (92%)
Adjusted rate	95.6%	100.0%	100.0%	95.8%
Terminal rate	27/29 (93%)	28/28 (100%)	26/26 (100%)	19/21 (90%)
First incidence (days)	366	302	450	433
Life table test	P = 0.046	P = 0.326	P = 0.092	P = 0.067
Logistic regression test	P = 0.584	P = 0.184	P = 0.081	P = 0.454
Cochran-Armitage test	P = 0.588N			
Fisher exact test		P = 0.210	P = 0.098	P = 0.487
All Organs: Malignant Neoplasms				
Overall rate	26/49 (53%)	26/50 (52%)	31/50 (62%)	37/50 (74%)
Adjusted rate	60.2%	61.5%	68.2%	89.7%
Terminal rate	13/29 (45%)	12/28 (43%)	12/26 (46%)	17/21 (81%)
First incidence (days)	366	485	470	525
Life table test	P = 0.002	P = 0.539N	P = 0.168	P = 0.008
Logistic regression test	P = 0.020	P = 0.538N	P = 0.322	P = 0.027
Cochran-Armitage test	P = 0.009			
Fisher exact test		P = 0.538N	P = 0.243	P = 0.025
All Organs: Benign or Malignant Neoplasms				
Overall rate	47/49 (96%)	50/50 (100%)	50/50 (100%)	49/50 (98%)
Adjusted rate	95.9%	100.0%	100.0%	98.0%
Terminal rate	27/29 (93%)	28/28 (100%)	26/26 (100%)	20/21 (95%)
First incidence (days)	366	302	450	433
Life table test	P = 0.044	P = 0.396	P = 0.163	P = 0.071
Logistic regression test	P = 0.666	P = 0.246	P = 0.262	P = 0.613
Cochran-Armitage test	P = 0.575			
Fisher exact test		P = 0.242	P = 0.242	P = 0.492

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

TABLE B4a
Historical Incidence of Oral Cavity Neoplasms in Chamber Control Female F344/N Rats[a]

Study	Incidence in Controls		
	Squamous Cell Papilloma	Squamous Cell Carcinoma	Squamous Cell Papilloma or Carcinoma
Historical Incidence at Battelle Pacific Northwest Laboratories			
o-Chlorobenzalmalononitrile	0/50	0/50	0/50
Acetonitrile	1/48	0/48	1/48
2-Chloroacetophenone	0/50	0/50	0/50
l-Epinephrine Hydrochloride	0/50	0/50	0/50
Chloroethane	1/50	0/50	1/50
Hexachlorocyclopentadiene	0/50	1/50	1/50
Ozone	1/50	0/50	1/50
Overall Historical Incidence			
Total	3/653 (0.5%)	5/653 (0.8%)	8/653 (1.2%)
Standard deviation	0.9%	1.7%	1.7%
Range	0%-2%	0%-6%	0%-6%

[a] Data as of 12 May 1995

TABLE B4b
Historical Incidence of Thyroid Gland Follicular Cell Neoplasms in Chamber Control Female F344/N Rats[a]

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Battelle Pacific Northwest Laboratories			
o-Chlorobenzalmalononitrile	0/48	0/48	0/48
Acetonitrile	0/48	1/48	1/48
2-Chloroacetophenone	0/47	2/47	2/47
l-Epinephrine Hydrochloride	0/50	0/50	0/50
Chloroethane	1/49	2/49	3/49
Hexachlorocyclopentadiene	1/50	0/50	1/50
Ozone	0/50	1/50	1/50
Overall Historical Incidence			
Total	2/642 (0.3%)	6/642 (0.9%)	8/642 (1.3%)
Standard deviation	0.8%	1.6%	1.9%
Range	0%-2%	0%-4%	0%-6%

[a] Data as of 12 May 1995

TABLE B4c
Historical Incidence of Alveolar/bronchiolar Adenoma in Chamber Control Female F344/N Rats[a]

Study	Incidence in Controls
Historical Incidence at Battelle Pacific Northwest Laboratories	
o-Chlorobenzalmalononitrile	2/49
Acetonitrile	0/48
2-Chloroacetophenone	1/49
l-Epinephrine Hydrochloride	0/50
Chloroethane	0/50
Hexachlorocyclopentadiene	1/50
Ozone	0/50
Overall Historical Incidence	
Total	7/650 (1.1%)
Standard deviation	1.6%
Range	0%-4%

[a] Data as of 12 May 1995

TABLE B4d
Historical Incidence of Mammary Gland Fibroadenoma in Chamber Control Female F344/N Rats[a]

Study	Incidence in Controls
Historical Incidence at Battelle Pacific Northwest Laboratories	
o-Chlorobenzalmalononitrile	16/50
Acetonitrile	16/48
2-Chloroacetophenone	12/50
l-Epinephrine Hydrochloride	10/50
Chloroethane	11/50
Hexachlorocyclopentadiene	12/50
Ozone	20/50
Overall Historical Incidence	
Total	180/653 (27.6%)
Standard deviation	7.7%
Range	16%-42%

[a] Data as of 12 May 1995

TABLE B4e
Historical Incidence of Renal Tubule Neoplasms in Chamber Control Female F344/N Rats[a]

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Battelle Pacific Northwest Laboratories			
o-Chlorobenzalmalononitrile	0/49	0/49	0/49
Acetonitrile	0/48	0/48	0/48
2-Chloroacetophenone	0/49	0/49	0/49
l-Epinephrine Hydrochloride	0/50	0/50	0/50
Chloroethane	0/50	0/50	0/50
Hexachlorocyclopentadiene	0/50	1/50	1/50
Ozone	1/50	0/50	1/50
Overall Historical Incidence			
Total	1/650 (0.2%)	1/650 (0.2%)	2/650 (0.3%)
Standard deviation	0.6%	0.6%	0.8%
Range	0%-2%	0%-2%	0%-2%

[a] Data as of 12 May 1995

TABLE B4f
Historical Incidence of Urinary Bladder Carcinoma in Chamber Control Female F344/N Rats[a]

Study	Incidence in Controls
Historical Incidence at Battelle Pacific Northwest Laboratories	
o-Chlorobenzalmalononitrile	0/47
Acetonitrile	0/48
2-Chloroacetophenone	0/48
l-Epinephrine Hydrochloride	0/49
Chloroethane	0/49
Hexachlorocyclopentadiene	0/50
Ozone	0/50
Overall Historical Incidence	
Total	0/644

[a] Data as of 12 May 1995

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Inhalation Study of Chloroprene[a]

	Chamber Control	12.8 ppm	32 ppm	80 ppm
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Moribund	19	21	23	27
Natural deaths	1	1	1	2
Survivors				
Terminal sacrifice	29	28	26	21
Pregnant	1			
Animals examined microscopically	49	50	50	50
Alimentary System				
Intestine large, colon	(49)	(49)	(50)	(49)
Parasite metazoan	4 (8%)		6 (12%)	2 (4%)
Intestine large, rectum	(49)	(49)	(50)	(50)
Inflammation, acute		1 (2%)		
Mineralization	2 (4%)			1 (2%)
Parasite metazoan	2 (4%)	5 (10%)	7 (14%)	2 (4%)
Intestine large, cecum	(48)	(49)	(50)	(49)
Inflammation, acute	1 (2%)	1 (2%)		
Parasite metazoan	5 (10%)	4 (8%)	8 (16%)	5 (10%)
Intestine small, jejunum	(49)	(49)	(49)	(48)
Inflammation, chronic active				1 (2%)
Intestine small, ileum	(48)	(49)	(49)	(48)
Parasite metazoan	1 (2%)		1 (2%)	
Liver	(49)	(50)	(50)	(50)
Angiectasis	3 (6%)	7 (14%)	5 (10%)	8 (16%)
Basophilic focus	39 (80%)	43 (86%)	45 (90%)	44 (88%)
Clear cell focus	15 (31%)	16 (32%)	14 (28%)	6 (12%)
Degeneration, cystic				2 (4%)
Degeneration, fatty	5 (10%)	5 (10%)	3 (6%)	3 (6%)
Eosinophilic focus	2 (4%)		1 (2%)	2 (4%)
Hepatodiaphragmatic nodule	4 (8%)	7 (14%)	9 (18%)	9 (18%)
Mixed cell focus	7 (14%)	6 (12%)	6 (12%)	9 (18%)
Necrosis	1 (2%)	1 (2%)		2 (4%)
Bile duct, hyperplasia	9 (18%)	10 (20%)	11 (22%)	16 (32%)
Centrilobular, necrosis	1 (2%)	3 (6%)	5 (10%)	8 (16%)
Mesentery	(5)	(6)	(8)	(11)
Inflammation, chronic active	1 (20%)			1 (9%)
Fat, necrosis	4 (80%)	6 (100%)	7 (88%)	9 (82%)
Pancreas	(49)	(50)	(50)	(50)
Atrophy	18 (37%)	14 (28%)	17 (34%)	9 (18%)
Basophilic focus	1 (2%)	1 (2%)	1 (2%)	3 (6%)
Hyperplasia		2 (4%)	1 (2%)	2 (4%)
Lipomatosis		1 (2%)	2 (4%)	
Metaplasia, hepatocyte			1 (2%)	
Artery, inflammation				1 (2%)
Salivary glands	(49)	(50)	(50)	(50)
Atrophy			1 (2%)	3 (6%)
Basophilic focus			1 (2%)	

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

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Inhalation Study of Chloroprene

	Chamber Control	12.8 ppm	32 ppm	80 ppm
Alimentary System (continued)				
Stomach, forestomach	(49)	(50)	(50)	(50)
Hyperplasia, squamous	1 (2%)		1 (2%)	3 (6%)
Mineralization	1 (2%)			1 (2%)
Necrosis		2 (4%)	3 (6%)	1 (2%)
Ulcer	1 (2%)		1 (2%)	
Stomach, glandular	(49)	(50)	(50)	(50)
Mineralization	1 (2%)	1 (2%)	4 (8%)	3 (6%)
Necrosis			1 (2%)	
Tongue	(1)	(4)	(5)	(12)
Hyperplasia, squamous	1 (100%)	1 (25%)	1 (20%)	1 (8%)
Cardiovascular System				
Heart	(49)	(50)	(50)	(50)
Cardiomyopathy	38 (78%)	38 (76%)	31 (62%)	41 (82%)
Artery, inflammation, chronic	1 (2%)			1 (2%)
Atrium, thrombosis		1 (2%)		
Schwann cell, hyperplasia				1 (2%)
Endocrine System				
Adrenal cortex	(49)	(50)	(50)	(50)
Atrophy		1 (2%)		
Hyperplasia	23 (47%)	22 (44%)	22 (44%)	20 (40%)
Hypertrophy	8 (16%)	10 (20%)	7 (14%)	10 (20%)
Necrosis	2 (4%)		1 (2%)	
Vacuolization cytoplasmic	9 (18%)	5 (10%)	10 (20%)	8 (16%)
Adrenal medulla	(49)	(50)	(50)	(50)
Hyperplasia	7 (14%)	11 (22%)	7 (14%)	10 (20%)
Islets, pancreatic	(49)	(50)	(50)	(50)
Hyperplasia	1 (2%)	1 (2%)	3 (6%)	
Parathyroid gland	(48)	(50)	(50)	(48)
Fibrosis		1 (2%)		
Hyperplasia		2 (4%)		1 (2%)
Pituitary gland	(48)	(50)	(50)	(50)
Pars distalis, hyperplasia	9 (19%)	5 (10%)	3 (6%)	10 (20%)
Thyroid gland	(49)	(50)	(50)	(50)
Fibrosis		1 (2%)		
C-cell, hyperplasia	38 (78%)	38 (76%)	35 (70%)	28 (56%)
Follicular cell, hyperplasia				2 (4%)
General Body System				
None				
Genital System				
Clitoral gland	(46)	(48)	(46)	(46)
Hyperplasia	2 (4%)	1 (2%)	4 (9%)	4 (9%)
Inflammation, chronic active	4 (9%)	4 (8%)	6 (13%)	4 (9%)
Ovary	(49)	(50)	(50)	(50)
Cyst	7 (14%)	6 (12%)	1 (2%)	3 (6%)
Inflammation, granulomatous	2 (4%)	1 (2%)	1 (2%)	
Uterus	(49)	(50)	(50)	(50)
Hydrometra			1 (2%)	
Cervix, hypertrophy		1 (2%)		

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Inhalation Study of Chloroprene

	Chamber Control	12.8 ppm	32 ppm	80 ppm
Hematopoietic System				
Bone marrow	(49)	(50)	(50)	(50)
Atrophy	3 (6%)			1 (2%)
Hyperplasia, histiocytic			2 (4%)	
Lymph node	(1)	(4)	(4)	(5)
Iliac, ectasia			1 (25%)	1 (20%)
Renal, infiltration cellular, plasma cell		1 (25%)		
Lymph node, mandibular	(44)	(48)	(37)	(50)
Hemorrhage		1 (2%)		
Spleen	(48)	(50)	(50)	(50)
Accessory spleen		1 (2%)		1 (2%)
Angiectasis				1 (2%)
Fibrosis	3 (6%)	1 (2%)	3 (6%)	5 (10%)
Hematopoietic cell proliferation	1 (2%)	4 (8%)	4 (8%)	6 (12%)
Hemorrhage	4 (8%)			
Integumentary System				
Mammary gland	(49)	(50)	(50)	(50)
Galactocele	1 (2%)	1 (2%)	2 (4%)	
Skin	(49)	(50)	(50)	(50)
Cyst epithelial inclusion				1 (2%)
Hyperkeratosis	1 (2%)			
Inflammation, acute	1 (2%)			
Inflammation, chronic active	3 (6%)	5 (10%)	2 (4%)	3 (6%)
Musculoskeletal System				
Bone	(49)	(50)	(50)	(50)
Fracture				1 (2%)
Hyperostosis	4 (8%)	5 (10%)	4 (8%)	3 (6%)
Hyperplasia				1 (2%)
Nervous System				
Brain	(49)	(50)	(50)	(50)
Hemorrhage			1 (2%)	1 (2%)
Respiratory System				
Larynx	(49)	(50)	(50)	(50)
Lung	(49)	(50)	(50)	(50)
Congestion, chronic		1 (2%)		
Hemorrhage		1 (2%)		
Inflammation, chronic active	1 (2%)	1 (2%)	1 (2%)	2 (4%)
Alveolar epithelium, hyperplasia	6 (12%)	22 (44%)	22 (44%)	34 (68%)
Artery, mediastinum, inflammation				1 (2%)
Trachea	(49)	(50)	(50)	(50)

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Inhalation Study of Chloroprene

	Chamber Control	12.8 ppm	32 ppm	80 ppm
Respiratory System (continued)				
Nose	(49)	(50)	(50)	(50)
Inflammation, suppurative	1 (2%)	2 (4%)		
Thrombosis		1 (2%)	1 (2%)	3 (6%)
Nasolacrimal duct, hyperplasia, squamous				1 (2%)
Olfactory epithelium, atrophy		1 (2%)	40 (80%)	50 (100%)
Olfactory epithelium, fibrosis				49 (98%)
Olfactory epithelium, hyperplasia, basal cell			17 (34%)	49 (98%)
Olfactory epithelium, hyperplasia, adenomatous				27 (54%)
Olfactory epithelium, inflammation, chronic active			2 (4%)	33 (66%)
Olfactory epithelium, metaplasia		1 (2%)	35 (70%)	50 (100%)
Olfactory epithelium, necrosis			8 (16%)	12 (24%)
Olfactory epithelium, glands, atypia cellular				2 (4%)
Turbinate, fibrosis, focal		1 (2%)	3 (6%)	
Special Senses System				
Eye	(1)	(1)	(3)	(2)
Cataract	1 (100%)		2 (67%)	2 (100%)
Degeneration		1 (100%)		
Retina, atrophy			2 (67%)	2 (100%)
Urinary System				
Kidney	(49)	(50)	(50)	(50)
Hydronephrosis	1 (2%)			
Hyperplasia, oncocytic				1 (2%)
Infarct		1 (2%)		1 (2%)
Mineralization				1 (2%)
Nephropathy	43 (88%)	48 (96%)	49 (98%)	49 (98%)
Artery, inflammation				1 (2%)
Pelvis, inflammation, acute				1 (2%)
Renal tubule, hyperplasia			1 (2%)	4 (8%)
Urinary bladder	(49)	(50)	(50)	(50)
Hemorrhage	1 (2%)			
Transitional epithelium, hyperplasia			1 (2%)	1 (2%)

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

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

	Chamber Control	12.8 ppm	32 ppm	80 ppm
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Moribund	15	16	26	34
Natural deaths	8	7	10	3
Survivors				
Terminal sacrifice	27	27	14	13
Animals examined microscopically	50	50	50	50
Alimentary System				
Gallbladder	(41)	(40)	(37)	(40)
Intestine large, cecum	(48)	(44)	(45)	(48)
Hemangioma		1 (2%)		
Muscularis, leiomyoma	1 (2%)			
Intestine small, jejunum	(46)	(43)	(47)	(49)
Intestine small, ileum	(46)	(45)	(46)	(48)
Liver	(50)	(50)	(50)	(49)
Alveolar/bronchiolar carcinoma, metastatic, lung				1 (2%)
Cholangiocarcinoma			1 (2%)	
Hemangiosarcoma	2 (4%)	5 (10%)	6 (12%)	8 (16%)
Hepatoblastoma		2 (4%)	3 (6%)	1 (2%)
Hepatocellular carcinoma	10 (20%)	18 (36%)	18 (36%)	16 (33%)
Hepatocellular carcinoma, multiple	14 (28%)	10 (20%)	19 (38%)	17 (35%)
Hepatocellular adenoma	8 (16%)	11 (22%)	12 (24%)	11 (22%)
Hepatocellular adenoma, multiple	14 (28%)	5 (10%)	7 (14%)	10 (20%)
Hepatocholangiocarcinoma		1 (2%)		1 (2%)
Histiocytic sarcoma	1 (2%)		1 (2%)	
Sarcoma		1 (2%)		
Mesentery	(2)	(8)	(16)	(11)
Hemangioma			1 (6%)	2 (18%)
Hemangiosarcoma		3 (38%)	13 (81%)	7 (64%)
Hepatocholangiocarcinoma, metastatic, liver		1 (13%)		
Sarcoma, metastatic, liver		1 (13%)		
Oral mucosa				(1)
Gingival, squamous cell carcinoma				1 (100%)
Pancreas	(50)	(48)	(49)	(50)
Hemangiosarcoma		1 (2%)		
Hemangiosarcoma, metastatic, mesentery			1 (2%)	
Hepatocholangiocarcinoma, metastatic, liver		1 (2%)		1 (2%)
Sarcoma, metastatic, liver		1 (2%)		
Stomach, forestomach	(50)	(48)	(49)	(50)
Squamous cell carcinoma				1 (2%)
Squamous cell papilloma	1 (2%)		2 (4%)	4 (8%)
Cardiovascular System				
Heart	(50)	(49)	(50)	(50)
Alveolar/bronchiolar carcinoma, metastatic, lung				2 (4%)
Hemangioma			1 (2%)	
Hepatocholangiocarcinoma, metastatic, liver				1 (2%)

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

	Chamber Control	12.8 ppm	32 ppm	80 ppm
Endocrine System				
Adrenal cortex	(50)	(49)	(50)	(50)
Alveolar/bronchiolar carcinoma, metastatic, lung				2 (4%)
Capsule, adenoma	1 (2%)			
Adrenal medulla	(50)	(49)	(50)	(49)
Pheochromocytoma malignant	1 (2%)			
Pheochromocytoma benign			1 (2%)	1 (2%)
Pituitary gland	(49)	(47)	(47)	(48)
Pars distalis, adenoma	1 (2%)			
Thyroid gland	(50)	(49)	(50)	(50)
Follicular cell, adenoma	1 (2%)	1 (2%)	1 (2%)	1 (2%)
General Body System				
None				
Genital System				
Epididymis	(50)	(49)	(50)	(50)
Hemangiosarcoma, metastatic, mesentery			1 (2%)	
Hepatocholangiocarcinoma, metastatic, liver		1 (2%)		
Histiocytic sarcoma				1 (2%)
Leiomyoma			1 (2%)	
Leiomyosarcoma			1 (2%)	
Preputial gland	(50)	(47)	(47)	(50)
Hemangiosarcoma				2 (4%)
Prostate	(49)	(48)	(48)	(49)
Hemangiosarcoma, metastatic, mesentery			1 (2%)	
Seminal vesicle	(49)	(48)	(49)	(48)
Sarcoma, metastatic, liver		1 (2%)		
Testes	(50)	(49)	(50)	(50)
Hemangiosarcoma		1 (2%)		
Interstitial cell, adenoma	1 (2%)			
Hematopoietic System				
Bone marrow	(50)	(49)	(50)	(50)
Hemangiosarcoma		1 (2%)	2 (4%)	1 (2%)
Histiocytic sarcoma	1 (2%)			
Lymph node		(1)	(2)	(3)
Renal, hemangiosarcoma				1 (33%)
Lymph node, bronchial	(32)	(23)	(33)	(28)
Alveolar/bronchiolar carcinoma, metastatic, lung				4 (14%)
Hepatocholangiocarcinoma, metastatic, liver				1 (4%)
Histiocytic sarcoma			1 (3%)	
Lymph node, mandibular	(32)	(28)	(27)	(34)
Histiocytic sarcoma			1 (4%)	
Lymph node, mesenteric	(47)	(48)	(46)	(48)
Hemangiosarcoma			1 (2%)	
Histiocytic sarcoma	2 (4%)		1 (2%)	
Lymph node, mediastinal	(34)	(38)	(37)	(37)
Alveolar/bronchiolar carcinoma, metastatic, lung				1 (3%)
Hepatocholangiocarcinoma, metastatic, liver		1 (3%)		
Sarcoma, metastatic, liver		1 (3%)		

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

	Chamber Control	12.8 ppm	32 ppm	80 ppm
Hematopoietic System (continued)				
Spleen	(50)	(49)	(50)	(50)
Hemangiosarcoma		2 (4%)	2 (4%)	1 (2%)
Histiocytic sarcoma	1 (2%)		1 (2%)	
Thymus	(34)	(28)	(25)	(34)
Alveolar/bronchiolar carcinoma, metastatic, lung				1 (3%)
Integumentary System				
Skin	(49)	(48)	(50)	(50)
Subcutaneous tissue, hemangiosarcoma	1 (2%)	3 (6%)	1 (2%)	7 (14%)
Subcutaneous tissue, hemangiosarcoma, multiple		1 (2%)		
Subcutaneous tissue, histiocytic sarcoma	1 (2%)		1 (2%)	
Subcutaneous tissue, sarcoma, multiple			1 (2%)	
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Alveolar/bronchiolar carcinoma, metastatic, lung				1 (2%)
Hemangiosarcoma	1 (2%)			
Skeletal muscle				(1)
Hepatocholangiocarcinoma, metastatic, liver				1 (100%)
Nervous System				
None				
Respiratory System				
Larynx	(50)	(47)	(50)	(50)
Lung	(50)	(50)	(50)	(50)
Alveolar/bronchiolar adenoma	8 (16%)	12 (24%)	15 (30%)	15 (30%)
Alveolar/bronchiolar adenoma, multiple		6 (12%)	7 (14%)	13 (26%)
Alveolar/bronchiolar carcinoma	4 (8%)	8 (16%)	13 (26%)	13 (26%)
Alveolar/bronchiolar carcinoma, multiple	2 (4%)	4 (8%)	10 (20%)	15 (30%)
Hemangiosarcoma, metastatic, mesentery				1 (2%)
Hemangiosarcoma, metastatic, skin		1 (2%)		
Hepatoblastoma, metastatic, liver			1 (2%)	1 (2%)
Hepatocellular carcinoma, metastatic, liver	8 (16%)	10 (20%)	5 (10%)	4 (8%)
Hepatocholangiocarcinoma, metastatic, liver		1 (2%)		1 (2%)
Histiocytic sarcoma	1 (2%)			
Sarcoma, metastatic, liver		1 (2%)		
Bronchiole, adenoma			1 (2%)	
Mediastinum, alveolar/bronchiolar carcinoma, metastatic, lung				4 (8%)
Mediastinum, hepatocholangiocarcinoma, metastatic, liver		1 (2%)		1 (2%)
Nose	(50)	(48)	(50)	(50)
Adenoma				1 (2%)
Alveolar/bronchiolar carcinoma, metastatic, lung				1 (2%)
Carcinoma, metastatic, harderian gland			1 (2%)	
Respiratory epithelium, adenoma				1 (2%)
Trachea	(50)	(48)	(50)	(50)
Adenoma		1 (2%)	1 (2%)	

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

	Chamber Control	12.8 ppm	32 ppm	80 ppm
Special Senses System				
Harderian gland	(2)	(5)	(11)	(12)
Adenoma	2 (100%)	5 (100%)	8 (73%)	9 (75%)
Carcinoma			2 (18%)	2 (17%)
Bilateral, adenoma				1 (8%)
Urinary System				
Kidney	(50)	(49)	(50)	(50)
Alveolar/bronchiolar carcinoma, metastatic, lung				1 (2%)
Hemangiosarcoma				1 (2%)
Hemangiosarcoma, metastatic, mesentery			4 (8%)	
Hepatocholangiocarcinoma, metastatic, liver				1 (2%)
Histiocytic sarcoma	1 (2%)		1 (2%)	
Renal tubule, adenoma		1 (2%)	1 (2%)	3 (6%)
Systemic Lesions				
Multiple organs[b]	(50)	(50)	(50)	(50)
Histiocytic sarcoma	3 (6%)		2 (4%)	1 (2%)
Lymphoma malignant	2 (4%)	2 (4%)	2 (4%)	4 (8%)
Neoplasm Summary				
Total animals with primary neoplasms[c]	48	48	50	50
Total primary neoplasms	78	106	156	172
Total animals with benign neoplasms	31	31	38	43
Total benign neoplasms	38	43	59	72
Total animals with malignant neoplasms	34	40	50	47
Total malignant neoplasms	40	63	97	100
Total animals with metastatic neoplasms	8	13	12	12
Total metastatic neoplasms	8	22	14	31

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

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

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

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

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Chloroprene: Chamber 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 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	
Carcass ID Number	0 0 5	0 0 6	0 0 7	0 0 9	0 1 7	0 2 2	0 2 3	0 2 5	0 2 9	0 3 1	0 3 2	0 3 6	0 3 8	0 3 9	0 4 8	0 1 0	0 1 4	0 1 6	0 1 8	0 2 1	0 2 4	0 2 6	0 4 0	0 4 4	0 5 0	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	41
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Muscularis, leiomyoma																X										1
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma								X																	X	2
Hepatocellular carcinoma					X																					10
Hepatocellular carcinoma, multiple	X	X							X							X							X			14
Hepatocellular adenoma						X					X		X	X												8
Hepatocellular adenoma, multiple			X	X			X					X			X					X		X		X	X	14
Histiocytic sarcoma																										1
Mesentery															+											2
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma																			X							1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tooth																										2
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Capsule, adenoma								X																		1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant		X																								1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	+	+	M	+	+	M	+	M	I	+	M	M	+	M	I	M	+	+	M	+	+	35
Pituitary gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, adenoma																										1
General Body System																										
None																										
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Prostate	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell, adenoma																										1

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

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

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Chloroprene: Chamber 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 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	
Carcass ID Number	0 0 0 5	0 0 0 6	0 0 0 7	0 0 0 9	0 0 1 7	0 0 2 2	0 0 2 3	0 0 2 5	0 0 2 9	0 0 3 1	0 0 3 2	0 0 3 6	0 0 3 8	0 0 3 9	0 0 4 8	0 1 0	0 1 4	0 1 6	0 1 8	0 2 1	0 2 4	0 2 6	0 4 0	0 4 4	0 5 0	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Lymph node, bronchial	M	+	+	+	+	+	+	+	M	M	+	+	+	+	M	+	+	+	+	+	M	+	+	+	M	32
Lymph node, mandibular	M	M	+	M	+	+	I	M	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	32
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Histiocytic sarcoma																										2
Lymph node, mediastinal	+	+	M	+	+	M	M	+	M	+	+	M	+	M	+	+	M	+	+	+	M	M	+	+	M	34
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Thymus	M	+	+	M	M	M	+	+	M	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	34
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	1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Subcutaneous tissue, hemangiosarcoma																			X							1
Subcutaneous tissue, histiocytic sarcoma														X												1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																			X							1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma													X		X							X				8
Alveolar/bronchiolar carcinoma								X												X					X	4
Alveolar/bronchiolar carcinoma, multiple																								X		2
Hepatocellular carcinoma, metastatic, liver																X										8
Histiocytic sarcoma																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye																		+								1
Harderian gland																		+								2
Adenoma																		X								2
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Ureter																					+					1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma														X												3
Lymphoma malignant																	X									2

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Chloroprene: 12.8 ppm

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

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Chloroprene: 12.8 ppm

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 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 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	
Carcass ID Number	2 0 5	2 0 6	2 1 0	2 1 3	2 1 5	2 2 0	2 2 2	2 2 7	2 2 8	2 3 0	2 3 1	2 3 2	2 3 5	2 3 6	2 4 0	2 4 3	2 4 9	2 0 3	2 0 7	2 0 8	2 1 6	2 2 5	2 2 6	2 3 4	2 4 1	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	40
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Hemangioma					X																					1
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma												X			X											5
Hepatoblastoma	X																									2
Hepatocellular carcinoma		X						X							X	X		X				X				18
Hepatocellular carcinoma, multiple			X	X		X	X					X														10
Hepatocellular adenoma					X		X						X									X	X	X		11
Hepatocellular adenoma, multiple		X									X	X					X									5
Hepatocholangiocarcinoma																										1
Sarcoma																										1
Mesentery			+																	+			+			8
Hemangiosarcoma			X																	X						3
Hepatocholangiocarcinoma, metastatic, liver																										1
Sarcoma, metastatic, liver																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Hemangiosarcoma																										1
Hepatocholangiocarcinoma, metastatic, liver																										1
Sarcoma, metastatic, liver																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Tooth										+													+			2
Cardiovascular System																										
Blood vessel				+																						2
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Parathyroid gland	+	+	+	M	I	+	M	+	M	+	I	+	+	M	M	+	M	+	M	+	+	+	+	+	+	32
Pituitary gland	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Follicular cell, adenoma																						X				1
General Body System																										
None																										

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Chloroprene: 12.8 ppm

Number of Days on Study	4 3 9	5 2 3	5 3 0	5 4 6	5 7 9	5 8 2	5 8 3	5 9 6	6 0 7	6 1 4	6 2 6	6 3 5	6 3 5	6 3 8	6 5 9	6 6 7	6 8 0	6 8 8	6 9 1	6 9 1	7 0 1	7 0 8	7 2 2	7 3 3	7 3 3
Carcass ID Number	2 3 7	2 1 4	2 4 5	2 0 9	2 1 7	2 0 1	2 1 2	2 1 8	2 4 4	2 3 8	2 4 2	2 1 9	2 2 4	2 2 9	2 4 7	2 5 0	2 3 3	2 2 1	2 1 1	2 3 9	2 4 8	2 4 6	2 2 3	2 0 2	2 0 4
Genital System																									
Epididymis	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocholangiocarcinoma, metastatic, liver											X														
Preputial gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	A	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, metastatic, liver										X															
Testes	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Hematopoietic System																									
Bone marrow	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Lymph node																									
Lymph node, bronchial	M	+	M	M	+	+	M	M	M	M	M	+	+	M	M	M	M	+	M	M	+	M	+	+	M
Lymph node, mandibular	+	+	A	+	+	+	M	+	M	+	+	+	+	M	M	+	+	M	M	+	M	M	+	M	+
Lymph node, mesenteric	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal	M	+	A	M	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	M	+	+	+	+	+
Hepatocholangiocarcinoma, metastatic, liver											X														
Sarcoma, metastatic, liver										X															
Spleen	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Thymus	M	+	M	+	+	M	+	M	+	M	M	M	M	+	+	M	M	M	+	+	+	M	+	+	+
Integumentary System																									
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Skin	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Subcutaneous tissue, hemangiosarcoma															X							X			
Subcutaneous tissue, hemangiosarcoma, multiple																		X							
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spinal cord																									
Respiratory System																									
Larynx	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma			X						X			X							X		X			X
Alveolar/bronchiolar adenoma, multiple																									
Alveolar/bronchiolar carcinoma														X			X								
Alveolar/bronchiolar carcinoma, multiple																			X				X		
Hemangiosarcoma, metastatic, skin																						X			
Hepatocellular carcinoma, metastatic, liver				X	X		X						X	X	X										
Hepatocholangiocarcinoma, metastatic, liver											X														
Sarcoma, metastatic, liver										X															
Mediastinum, hepatocholangiocarcinoma, metastatic, liver											X														
Nose	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																				X					

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Chloroprene: 12.8 ppm

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 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 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	
Carcass ID Number	2 0 5	2 0 6	2 1 0	2 1 3	2 1 5	2 2 0	2 2 2	2 2 7	2 2 8	2 3 0	2 3 1	2 3 2	2 3 5	2 3 6	2 4 0	2 4 3	2 4 9	2 0 3	2 0 7	2 0 8	2 1 6	2 2 5	2 2 6	2 3 4	2 4 1	Total Tissues/ Tumors
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatocholangiocarcinoma, metastatic, liver																										1
Preputial gland	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	47
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Sarcoma, metastatic, liver																										1
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma															X											1
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma																			X							1
Lymph node								+																		1
Lymph node, bronchial	M	+	M	+	+	M	+	M	M	M	M	M	+	M	+	+	+	+	+	M	+	+	+	+	M	23
Lymph node, mandibular	+	M	+	M	+	+	M	+	+	M	M	M	+	M	+	M	M	+	+	M	+	+	I	M	+	28
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph node, mediastinal	+	M	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	M	M	+	+	M	+	+	M	38
Hepatocholangiocarcinoma, metastatic, liver																										1
Sarcoma, metastatic, liver																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma												X								X						2
Thymus	+	M	+	+	+	M	I	+	M	+	M	M	+	+	+	M	M	+	+	+	M	I	+	+	+	28
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Subcutaneous tissue, hemangiosarcoma											X															3
Subcutaneous tissue, hemangiosarcoma, multiple																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spinal cord				+																						1
Respiratory System																										
Larynx	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma					X	X	X											X		X			X			12
Alveolar/bronchiolar adenoma, multiple			X							X	X				X						X	X				6
Alveolar/bronchiolar carcinoma	X											X	X	X					X			X				8
Alveolar/bronchiolar carcinoma, multiple		X							X																	4
Hemangiosarcoma, metastatic, skin																										1
Hepatocellular carcinoma, metastatic, liver								X							X	X		X								10
Hepatocholangiocarcinoma, metastatic, liver																										1
Sarcoma, metastatic, liver																										1
Mediastinum, hepatocholangiocarcinoma, metastatic, liver																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma																										1

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Chloroprene: 12.8 ppm

Number of Days on Study	439	523	530	546	579	582	583	596	607	614	626	635	655	689	697	700	708	711	711	722	723	733
Carcass ID Number	237	214	245	209	217	201	212	218	244	233	242	219	242	249	270	253	211	211	239	246	232	204
Special Senses System																						
Eye																			+			
Harderian gland																			+			
Adenoma																			X			
Urinary System																						
Kidney	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Renal tubule, adenoma																				X		
Urinary bladder	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																						
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant																						

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Chloroprene: 12.8 ppm

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 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 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	
Carcass ID Number	2 0 5	2 0 6	2 1 0	2 1 3	2 1 5	2 2 0	2 2 2	2 2 7	2 2 8	2 3 0	2 3 1	2 3 2	2 3 5	2 3 6	2 4 0	2 4 3	2 4 9	2 0 3	2 0 7	2 0 8	2 1 6	2 2 5	2 2 6	2 3 4	2 4 1	Total Tissues/ Tumors
Special Senses System																										
Eye																										1
Harderian gland					+															+		+		+		5
Adenoma					X															X		X		X		5
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Renal tubule, adenoma																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant								X			X															2

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Chloroprene: 32 ppm

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

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Chloroprene: 32 ppm

Number of Days on Study	6 7 9	6 7 9	6 8 0	6 8 8	6 8 8	6 9 3	7 0 1	7 0 5	7 1 3	7 1 5	7 1 7	7 3 3	7 3 3	7 3 3	7 3 3	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	
Carcass ID Number	4 3 0	4 3 2	4 4 9	4 1 8	4 2 6	4 2 7	4 4 8	4 1 1	4 0 5	4 1 6	4 2 2	4 0 1	4 0 9	4 2 3	4 4 2	4 1 2	4 1 3	4 1 4	4 1 7	4 2 9	4 3 5	4 3 7	4 3 9	4 4 6	4 4 7	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	M	+	+	+	+	+	+	+	A	M	M	+	+	+	+	+	+	M	+	+	+	+	+	+	37
Intestine large, colon	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, rectum	+	+	+	+	A	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine large, cecum	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine small, duodenum	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, ileum	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cholangiocarcinoma						X																				1
Hemangiosarcoma					X									X	X											6
Hepatoblastoma											X															3
Hepatocellular carcinoma						X		X		X		X		X			X					X			X	18
Hepatocellular carcinoma, multiple					X		X		X		X				X	X			X	X	X			X		19
Hepatocellular adenoma		X		X		X	X							X				X		X		X				12
Hepatocellular adenoma, multiple								X				X	X				X								X	7
Histiocytic sarcoma																										1
Mesentery	+	+	+	+				+	+		+		+			+		+					+			16
Hemangioma																										1
Hemangiosarcoma	X	X	X	X				X	X				X			X		X					X			13
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma, metastatic, mesentery				X																				1		
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Squamous cell papilloma																	X		X							2
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Blood vessel																										1
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangioma					X																					1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign					X																					1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Parathyroid gland	M	+	+	+	M	+	+	M	+	+	+	M	+	+	+	+	M	+	M	+	+	M	+	+	+	31
Pituitary gland	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	47
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, adenoma																										1
General Body System																										
None																										

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Chloroprene: 32 ppm

Number of Days on Study	3 8 2	4 3 9	4 7 0	4 9 1	4 9 5	5 0 2	5 4 5	5 5 1	5 6 5	5 6 7	5 7 9	5 9 6	6 0 2	6 0 6	6 0 7	6 0 7	6 0 7	6 2 0	6 2 3	6 2 9	6 3 5	6 4 9	6 6 3	6 6 6	6 6 6
Carcass ID Number	4 4 3	4 1 9	4 2 4	4 1 0	4 0 8	4 4 4	4 4 1	4 3 3	4 4 0	4 2 1	4 5 0	4 3 4	4 2 0	4 3 8	4 3 3	4 0 6	4 0 6	4 3 6	4 1 5	4 4 5	4 0 7	4 0 4	4 0 2	4 2 8	4 2 5	4 3 1
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma, metastatic, mesentery																								X	
Leiomyoma																		X							
Leiomyosarcoma																									
Penis										+															
Preputial gland	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma, metastatic, mesentery													X												
Seminal vesicle	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																		X							
Lymph node											+						+								
Lymph node, bronchial	+	+	+	M	M	+	+	M	+	M	+	M	+	+	M	+	M	+	+	+	M	+	+	I	+
Histiocytic sarcoma																									X
Lymph node, mandibular	+	M	M	+	+	M	+	+	M	M	M	+	M	M	M	M	+	M	+	+	M	+	M	M	+
Histiocytic sarcoma																									X
Lymph node, mesenteric	+	+	M	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Hemangiosarcoma																									
Histiocytic sarcoma																									X
Lymph node, mediastinal	+	M	M	+	+	+	+	+	M	+	+	+	+	M	+	M	+	M	+	M	+	M	+	+	M
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																		X							
Histiocytic sarcoma																									X
Thymus	M	+	+	+	M	+	M	M	+	M	+	+	+	+	+	M	M	M	M	M	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
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, hemangiosarcoma																						X			
Subcutaneous tissue, histiocytic sarcoma																		X							
Subcutaneous tissue, sarcoma, multiple															X										
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Chloroprene: 32 ppm

Number of Days on Study	6 7 9	6 7 9	6 8 0	6 8 8	6 8 8	6 9 3	7 0 1	7 0 5	7 1 3	7 1 5	7 1 7	7 3 3	7 3 3	7 3 3	7 3 3	7 3 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	
Carcass ID Number	4 3 0	4 3 2	4 4 9	4 1 8	4 2 6	4 2 7	4 4 8	4 1 1	4 0 5	4 1 6	4 2 2	4 0 1	4 0 9	4 2 3	4 4 2	4 1 2	4 1 3	4 1 4	4 1 7	4 2 9	4 3 5	4 3 7	4 3 9	4 4 6	4 4 7	Total Tissues/ Tumors
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma, metastatic, mesentery																										1
Leiomyoma																										1
Leiomyosarcoma									X																	1
Penis																										1
Preputial gland	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	47
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	48
Hemangiosarcoma, metastatic, mesentery																										1
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma									X																	2
Lymph node																										2
Lymph node, bronchial	+	+	+	+	+	M	+	+	M	+	+	+	+	M	+	+	M	+	+	M	M	+	M	+	M	33
Histiocytic sarcoma																										1
Lymph node, mandibular	M	+	M	M	M	+	+	+	+	M	M	+	M	+	+	+	+	+	M	+	M	+	+	+	+	27
Histiocytic sarcoma																										1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Hemangiosarcoma							X																			1
Histiocytic sarcoma																										1
Lymph node, mediastinal	M	+	+	+	M	+	+	M	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	37
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma									X																	2
Histiocytic sarcoma																										1
Thymus	+	M	M	+	M	M	+	M	M	I	M	+	+	+	+	+	+	+	+	+	+	M	M	M	M	25
Integumentary System																										
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, hemangiosarcoma																										1
Subcutaneous tissue, histiocytic sarcoma																										1
Subcutaneous tissue, sarcoma, multiple																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Chloroprene: 32 ppm

Number of Days on Study	382	390	470	491	495	502	545	551	565	567	579	596	602	606	607	607	607	620	623	629	635	649	663	666	666
Carcass ID Number	4043	4019	4024	4010	4008	4044	4041	4033	4040	4021	4050	4034	4020	4038	4033	4006	4036	4015	4045	4027	4004	4002	4028	4025	4031
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma	X		X	X		X										X				X		X	X		
Alveolar/bronchiolar adenoma, multiple																					X				
Alveolar/bronchiolar carcinoma										X	X	X			X		X								
Alveolar/bronchiolar carcinoma, multiple														X				X							X
Hepatoblastoma, metastatic, liver																								X	
Hepatocellular carcinoma, metastatic, liver		X																X							
Bronchiole, adenoma																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, harderian gland																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Special Senses System																									
Harderian gland												+		+				+		+					
Adenoma												X		X				X							
Carcinoma																				X					
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma, metastatic, mesentery						X																			
Histiocytic sarcoma																									X
Renal tubule, adenoma																									
Urinary bladder	I	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																		X							X
Lymphoma malignant																									

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Chloroprene: 32 ppm

Number of Days on Study	6 7 9	6 7 9	6 8 0	6 8 8	6 8 8	6 9 3	7 0 1	7 0 5	7 1 3	7 1 5	7 1 7	7 3 3	7 3 3	7 3 3	7 3 3	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	
Carcass ID Number	4 3 0	4 3 2	4 4 9	4 1 8	4 2 6	4 2 7	4 4 8	4 1 1	4 0 5	4 1 6	4 2 2	4 0 1	4 0 9	4 2 3	4 4 2	4 1 2	4 1 3	4 1 4	4 1 7	4 2 9	4 3 5	4 3 7	4 3 9	4 4 6	4 4 7	Total Tissues/ Tumors
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma	X			X	X		X		X										X				X			15
Alveolar/bronchiolar adenoma, multiple		X	X									X					X						X		X	7
Alveolar/bronchiolar carcinoma	X		X						X				X				X			X			X		X	13
Alveolar/bronchiolar carcinoma, multiple				X			X			X	X				X						X			X		10
Hepatoblastoma, metastatic, liver																										1
Hepatocellular carcinoma, metastatic, liver										X							X								X	5
Bronchiole, adenoma				X																						1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, harderian gland								X																		1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma												X														1
Special Senses System																										
Harderian gland	+							+				+	+									+	+			11
Adenoma	X											X	X									X	X			8
Carcinoma								X																		2
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma, metastatic, mesentery				X					X														X			4
Histiocytic sarcoma																										1
Renal tubule, adenoma												X														1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										2
Lymphoma malignant														X					X							2

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Chloroprene: 80 ppm

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

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Chloroprene: 80 ppm

Number of Days on Study	6 5 6	6 5 7	6 5 9	6 5 9	6 6 3	6 7 2	6 7 7	6 7 7	6 8 0	6 8 7	7 0 1	7 0 1	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 4	7 3 4	
Carcass ID Number	6 5 0	6 2 4	6 2 2	6 2 5	6 4 7	6 3 9	6 3 7	6 4 5	6 0 7	6 2 1	6 1 7	6 1 9	6 0 3	6 0 5	6 0 9	6 1 5	6 2 0	6 2 7	6 3 0	6 3 2	6 4 0	6 4 3	6 4 6	6 0 1	6 1 0	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	M	+	+	A	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	40
Intestine large, colon	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, rectum	+	+	+	M	+	A	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	45
Intestine large, cecum	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, duodenum	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, jejunum	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, ileum	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar carcinoma, metastatic, lung		X																								1
Hemangiosarcoma	X		X		X					X			X													8
Hepatoblastoma																										1
Hepatocellular carcinoma	X	X	X	X				X	X					X					X	X			X		X	16
Hepatocellular carcinoma, multiple					X		X					X			X						X	X		X		17
Hepatocellular adenoma				X					X				X						X							11
Hepatocellular adenoma, multiple			X		X									X	X		X			X						10
Hepatocholangiocarcinoma											X															1
Mesentery							+	+		+			+	+	+			+		+	+				+	11
Hemangioma								X										X								2
Hemangiosarcoma							X			X			X	X						X	X					7
Oral mucosa									+																	1
Gingival, squamous cell carcinoma									X																	1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocholangiocarcinoma, metastatic, liver											X															1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma																										1
Squamous cell papilloma							X																			4
Stomach, glandular	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Cardiovascular System																										
Blood vessel																										1
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma, metastatic, lung		X																								2
Hepatocholangiocarcinoma, metastatic, liver											X															1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma, metastatic, lung		X																								2
Adrenal medulla	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma benign													X													1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	M	M	+	+	+	+	+	+	M	+	M	+	M	M	+	M	+	+	M	+	M	+	M	+	+	30
Pituitary gland	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, adenoma																		X								1
General Body System																										
None																										

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Chloroprene: 80 ppm

Number of Days on Study	3 9 2	4 2 2	4 5 4	5 2 3	5 2 4	5 6 7	5 7 9	5 8 7	5 8 9	5 9 5	6 0 0	6 0 3	6 0 8	6 2 0	6 2 4	6 2 4	6 2 8	6 3 5	6 3 5	6 3 7	6 4 4	6 4 4	6 4 9	6 4 9	6 4 9
Carcass ID Number	6 0 4	6 0 2	6 1 6	6 4 2	6 1 1	6 4 8	6 1 8	6 2 8	6 4 9	6 2 6	6 3 4	6 0 8	6 1 2	6 3 8	6 0 6	6 4 4	6 3 5	6 1 4	6 2 9	6 3 6	6 1 3	6 3 3	6 2 3	6 3 1	6 4 1
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma												X													
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																					X				
Lymph node												+													
Renal, hemangiosarcoma																									
Lymph node, bronchial	+	+	+	+	M	M	+	M	+	+	+	M	M	+	M	M	+	M	+	+	+	+	M	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung									X					X											
Hepatocholangiocarcinoma, metastatic, liver																									
Lymph node, mandibular	+	+	+	M	M	+	+	+	M	M	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal	+	+	+	M	M	+	M	+	+	+	M	I	+	+	+	+	+	+	+	+	+	+	+	+	M
Alveolar/bronchiolar carcinoma, metastatic, lung														X											
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma												X													
Thymus	I	M	+	+	M	M	M	+	M	+	+	+	+	+	M	M	M	+	+	+	+	+	+	I	+
Alveolar/bronchiolar carcinoma, metastatic, lung														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
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, hemangiosarcoma			X									X							X						
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung																									
Skeletal muscle																									
Hepatocholangiocarcinoma, metastatic, liver																									
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Chloroprene: 80 ppm

Number of Days on Study	6 5 6	6 5 7	6 5 9	6 5 9	6 6 3	6 7 2	6 7 7	6 7 7	6 8 0	6 8 7	7 0 1	7 0 1	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 4	7 3 4	
Carcass ID Number	6 5 0	6 2 4	6 2 2	6 2 5	6 4 7	6 3 9	6 3 7	6 4 5	6 0 7	6 2 1	6 1 7	6 1 9	6 0 3	6 0 5	6 0 9	6 1 5	6 2 0	6 2 7	6 3 0	6 3 2	6 4 0	6 4 3	6 4 6	6 0 1	6 1 0	Total Tissues/ Tumors
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma	X																									1
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																									X	2
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Seminal vesicle	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Lymph node													+										+			3
Renal, hemangiosarcoma													X													1
Lymph node, bronchial	M	+	M	M	+	M	M	+	M	+	+	M	M	+	+	+	M	M	M	+	+	M	+	+	M	28
Alveolar/bronchiolar carcinoma, metastatic, lung		X													X											4
Hepatocholangiocarcinoma, metastatic, liver											X															1
Lymph node, mandibular	+	+	+	+	M	+	+	M	M	M	M	M	+	+	+	M	M	+	M	M	+	+	+	+	+	34
Lymph node, mesenteric	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph node, mediastinal	M	+	M	+	+	+	+	M	M	+	+	+	+	M	+	+	+	I	+	M	+	+	+	+	+	37
Alveolar/bronchiolar carcinoma, metastatic, lung																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Thymus	+	M	+	+	+	+	+	+	M	+	M	M	+	+	+	M	+	+	I	+	+	+	+	+	+	34
Alveolar/bronchiolar carcinoma, metastatic, lung																										1
Integumentary System																										
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, hemangiosarcoma										X		X											X		X	7
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma, metastatic, lung		X																								1
Skeletal muscle											+															1
Hepatocholangiocarcinoma, metastatic, liver											X															1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Chloroprene: 80 ppm

Number of Days on Study	3 9 2	4 2 2	4 5 4	5 2 3	5 2 4	5 6 7	5 7 9	5 8 7	5 8 9	5 9 5	6 0 0	6 0 3	6 0 8	6 2 0	6 2 4	6 2 4	6 2 8	6 3 5	6 3 5	6 3 7	6 4 4	6 4 4	6 4 9	6 4 9	6 4 9
Carcass ID Number	6 0 4	6 0 2	6 1 6	6 4 2	6 1 1	6 4 8	6 1 8	6 2 8	6 4 9	6 2 6	6 3 4	6 0 8	6 1 2	6 3 8	6 0 6	6 4 4	6 3 5	6 1 4	6 2 9	6 3 6	6 1 3	6 3 3	6 2 3	6 3 1	6 4 1
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma				X			X				X		X		X				X	X			X	X	X
Alveolar/bronchiolar adenoma, multiple								X		X								X							
Alveolar/bronchiolar carcinoma					X			X	X				X										X		
Alveolar/bronchiolar carcinoma, multiple						X								X		X					X			X	X
Hemangiosarcoma, metastatic, mesentery																									
Hepatoblastoma, metastatic, liver																		X							
Hepatocellular carcinoma, metastatic, liver	X				X																		X		
Hepatocholangiocarcinoma, metastatic, liver																									
Mediastinum, alveolar/bronchiolar carcinoma, metastatic, lung						X			X					X											
Mediastinum, hepatocholangiocarcinoma, metastatic, liver																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Alveolar/bronchiolar carcinoma, metastatic, lung																									
Respiratory epithelium, adenoma																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye																									
Harderian gland		M							+										+		+				
Adenoma									X										X		X				
Carcinoma																									
Bilateral, adenoma																									
Zymbal's gland		M																							
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung																									
Hemangiosarcoma																						X			
Hepatocholangiocarcinoma, metastatic, liver																									
Renal tubule, adenoma								X																	
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Lymphoma malignant												X	X											X	

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Chloroprene: 80 ppm

Number of Days on Study	6 5 6	6 5 7	6 5 9	6 5 9	6 6 3	6 7 2	6 7 7	6 7 7	6 8 0	6 8 7	7 0 1	7 0 1	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 4	7 3 4	
Carcass ID Number	6 5 0	6 2 4	6 2 2	6 2 5	6 4 7	6 3 9	6 3 7	6 4 5	6 0 7	6 2 1	6 1 7	6 1 9	6 0 3	6 0 5	6 0 9	6 1 5	6 2 0	6 2 7	6 3 0	6 3 2	6 4 0	6 4 3	6 4 6	6 0 1	6 1 0	Total Tissues/ Tumors
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma			X								X								X	X					X	15
Alveolar/bronchiolar adenoma, multiple	X				X	X			X						X	X		X			X		X	X		13
Alveolar/bronchiolar carcinoma	X					X		X				X			X					X	X		X			13
Alveolar/bronchiolar carcinoma, multiple		X	X	X			X						X	X			X		X			X				15
Hemangiosarcoma, metastatic, mesentery																				X						1
Hepatoblastoma, metastatic, liver																										1
Hepatocellular carcinoma, metastatic, liver							X																			4
Hepatocholangiocarcinoma, metastatic, liver											X															1
Mediastinum, alveolar/bronchiolar carcinoma, metastatic, lung		X																								4
Mediastinum, hepatocholangiocarcinoma, metastatic, liver											X															1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																							X			1
Alveolar/bronchiolar carcinoma, metastatic, lung		X																								1
Respiratory epithelium, adenoma									X																	1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye																+										1
Harderian gland					+		+			+			M	+		+	+	+		+				+		12
Adenoma					X		X			X						X	X			X						9
Carcinoma														X				X								2
Bilateral, adenoma																								X		1
Zymbal's gland													M											M		
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma, metastatic, lung		X																								1
Hemangiosarcoma																										1
Hepatocholangiocarcinoma, metastatic, liver											X															1
Renal tubule, adenoma				X															X							3
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma	X																									1
Lymphoma malignant																						X				4

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

	Chamber Control	12.8 ppm	32 ppm	80 ppm
Harderian Gland: Adenoma				
Overall rate[a]	2/50 (4%)	5/50 (10%)	8/50 (16%)	10/50 (20%)
Adjusted rate[b]	5.8%	17.7%	36.8%	46.4%
Terminal rate[c]	1/27 (4%)	4/27 (15%)	4/14 (29%)	4/13 (31%)
First incidence (days)	596	701	596	589
Life table test[d]	P < 0.001	P = 0.213	P = 0.009	P = 0.001
Logistic regression test[d]	P = 0.004	P = 0.205	P = 0.035	P = 0.007
Cochran-Armitage test[d]	P = 0.013			
Fisher exact test[d]		P = 0.218	P = 0.046	P = 0.014
Harderian Gland: Adenoma or Carcinoma				
Overall rate	2/50 (4%)	5/50 (10%)	10/50 (20%)	12/50 (24%)
Adjusted rate	5.8%	17.7%	42.3%	58.3%
Terminal rate	1/27 (4%)	4/27 (15%)	4/14 (29%)	6/13 (46%)
First incidence (days)	596	701	596	589
Life table test	P < 0.001	P = 0.213	P = 0.002	P < 0.001
Logistic regression test	P < 0.001	P = 0.205	P = 0.010	P = 0.001
Cochran-Armitage test	P = 0.003			
Fisher exact test		P = 0.218	P = 0.014	P = 0.004
Kidney (Renal Tubule): Adenoma (Single Section)				
Overall rate	0/50 (0%)	1/49 (2%)	1/50 (2%)	3/50 (6%)
Adjusted rate	0.0%	3.6%	7.1%	13.8%
Terminal rate	0/27 (0%)	0/27 (0%)	1/14 (7%)	1/13 (8%)
First incidence (days)	—[e]	722	733 (T)	587
Life table test	P = 0.014	P = 0.486	P = 0.369	P = 0.060
Logistic regression test	P = 0.039	P = 0.492	P = 0.369	P = 0.121
Cochran-Armitage test	P = 0.060			
Fisher exact test		P = 0.495	P = 0.500	P = 0.121
Kidney (Renal Tubule): Adenoma (Step Section)				
Overall rate	0/50 (0%)	1/49 (2%)	2/50 (4%)	6/50 (12%)
Adjusted rate	0.0%	3.7%	12.9%	30.2%
Terminal rate	0/27 (0%)	1/27 (4%)	1/14 (7%)	2/13 (15%)
First incidence (days)	—	733 (T)	715	567
Life table test	P < 0.001	P = 0.500	P = 0.111	P = 0.003
Logistic regression test	P < 0.001	P = 0.500	P = 0.135	P = 0.011
Cochran-Armitage test	P = 0.002			
Fisher exact test		P = 0.495	P = 0.247	P = 0.013
Kidney (Renal Tubule): Adenoma (Single and Step Sections)				
Overall rate	0/50 (0%)	2/49 (4%)	3/50 (6%)	9/50 (18%)
Adjusted rate	0.0%	7.1%	19.6%	40.7%
Terminal rate	0/27 (0%)	1/27 (4%)	2/14 (14%)	3/13 (23%)
First incidence (days)	—	722	715	567
Life table test	P < 0.001	P = 0.232	P = 0.035	P < 0.001
Logistic regression test	P < 0.001	P = 0.227	P = 0.042	P = 0.002
Cochran-Armitage test	P < 0.001			
Fisher exact test		P = 0.242	P = 0.121	P = 0.001

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

	Chamber Control	12.8 ppm	32 ppm	80 ppm
Liver: Hemangiosarcoma				
Overall rate	2/50 (4%)	5/50 (10%)	6/50 (12%)	8/49 (16%)
Adjusted rate	7.4%	16.3%	25.4%	30.3%
Terminal rate	2/27 (7%)	3/27 (11%)	2/14 (14%)	1/13 (8%)
First incidence (days)	733 (T)	659	495	579
Life table test	P = 0.003	P = 0.219	P = 0.039	P = 0.008
Logistic regression test	P = 0.031	P = 0.201	P = 0.108	P = 0.036
Cochran-Armitage test	P = 0.045			
Fisher exact test		P = 0.218	P = 0.134	P = 0.043
Liver: Hepatocellular Adenoma				
Overall rate	22/50 (44%)	16/50 (32%)	19/50 (38%)	21/49 (43%)
Adjusted rate	64.4%	47.9%	72.3%	67.7%
Terminal rate	15/27 (56%)	11/27 (41%)	8/14 (57%)	6/13 (46%)
First incidence (days)	635	439	439	392
Life table test	P = 0.006	P = 0.175N	P = 0.090	P = 0.044
Logistic regression test	P = 0.183	P = 0.156N	P = 0.419	P = 0.381
Cochran-Armitage test	P = 0.397			
Fisher exact test		P = 0.151N	P = 0.342N	P = 0.535N
Liver: Hepatocellular Carcinoma				
Overall rate	24/50 (48%)	28/50 (56%)	37/50 (74%)	33/49 (67%)
Adjusted rate	50.8%	63.2%	91.5%	87.2%
Terminal rate	6/27 (22%)	12/27 (44%)	11/14 (79%)	9/13 (69%)
First incidence (days)	452	523	382	392
Life table test	P < 0.001	P = 0.301	P < 0.001	P = 0.003
Logistic regression test	P = 0.131	P = 0.295	P = 0.047	P = 0.189
Cochran-Armitage test	P = 0.033			
Fisher exact test		P = 0.274	P = 0.007	P = 0.040
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rate	43/50 (86%)	37/50 (74%)	42/50 (84%)	41/49 (84%)
Adjusted rate	87.7%	81.5%	97.5%	94.6%
Terminal rate	21/27 (78%)	19/27 (70%)	13/14 (93%)	11/13 (85%)
First incidence (days)	452	439	382	392
Life table test	P = 0.002	P = 0.272N	P = 0.014	P = 0.015
Logistic regression test	P = 0.530	P = 0.087N	P = 0.463N	P = 0.402N
Cochran-Armitage test	P = 0.432			
Fisher exact test		P = 0.105N	P = 0.500N	P = 0.483N
Liver: Hepatoblastoma				
Overall rate	0/50 (0%)	2/50 (4%)	3/50 (6%)	1/49 (2%)
Adjusted rate	0.0%	5.7%	12.6%	3.0%
Terminal rate	0/27 (0%)	1/27 (4%)	0/14 (0%)	0/13 (0%)
First incidence (days)	—	523	607	635
Life table test	P = 0.392	P = 0.240	P = 0.063	P = 0.462
Logistic regression test	P = 0.591	P = 0.254	P = 0.116	P = 0.540
Cochran-Armitage test	P = 0.544			
Fisher exact test		P = 0.247	P = 0.121	P = 0.495

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

	Chamber Control	12.8 ppm	32 ppm	80 ppm
Liver: Hepatocellular Carcinoma or Hepatoblastoma				
Overall rate	24/50 (48%)	29/50 (58%)	39/50 (78%)	34/49 (69%)
Adjusted rate	50.8%	65.7%	92.1%	87.6%
Terminal rate	6/27 (22%)	13/27 (48%)	11/14 (79%)	9/13 (69%)
First incidence (days)	452	523	382	392
Life table test	P < 0.001	P = 0.253	P < 0.001	P = 0.002
Logistic regression test	P = 0.099	P = 0.221	P = 0.018	P = 0.141
Cochran-Armitage test	P = 0.022			
Fisher exact test		P = 0.212	P = 0.002	P = 0.025
Liver: Hepatocellular Adenoma, Hepatocellular Carcinoma, or Hepatoblastoma				
Overall rate	43/50 (86%)	38/50 (76%)	43/50 (86%)	42/49 (86%)
Adjusted rate	87.7%	83.8%	97.6%	94.8%
Terminal rate	21/27 (78%)	20/27 (74%)	13/14 (93%)	11/13 (85%)
First incidence (days)	452	439	382	392
Life table test	P = 0.001	P = 0.320N	P = 0.010	P = 0.011
Logistic regression test	P = 0.441	P = 0.132N	P = 0.580N	P = 0.503N
Cochran-Armitage test	P = 0.353			
Fisher exact test		P = 0.154N	P = 0.613N	P = 0.597N
Lung: Alveolar/bronchiolar Adenoma				
Overall rate	8/50 (16%)	18/50 (36%)	22/50 (44%)	28/50 (56%)
Adjusted rate	23.8%	54.8%	68.3%	84.7%
Terminal rate	4/27 (15%)	13/27 (48%)	6/14 (43%)	9/13 (69%)
First incidence (days)	635	530	382	523
Life table test	P < 0.001	P = 0.023	P < 0.001	P < 0.001
Logistic regression test	P < 0.001	P = 0.016	P = 0.002	P < 0.001
Cochran-Armitage test	P < 0.001			
Fisher exact test		P = 0.020	P = 0.002	P < 0.001
Lung: Alveolar/bronchiolar Carcinoma				
Overall rate	6/50 (12%)	12/50 (24%)	23/50 (46%)	28/50 (56%)
Adjusted rate	21.3%	37.9%	76.7%	85.1%
Terminal rate	5/27 (19%)	8/27 (30%)	8/14 (57%)	9/13 (69%)
First incidence (days)	729	638	567	524
Life table test	P < 0.001	P = 0.096	P < 0.001	P < 0.001
Logistic regression test	P < 0.001	P = 0.075	P < 0.001	P < 0.001
Cochran-Armitage test	P < 0.001			
Fisher exact test		P = 0.096	P < 0.001	P < 0.001
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rate	13/50 (26%)	28/50 (56%)	36/50 (72%)	43/50 (86%)
Adjusted rate	39.2%	79.4%	89.0%	100.0%
Terminal rate	8/27 (30%)	20/27 (74%)	10/14 (71%)	13/13 (100%)
First incidence (days)	635	530	382	523
Life table test	P < 0.001	P = 0.003	P < 0.001	P < 0.001
Logistic regression test	P < 0.001	P < 0.001	P < 0.001	P < 0.001
Cochran-Armitage test	P < 0.001			
Fisher exact test		P = 0.002	P < 0.001	P < 0.001

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

	Chamber Control	12.8 ppm	32 ppm	80 ppm
Mesentery: Hemangiosarcoma				
Overall rate	0/50 (0%)	3/50 (6%)	13/50 (26%)	7/50 (14%)
Adjusted rate	0.0%	10.1%	51.1%	40.3%
Terminal rate	0/27 (0%)	2/27 (7%)	4/14 (29%)	4/13 (31%)
First incidence (days)	—	680	502	628
Life table test	P < 0.001	P = 0.123	P < 0.001	P < 0.001
Logistic regression test	P = 0.006	P = 0.114	P < 0.001	P = 0.001
Cochran-Armitage test	P = 0.023			
Fisher exact test		P = 0.121	P < 0.001	P = 0.006
Mesentery: Hemangioma or Hemangiosarcoma				
Overall rate	0/50 (0%)	3/50 (6%)	14/50 (28%)	9/50 (18%)
Adjusted rate	0.0%	10.1%	52.5%	49.9%
Terminal rate	0/27 (0%)	2/27 (7%)	4/14 (29%)	5/13 (38%)
First incidence (days)	—	680	502	628
Life table test	P < 0.001	P = 0.123	P < 0.001	P < 0.001
Logistic regression test	P = 0.001	P = 0.114	P < 0.001	P < 0.001
Cochran-Armitage test	P = 0.005			
Fisher exact test		P = 0.121	P < 0.001	P = 0.001
Skin (Subcutaneous Tissue): Hemangiosarcoma				
Overall rate	1/50 (2%)	4/50 (8%)	1/50 (2%)	7/50 (14%)
Adjusted rate	3.7%	12.3%	3.4%	31.5%
Terminal rate	1/27 (4%)	1/27 (4%)	0/14 (0%)	2/13 (15%)
First incidence (days)	733 (T)	659	649	454
Life table test	P = 0.002	P = 0.183	P = 0.659	P = 0.005
Logistic regression test	P = 0.017	P = 0.172	P = 0.731	P = 0.033
Cochran-Armitage test	P = 0.022			
Fisher exact test		P = 0.181	P = 0.753N	P = 0.030
Stomach (Forestomach): Squamous Cell Papilloma				
Overall rate	1/50 (2%)	0/50 (0%)	2/50 (4%)	4/50 (8%)
Adjusted rate	3.7%	0.0%	14.3%	12.7%
Terminal rate	1/27 (4%)	0/27 (0%)	2/14 (14%)	0/13 (0%)
First incidence (days)	733 (T)	—	733 (T)	587
Life table test	P = 0.009	P = 0.500N	P = 0.276	P = 0.099
Logistic regression test	P = 0.030	P = 0.500N	P = 0.276	P = 0.216
Cochran-Armitage test	P = 0.037			
Fisher exact test		P = 0.500N	P = 0.500	P = 0.181
Stomach (Forestomach): Squamous Cell Papilloma or Squamous Cell Carcinoma				
Overall rate	1/50 (2%)	0/50 (0%)	2/50 (4%)	5/50 (10%)
Adjusted rate	3.7%	0.0%	14.3%	15.3%
Terminal rate	1/27 (4%)	0/27 (0%)	2/14 (14%)	0/13 (0%)
First incidence (days)	733 (T)	—	733 (T)	587
Life table test	P = 0.002	P = 0.500N	P = 0.276	P = 0.052
Logistic regression test	P = 0.010	P = 0.500N	P = 0.276	P = 0.132
Cochran-Armitage test	P = 0.012			
Fisher exact test		P = 0.500N	P = 0.500	P = 0.102

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

	Chamber Control	12.8 ppm	32 ppm	80 ppm
All Organs: Hemangiosarcoma (excludes liver)				
Overall test	1/50 (2%)	11/50 (22%)	16/50 (32%)	15/50 (30%)
Adjusted test	3.7%	33.4%	56.5%	62.6%
Terminal rate	1/27 (4%)	6/27 (22%)	4/14 (29%)	6/13 (46%)
First incidence (days)	733 (T)	659	502	454
Life table test	P < 0.001	P = 0.004	P < 0.001	P < 0.001
Logistic regression test	P < 0.001	P = 0.002	P < 0.001	P < 0.001
Cochran-Armitage test	P = 0.003			
Fisher exact test		P = 0.002	P < 0.001	P < 0.001
All Organs: Hemangiosarcoma				
Overall rate	3/50 (6%)	13/50 (26%)	22/50 (44%)	19/50 (38%)
Adjusted rate	11.1%	38.6%	69.8%	68.0%
Terminal rate	3/27 (11%)	7/27 (26%)	6/14 (43%)	6/13 (46%)
First incidence (days)	733 (T)	659	495	454
Life table test	P < 0.001	P = 0.009	P < 0.001	P < 0.001
Logistic regression test	P < 0.001	P = 0.006	P < 0.001	P < 0.001
Cochran-Armitage test	P = 0.001			
Fisher exact test		P = 0.006	P < 0.001	P < 0.001
All Organs: Hemangioma or Hemangiosarcoma (excludes liver)				
Overall rate	1/50 (2%)	12/50 (24%)	18/50 (36%)	17/50 (34%)
Adjusted rate	3.7%	36.6%	59.8%	69.7%
Terminal rate	1/27 (4%)	7/27 (26%)	4/14 (29%)	7/13 (54%)
First incidence (days)	733 (T)	659	502	454
Life table test	P < 0.001	P = 0.002	P < 0.001	P < 0.001
Logistic regression test	P < 0.001	P = 0.001	P < 0.001	P < 0.001
Cochran-Armitage test	P < 0.001			
Fisher exact test		P < 0.001	P < 0.001	P < 0.001
All Organs: Hemangioma or Hemangiosarcoma				
Overall rate	3/50 (6%)	14/50 (28%)	23/50 (46%)	21/50 (42%)
Adjusted rate	11.1%	41.7%	70.7%	74.1%
Terminal rate	3/27 (11%)	8/27 (30%)	6/14 (43%)	7/13 (54%)
First incidence (days)	733 (T)	659	495	454
Life table test	P < 0.001	P = 0.005	P < 0.001	P < 0.001
Logistic regression test	P < 0.001	P = 0.003	P < 0.001	P < 0.001
Cochran-Armitage test	P < 0.001			
Fisher exact test		P = 0.003	P < 0.001	P < 0.001
All Organs: Histiocytic Sarcoma (excludes liver)				
Overall rate	3/50 (6%)	0/50 (0%)	2/50 (4%)	1/50 (2%)
Adjusted rate	8.5%	0.0%	6.4%	4.0%
Terminal rate	1/27 (4%)	0/27 (0%)	0/14 (0%)	0/13 (0%)
First incidence (days)	603	—	607	656
Life table test	P = 0.556N	P = 0.130N	P = 0.640N	P = 0.480N
Logistic regression test	P = 0.370N	P = 0.116N	P = 0.463N	P = 0.290N
Cochran-Armitage test	P = 0.397N			
Fisher exact test		P = 0.121N	P = 0.500N	P = 0.309N

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

	Chamber Control	12.8 ppm	32 ppm	80 ppm
All Organs: Histiocytic Sarcoma				
Overall rate	3/50 (6%)	0/50 (0%)	2/50 (4%)	1/50 (2%)
Adjusted rate	8.5%	0.0%	6.4%	4.0%
Terminal rate	1/27 (4%)	0/27 (0%)	0/14 (0%)	0/13 (0%)
First incidence (days)	603	—	607	656
Life table test	P = 0.556N	P = 0.130N	P = 0.640N	P = 0.480N
Logistic regression test	P = 0.370N	P = 0.116N	P = 0.463N	P = 0.290N
Cochran-armitage test	P = 0.397N			
Fisher exact test		P = 0.121N	P = 0.500N	P = 0.309N
All Organs: Malignant Lymphoma				
Overall rate	2/50 (4%)	2/50 (4%)	2/50 (4%)	4/50 (8%)
Adjusted rate	6.5%	7.4%	14.3%	15.6%
Terminal rate	1/27 (4%)	2/27 (7%)	2/14 (14%)	1/13 (8%)
First incidence (days)	680	733 (T)	733 (T)	603
Life table test	P = 0.057	P = 0.694	P = 0.469	P = 0.166
Logistic regression test	P = 0.133	P = 0.683	P = 0.538	P = 0.329
Cochran-Armitage test	P = 0.216			
Fisher exact test		P = 0.691N	P = 0.691N	P = 0.339
All Organs: Benign Neoplasms				
Overall rate	31/50 (62%)	31/50 (62%)	38/50 (76%)	43/50 (86%)
Adjusted rate	79.3%	78.8%	91.9%	97.5%
Terminal rate	19/27 (70%)	19/27 (70%)	11/14 (79%)	12/13 (92%)
First incidence (days)	596	439	382	392
Life table test	P < 0.001	P = 0.540	P < 0.001	P < 0.001
Logistic regression test	P < 0.001	P = 0.532	P = 0.026	P < 0.001
Cochran-Armitage test	P = 0.002			
Fisher exact test		P = 0.582N	P = 0.097	P = 0.006
All Organs: Malignant Neoplasms				
Overall rate	34/50 (68%)	40/50 (80%)	50/50 (100%)	47/50 (94%)
Adjusted rate	71.4%	83.2%	100.0%	97.9%
Terminal rate	14/27 (52%)	19/27 (70%)	14/14 (100%)	12/13 (92%)
First incidence (days)	452	523	382	392
Life table test	P < 0.001	P = 0.223	P < 0.001	P < 0.001
Logistic regression test	P = 0.004	P = 0.126	P < 0.001	P = 0.014
Cochran-Armitage test	P < 0.001			
Fisher exact test		P = 0.127	P < 0.001	P < 0.001

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

	Chamber Control	12.8 ppm	32 ppm	80 ppm
All Organs: Benign or Malignant Neoplasms				
Overall rate	48/50 (96%)	48/50 (96%)	50/50 (100%)	50/50 (100%)
Adjusted rate	96.0%	97.9%	100.0%	100.0%
Terminal rate	25/27 (93%)	26/27 (96%)	14/14 (100%)	13/13 (100%)
First incidence (days)	452	439	382	392
Life table test	P < 0.001	P = 0.518	P = 0.002	P < 0.001
Logistic regression test	P = 0.171	P = 0.684N	P = 0.391	P = 0.409
Cochran-Armitage test	P = 0.106			
Fisher exact test		P = 0.691N	P = 0.247	P = 0.247

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

TABLE C4a
Historical Incidence of Alveolar/bronchiolar Neoplasms in Chamber Control Male B6C3F$_1$ Mice[a]

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Battelle Pacific Northwest Laboratories			
1,3-Butadiene	18/50	5/50	21/50
Acetonitrile	6/50	4/50	10/50
Allyl Glycidyl Ether	7/50	0/50	7/50
2-Chloroacetophenone	7/50	6/50	11/50
l-Epinephrine Hydrochloride	11/50	5/50	15/50
Chloroethane	3/50	2/50	5/50
Hexachlorocyclopentadiene	11/49	0/49	11/49
o-Chlorobenzalmalononitrile	7/49	7/49	14/49
Ozone	6/50	8/50	14/50
Overall Historical Incidence			
Total	141/947 (14.9%)	75/947 (7.9%)	205/947 (21.7%)
Standard deviation	7.0%	5.7%	8.0%
Range	6%-36%	0%-16%	10%-42%

[a] Data as of 12 May 1995

TABLE C4b
Historical Incidence of Hemangioma and Hemangiosarcoma (All Sites) in Chamber Control Male B6C3F$_1$ Mice[a]

Study	Incidence in Controls		
	Hemangioma	Hemangiosarcoma	Hemangioma or Hemangiosarcoma
Historical Incidence at Battelle Pacific Northwest Laboratories			
1,3-Butadiene	1/50	1/50	2/50
Acetonitrile	1/50	2/50	3/50
Allyl Glycidyl Ether	0/50	1/50	1/50
2-Chloroacetophenone	1/50	1/50	2/50
l-Epinephrine Hydrochloride	1/50	4/50	5/50
Chloroethane	0/50	0/50	0/50
Hexachlorocyclopentadiene	0/50	0/50	0/50
o-Chlorobenzalmalononitrile	1/50	0/50	1/50
Ozone	0/50	0/50	0/50
Overall Historical Incidence			
Total	8/950 (0.8%)	26/950 (2.7%)	34/950 (3.6%)
Standard deviation	1.0%	2.9%	3.4%
Range	0%-2%	0%-9%	0%-10%

[a] Data as of 12 May 1995

TABLE C4c
Historical Incidence of Harderian Gland Neoplasms in Chamber Control Male B6C3F$_1$ Mice[a]

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Battelle Pacific Northwest Laboratories			
1,3-Butadiene	6/50	0/50	6/50
Acetonitrile	5/50	0/50	5/50
Allyl Glycidyl Ether	4/50	0/50	4/50
2-Chloroacetophenone	3/50	0/50	3/50
l-Epinephrine Hydrochloride	2/50	0/50	2/50
Chloroethane	2/50	2/50	4/50
Hexachlorocyclopentadiene	7/50	0/50	7/50
o-Chlorobenzalmalononitrile	6/50	0/50	6/50
Ozone	1/50	0/50	1/50
Overall Historical Incidence			
Total	47/950 (5.0%)	2/950 (0.2%)	49/950 (5.2%)
Standard deviation	4.5%	0.9%	4.5%
Range	0%-14%	0%-4%	0%-14%

[a] Data as of 12 May 1995

TABLE C4d
Historical Incidence of Squamous Cell Papilloma of the Forestomach in Chamber Control Male B6C3F$_1$ Mice[a]

Study	Incidence in Controls
Historical Incidence at Battelle Pacific Northwest Laboratories	
1,3-Butadiene	1/50
Acetonitrile	0/50
Allyl Glycidyl Ether	1/50
2-Chloroacetophenone	2/50
l-Epinephrine Hydrochloride	0/50
Chloroethane	0/50
Hexachlorocyclopentadiene	0/50
o-Chlorobenzalmalononitrile	0/50
Ozone	0/50
Overall Historical Incidence	
Total	6/950 (0.6%)
Standard deviation	1.2%
Range	0%-4%

[a] Data as of 12 May 1995

TABLE C4e
Historical Incidence of Renal Tubule Adenoma in Chamber Control Male B6C3F$_1$ Mice[a]

Study	Incidence in Controls
Historical Incidence at Battelle Pacific Northwest Laboratories	
1,3-Butadiene	0/50
Acetonitrile	0/49
Allyl Glycidyl Ether	0/49
2-Chloroacetophenone	0/50
l-Epinephrine Hydrochloride	0/50
Chloroethane	0/50
Hexachlorocyclopentadiene	0/50
o-Chlorobenzalmalononitrile	0/49
Ozone	1/50
Overall Historical Incidence	
Total	2/946 (0.2%)
Standard deviation	0.5%
Range	0%-2%

[a] Data as of 12 May 1995

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

	Chamber Control	12.8 ppm	32 ppm	80 ppm
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Moribund	15	16	26	34
Natural deaths	8	7	10	3
Survivors				
Terminal sacrifice	27	27	14	13
Animals examined microscopically	50	50	50	50
Alimentary System				
Esophagus	(50)	(49)	(50)	(50)
Dysplasia				1 (2%)
Inflammation, suppurative				1 (2%)
Epithelium, hyperplasia				1 (2%)
Gallbladder	(41)	(40)	(37)	(40)
Degeneration, hyaline	5 (12%)	1 (3%)	2 (5%)	3 (8%)
Inflammation, suppurative	1 (2%)		1 (3%)	
Necrosis	1 (2%)			
Epithelium, hyperplasia	1 (2%)			
Intestine small, duodenum	(45)	(44)	(45)	(48)
Inflammation, suppurative				1 (2%)
Necrosis		1 (2%)		
Intestine small, jejunum	(46)	(43)	(47)	(49)
Peyer's patch, hyperplasia				1 (2%)
Intestine small, ileum	(46)	(45)	(46)	(48)
Peyer's patch, hyperplasia			1 (2%)	
Liver	(50)	(50)	(50)	(49)
Angiectasis	2 (4%)	3 (6%)		1 (2%)
Basophilic focus	4 (8%)	2 (4%)		1 (2%)
Clear cell focus	1 (2%)	1 (2%)		
Congestion	1 (2%)			
Degeneration, cystic	1 (2%)	1 (2%)		
Eosinophilic focus	7 (14%)	7 (14%)	3 (6%)	8 (16%)
Hematopoietic cell proliferation	1 (2%)	1 (2%)	1 (2%)	4 (8%)
Karyomegaly	19 (38%)	13 (26%)	20 (40%)	29 (59%)
Mitotic alteration			1 (2%)	
Necrosis	9 (18%)	7 (14%)	7 (14%)	6 (12%)
Regeneration	22 (44%)	25 (50%)	25 (50%)	27 (55%)
Vacuolization cytoplasmic	1 (2%)			
Bile duct, hyperplasia	34 (68%)	31 (62%)	34 (68%)	36 (73%)
Centrilobular, necrosis			1 (2%)	
Mesentery	(2)	(8)	(16)	(11)
Angiectasis			2 (13%)	
Inflammation, focal, granulomatous				1 (9%)
Thrombosis				1 (9%)
Fat, inflammation, chronic	1 (50%)	1 (13%)		
Fat, necrosis	1 (50%)	2 (25%)	1 (6%)	1 (9%)
Pancreas	(50)	(48)	(49)	(50)
Atrophy	4 (8%)	4 (8%)	2 (4%)	2 (4%)
Basophilic focus			1 (2%)	
Cytoplasmic alteration		1 (2%)	1 (2%)	
Hyperplasia				1 (2%)
Hypertrophy	1 (2%)	1 (2%)	1 (2%)	2 (4%)
Duct, cyst		1 (2%)		

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

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Inhalation Study of Chloroprene

	Chamber Control	12.8 ppm	32 ppm	80 ppm
Alimentary System (continued)				
Salivary glands	(50)	(49)	(50)	(50)
Inflammation	1 (2%)			
Stomach, forestomach	(50)	(48)	(49)	(50)
Infiltration cellular, mast cell		1 (2%)		
Inflammation, suppurative		1 (2%)	3 (6%)	5 (10%)
Ulcer	2 (4%)	3 (6%)	1 (2%)	12 (24%)
Epithelium, hyperplasia	4 (8%)	6 (13%)	7 (14%)	29 (58%)
Stomach, glandular	(50)	(48)	(50)	(48)
Inflammation, suppurative		1 (2%)	1 (2%)	
Mineralization	1 (2%)	1 (2%)		1 (2%)
Necrosis	2 (4%)		1 (2%)	1 (2%)
Pigmentation			1 (2%)	
Tooth	(2)	(2)		
Developmental malformation	2 (100%)	2 (100%)		
Cardiovascular System				
Blood vessel		(2)	(1)	(1)
Inflammation			1 (100%)	
Mineralization		1 (50%)		
Heart	(50)	(49)	(50)	(50)
Cardiomyopathy	43 (86%)	43 (88%)	40 (80%)	45 (90%)
Hyperplasia, atypical			1 (2%)	
Inflammation			1 (2%)	
Mineralization			1 (2%)	
Artery, inflammation			1 (2%)	
Atrium, thrombosis	1 (2%)			1 (2%)
Endocrine System				
Adrenal cortex	(50)	(49)	(50)	(50)
Hyperplasia	2 (4%)	4 (8%)	3 (6%)	
Hypertrophy	13 (26%)	15 (31%)	12 (24%)	9 (18%)
Capsule, hyperplasia	2 (4%)			1 (2%)
Adrenal medulla	(50)	(49)	(50)	(49)
Hyperplasia	3 (6%)	3 (6%)	5 (10%)	2 (4%)
Islets, pancreatic	(50)	(48)	(49)	(50)
Hyperplasia	1 (2%)	2 (4%)	2 (4%)	4 (8%)
Parathyroid gland	(35)	(32)	(31)	(30)
Hyperplasia	1 (3%)			
Pituitary gland	(49)	(47)	(47)	(48)
Pars distalis, hyperplasia	1 (2%)	2 (4%)	1 (2%)	
Pars intermedia, hyperplasia	1 (2%)			
Pars nervosa, inflammation			1 (2%)	
Thyroid gland	(50)	(49)	(50)	(50)
Follicular cell, hyperplasia	5 (10%)	5 (10%)	6 (12%)	7 (14%)
General Body System				
None				
Genital System				
Epididymis	(50)	(49)	(50)	(50)
Granuloma sperm	3 (6%)		1 (2%)	1 (2%)
Hyperplasia			1 (2%)	
Inflammation				1 (2%)

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Inhalation Study of Chloroprene

	Chamber Control	12.8 ppm	32 ppm	80 ppm
Genital System (continued)				
Preputial gland	(50)	(47)	(47)	(50)
Angiectasis				1 (2%)
Cyst	2 (4%)	7 (15%)	2 (4%)	3 (6%)
Fibrosis				1 (2%)
Inflammation	2 (4%)	4 (9%)	3 (6%)	1 (2%)
Prostate	(49)	(48)	(48)	(49)
Hyperplasia		1 (2%)		
Inflammation, suppurative	2 (4%)	1 (2%)	2 (4%)	
Seminal vesicle	(49)	(48)	(49)	(48)
Inflammation	2 (4%)	2 (4%)	1 (2%)	
Testes	(50)	(49)	(50)	(50)
Angiectasis			1 (2%)	
Atrophy	2 (4%)	3 (6%)	2 (4%)	4 (8%)
Inflammation, focal, granulomatous	1 (2%)			
Hematopoietic System				
Bone marrow	(50)	(49)	(50)	(50)
Hyperplasia	3 (6%)	1 (2%)	3 (6%)	5 (10%)
Infiltration cellular, mast cell		1 (2%)		
Lymph node		(1)	(2)	(3)
Iliac, hyperplasia			2 (100%)	
Lymph node, bronchial	(32)	(23)	(33)	(28)
Hyperplasia	4 (13%)	1 (4%)	2 (6%)	1 (4%)
Lymph node, mandibular	(32)	(28)	(27)	(34)
Hyperplasia	2 (6%)	2 (7%)	1 (4%)	
Infiltration cellular, mast cell		1 (4%)		
Lymph node, mesenteric	(47)	(48)	(46)	(48)
Angiectasis		3 (6%)	3 (7%)	2 (4%)
Hyperplasia	2 (4%)	2 (4%)	2 (4%)	
Lymph node, mediastinal	(34)	(38)	(37)	(37)
Hematopoietic cell proliferation			1 (3%)	
Hyperplasia	1 (3%)	4 (11%)	2 (5%)	4 (11%)
Spleen	(50)	(49)	(50)	(50)
Accessory spleen			1 (2%)	
Angiectasis				1 (2%)
Hematopoietic cell proliferation	26 (52%)	22 (45%)	35 (70%)	31 (62%)
Hyperplasia, lymphoid	5 (10%)	3 (6%)		
Infiltration cellular, histiocyte				1 (2%)
Thymus	(34)	(28)	(25)	(34)
Hyperplasia, lymphoid				1 (3%)
Integumentary System				
Skin	(49)	(48)	(50)	(50)
Edema			2 (4%)	
Inflammation, chronic active	1 (2%)	1 (2%)	1 (2%)	4 (8%)
Epidermis, hyperplasia				1 (2%)
Prepuce, inflammation, chronic active	4 (8%)	6 (13%)	5 (10%)	1 (2%)
Subcutaneous tissue, cyst			2 (4%)	
Subcutaneous tissue, inflammation, focal, granulomatous			2 (4%)	
Subcutaneous tissue, inflammation, suppurative				1 (2%)

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Inhalation Study of Chloroprene

	Chamber Control	12.8 ppm	32 ppm	80 ppm
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Fibrous osteodystrophy	1 (2%)	1 (2%)		1 (2%)
Nervous System				
Brain	(50)	(49)	(50)	(50)
Meninges, inflammation, chronic	1 (2%)		1 (2%)	
Respiratory System				
Larynx	(50)	(47)	(50)	(50)
Hyperplasia	3 (6%)	2 (4%)	1 (2%)	4 (8%)
Inflammation, suppurative				2 (4%)
Epiglottis, metaplasia, squamous	1 (2%)			1 (2%)
Lung	(50)	(50)	(50)	(50)
Hemorrhage		1 (2%)		
Infiltration cellular, histiocyte	7 (14%)	8 (16%)	11 (22%)	22 (44%)
Inflammation, chronic, focal		2 (4%)		1 (2%)
Thrombosis	1 (2%)			
Alveolar epithelium, hyperplasia	3 (6%)	5 (10%)	2 (4%)	2 (4%)
Bronchiole, hyperplasia		10 (20%)	18 (36%)	23 (46%)
Mediastinum, inflammation, chronic		1 (2%)		
Perivascular, infiltration cellular	1 (2%)			
Nose	(50)	(48)	(50)	(50)
Inflammation, suppurative	2 (4%)	1 (2%)	4 (8%)	6 (12%)
Lateral wall, necrosis				1 (2%)
Nasolacrimal duct, inflammation, suppurative		1 (2%)		
Olfactory epithelium, atrophy	7 (14%)	8 (17%)	7 (14%)	49 (98%)
Olfactory epithelium, degeneration, hyaline			1 (2%)	2 (4%)
Olfactory epithelium, hyperplasia, adenomatous	3 (6%)	2 (4%)	2 (4%)	48 (96%)
Olfactory epithelium, metaplasia	6 (12%)	5 (10%)	5 (10%)	49 (98%)
Respiratory epithelium, degeneration, hyaline	3 (6%)	4 (8%)	2 (4%)	10 (20%)
Respiratory epithelium, necrosis				1 (2%)
Respiratory epithelium, polyp, inflammatory		1 (2%)		
Trachea	(50)	(48)	(50)	(50)
Metaplasia, squamous	1 (2%)			
Special Senses System				
Eye	(1)	(1)		(1)
Inflammation	1 (100%)	1 (100%)		1 (100%)

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Inhalation Study of Chloroprene

	Chamber Control	12.8 ppm	32 ppm	80 ppm
Urinary System				
Kidney	(50)	(49)	(50)	(50)
Cyst	1 (2%)	2 (4%)	1 (2%)	
Glomerulosclerosis				2 (4%)
Hydronephrosis		1 (2%)	1 (2%)	1 (2%)
Inflammation, chronic active	4 (8%)	2 (4%)	3 (6%)	
Metaplasia, osseous	3 (6%)	1 (2%)		1 (2%)
Mineralization		1 (2%)		
Nephropathy	47 (94%)	44 (90%)	43 (86%)	42 (84%)
Pigmentation, hemosiderin			1 (2%)	1 (2%)
Papilla, necrosis	1 (2%)			
Renal tubule, hyperplasia		4 (8%)	5 (10%)	5 (10%)
Renal tubule, necrosis	1 (2%)			1 (2%)
Ureter	(1)			
Transitional epithelium, hyperplasia	1 (100%)			
Urinary bladder	(50)	(48)	(48)	(50)
Inflammation, suppurative	3 (6%)	1 (2%)	3 (6%)	
Transitional epithelium, hyperplasia	1 (2%)		1 (2%)	

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

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

	Chamber Control	12.8 ppm	32 ppm	80 ppm
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Accidental deaths		1		1
Moribund	13	27	38	41
Natural deaths	2	6	11	5
Survivors				
Died last week of study				1
Terminal sacrifice	35	16	1	2
Animals examined microscopically	50	50	50	50
Alimentary System				
Intestine large, colon	(50)	(47)	(48)	(49)
Sarcoma			1 (2%)	
Intestine small, duodenum	(49)	(45)	(42)	(48)
Intestine small, ileum	(50)	(45)	(46)	(49)
Liver	(50)	(49)	(50)	(50)
Hemangiosarcoma	1 (2%)		1 (2%)	
Hepatocellular carcinoma	4 (8%)	10 (20%)	7 (14%)	15 (30%)
Hepatocellular carcinoma, multiple		1 (2%)	7 (14%)	4 (8%)
Hepatocellular adenoma	12 (24%)	12 (24%)	9 (18%)	7 (14%)
Hepatocellular adenoma, multiple	5 (10%)	7 (14%)	2 (4%)	9 (18%)
Hepatocholangiocarcinoma		1 (2%)	1 (2%)	
Histiocytic sarcoma	1 (2%)	2 (4%)	3 (6%)	
Sarcoma, metastatic, mesentery		1 (2%)	1 (2%)	2 (4%)
Mesentery	(10)	(14)	(27)	(21)
Hemangioma			2 (7%)	1 (5%)
Hemangiosarcoma		4 (29%)	13 (48%)	4 (19%)
Hepatocholangiocarcinoma, metastatic, liver		1 (7%)		
Histiocytic sarcoma			1 (4%)	
Sarcoma		4 (29%)	8 (30%)	3 (14%)
Pancreas	(49)	(49)	(48)	(50)
Hemangiosarcoma	1 (2%)			
Hemangiosarcoma, metastatic, mesentery			1 (2%)	
Hepatocholangiocarcinoma, metastatic, liver		1 (2%)		
Sarcoma, metastatic, mesentery		2 (4%)	2 (4%)	
Salivary glands	(50)	(49)	(50)	(50)
Sarcoma, metastatic, skin			1 (2%)	
Stomach, forestomach	(50)	(49)	(49)	(50)
Squamous cell carcinoma	1 (2%)			
Squamous cell papilloma				4 (8%)
Stomach, glandular	(50)	(48)	(49)	(50)
Sarcoma, metastatic, mesentery		1 (2%)	2 (4%)	1 (2%)
Cardiovascular System				
Heart	(50)	(49)	(50)	(50)
Endocrine System				
Adrenal cortex	(50)	(48)	(49)	(50)
Hemangiosarcoma, metastatic, mesentery			1 (2%)	
Hepatocholangiocarcinoma, metastatic, liver		1 (2%)		
Adrenal medulla	(50)	(48)	(48)	(50)
Pheochromocytoma malignant		1 (2%)		
Pheochromocytoma benign	1 (2%)		1 (2%)	

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

	Chamber Control	12.8 ppm	32 ppm	80 ppm
Endocrine System (continued)				
Islets, pancreatic	(49)	(49)	(48)	(50)
Adenoma		1 (2%)	2 (4%)	
Pituitary gland	(49)	(48)	(48)	(50)
Pars distalis, adenoma	4 (8%)	6 (13%)	4 (8%)	4 (8%)
Pars intermedia, adenoma	1 (2%)			1 (2%)
Thyroid gland	(50)	(49)	(49)	(50)
Follicular cell, adenoma	1 (2%)	1 (2%)	1 (2%)	
Follicular cell, carcinoma		2 (4%)		
Thyroglossal duct, adenoma			1 (2%)	
General Body System				
None				
Genital System				
Ovary	(48)	(47)	(47)	(49)
Cystadenoma	1 (2%)	1 (2%)	1 (2%)	
Hemangiosarcoma				1 (2%)
Histiocytic sarcoma		2 (4%)	1 (2%)	
Luteoma		1 (2%)		
Sarcoma, metastatic, mesentery			1 (2%)	
Teratoma malignant		1 (2%)		
Uterus	(50)	(49)	(50)	(50)
Hemangioma				2 (4%)
Hemangiosarcoma			2 (4%)	
Histiocytic sarcoma	1 (2%)	2 (4%)	2 (4%)	
Leiomyosarcoma		1 (2%)		
Polyp stromal	2 (4%)	4 (8%)	2 (4%)	3 (6%)
Sarcoma, metastatic, mesentery				1 (2%)
Vagina			(1)	
Sarcoma			1 (100%)	
Hematopoietic System				
Bone marrow	(50)	(49)	(49)	(50)
Hemangiosarcoma		1 (2%)	1 (2%)	
Lymph node	(4)	(3)	(5)	(2)
Iliac, hemangiosarcoma, metastatic, mesentery			1 (20%)	
Iliac, sarcoma, metastatic, mesentery				1 (50%)
Lymph node, bronchial	(32)	(31)	(34)	(38)
Histiocytic sarcoma			1 (3%)	
Sarcoma, metastatic, mesentery				1 (3%)
Lymph node, mandibular	(32)	(40)	(33)	(40)
Lymph node, mesenteric	(48)	(45)	(48)	(46)
Hemangiosarcoma		2 (4%)	1 (2%)	1 (2%)
Hemangiosarcoma, metastatic, mesentery			3 (6%)	
Histiocytic sarcoma			2 (4%)	
Sarcoma			1 (2%)	
Sarcoma, metastatic, mesentery		1 (2%)	4 (8%)	
Sarcoma, metastatic, skin		1 (2%)		
Sarcoma, metastatic, intestine large, colon			1 (2%)	
Lymph node, mediastinal	(38)	(44)	(45)	(40)
Alveolar/bronchiolar carcinoma, metastatic, lung	1 (3%)			1 (3%)
Hepatocholangiocarcinoma, metastatic, liver		1 (2%)		
Sarcoma, metastatic, mesentery				1 (3%)
Sarcoma, metastatic, skin				1 (3%)

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

	Chamber Control	12.8 ppm	32 ppm	80 ppm
Hematopoietic System (continued)				
Spleen	(50)	(49)	(49)	(50)
Hemangiosarcoma	1 (2%)	1 (2%)	1 (2%)	
Histiocytic sarcoma	1 (2%)		1 (2%)	
Thymus	(44)	(35)	(39)	(39)
Alveolar/bronchiolar carcinoma, metastatic, lung				1 (3%)
Integumentary System				
Mammary gland	(49)	(49)	(50)	(50)
Adenoacanthoma		1 (2%)	3 (6%)	2 (4%)
Adenoma		1 (2%)	1 (2%)	
Carcinoma	3 (6%)	4 (8%)	6 (12%)	11 (22%)
Carcinoma, multiple			1 (2%)	1 (2%)
Skin	(49)	(49)	(50)	(50)
Basal cell adenoma	1 (2%)			
Squamous cell papilloma				1 (2%)
Subcutaneous tissue, hemangiosarcoma	2 (4%)	1 (2%)	2 (4%)	1 (2%)
Subcutaneous tissue, histiocytic sarcoma		1 (2%)		
Subcutaneous tissue, sarcoma		10 (20%)	10 (20%)	16 (32%)
Subcutaneous tissue, sarcoma, multiple		1 (2%)	1 (2%)	2 (4%)
Subcutaneous tissue, sarcoma, metastatic, mesentery			1 (2%)	
Musculoskeletal System				
Bone	(50)	(49)	(50)	(50)
Alveolar/bronchiolar carcinoma, metastatic, lung				1 (2%)
Skeletal muscle			(2)	(1)
Sarcoma, metastatic, mesentery			1 (50%)	
Sarcoma, metastatic, skin			1 (50%)	1 (100%)
Nervous System				
None				
Respiratory System				
Larynx	(50)	(49)	(50)	(50)
Lung	(50)	(49)	(50)	(50)
Adenoacanthoma, metastatic, mammary gland			3 (6%)	
Alveolar/bronchiolar adenoma	2 (4%)	10 (20%)	17 (34%)	10 (20%)
Alveolar/bronchiolar adenoma, multiple		6 (12%)	12 (24%)	16 (32%)
Alveolar/bronchiolar carcinoma	2 (4%)	8 (16%)	8 (16%)	11 (22%)
Alveolar/bronchiolar carcinoma, multiple		6 (12%)	8 (16%)	17 (34%)
Carcinoma, metastatic, harderian gland	1 (2%)	1 (2%)		
Carcinoma, metastatic, mammary gland			2 (4%)	2 (4%)
Carcinoma, metastatic, Zymbal's gland				2 (4%)
Hemangiosarcoma, metastatic, mesentery		1 (2%)	2 (4%)	
Hepatocellular carcinoma, metastatic, liver	1 (2%)	1 (2%)	1 (2%)	4 (8%)
Hepatocholangiocarcinoma, metastatic, liver		1 (2%)	1 (2%)	
Histiocytic sarcoma	1 (2%)		2 (4%)	
Sarcoma, metastatic, mesentery			2 (4%)	1 (2%)
Sarcoma, metastatic, skin		2 (4%)	1 (2%)	2 (4%)

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

	Chamber Control	12.8 ppm	32 ppm	80 ppm
Respiratory System (continued)				
Lung (continued)	(50)	(49)	(50)	(50)
Mediastinum, alveolar/bronchiolar carcinoma, metastatic, lung			1 (2%)	2 (4%)
Mediastinum, hemangiosarcoma			1 (2%)	
Mediastinum, sarcoma, metastatic, mesentery			1 (2%)	1 (2%)
Mediastinum, sarcoma, metastatic, skin		1 (2%)		1 (2%)
Nose	(50)	(49)	(49)	(50)
Respiratory epithelium, adenoma			1 (2%)	
Special Senses System				
Harderian gland	(2)	(6)	(4)	(9)
Adenoma	1 (50%)	3 (50%)	3 (75%)	8 (89%)
Carcinoma	1 (50%)	2 (33%)		1 (11%)
Zymbal's gland				(3)
Carcinoma				3 (100%)
Urinary System				
Kidney	(50)	(49)	(49)	(50)
Hemangiosarcoma, metastatic, mesentery			1 (2%)	
Hepatocholangiocarcinoma, metastatic, liver		1 (2%)		
Histiocytic sarcoma			1 (2%)	
Sarcoma, metastatic, mesentery			2 (4%)	
Urinary bladder	(50)	(47)	(46)	(47)
Hemangiosarcoma			1 (2%)	
Histiocytic sarcoma			1 (2%)	
Sarcoma, metastatic, mesentery			2 (4%)	
Systemic Lesions				
Multiple organs[b]	(50)	(50)	(50)	(50)
Histiocytic sarcoma	1 (2%)	2 (4%)	3 (6%)	
Lymphoma malignant	7 (14%)	7 (14%)	3 (6%)	1 (2%)
Neoplasm Summary				
Total animals with primary neoplasms[c]	34	47	50	48
Total primary neoplasms	55	124	151	160
Total animals with benign neoplasms	22	32	38	42
Total benign neoplasms	31	53	59	66
Total animals with malignant neoplasms	20	42	49	48
Total malignant neoplasms	24	71	92	94
Total animals with metastatic neoplasms	3	8	23	15
Total metastatic neoplasms	3	18	40	27

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

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

Number of Days on Study	0 3 5	4 7 7	4 8 6	4 9 3	5 2 7	5 4 1	6 1 0	6 3 5	6 3 7	6 6 3	6 7 7	6 8 1	7 0 5	7 0 6	7 2 9	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4
Carcass ID Number	1 4 1	1 1 0	1 3 8	1 0 7	1 3 0	1 3 5	1 2 6	1 0 5	1 4 6	1 2 4	1 3 3	1 0 3	1 2 7	1 3 2	1 1 2	1 0 2	1 1 4	1 1 7	1 1 9	1 2 2	1 2 3	1 2 9	1 3 1	1 3 6	1 4 5
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	M	+	+	M	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																							X		
Hepatocellular carcinoma				X											X									X	
Hepatocellular adenoma																					X			X	X
Hepatocellular adenoma, multiple									X													X			
Histiocytic sarcoma									X																
Mesentery								+				+										+		+	
Oral mucosa																									
Pancreas	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma																							X		
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel												+	+												
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	M	+	+	M	+	+	+	+	+	+	+	M	M	+	M	+	+	M	+	+	+	+	+	+
Pituitary gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma															X	X								X	
Pars intermedia, adenoma														X											
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																									
General Body System																									
Tissue NOS					+																				
Genital System																									
Clitoral gland	M	M	+	M	+	I	+	+	+	+	+	M	+	M	M	+	+	+	M	+	+	+	+	+	+
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Cystadenoma																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma									X																
Polyp stromal																									

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

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

Number of Days on Study	7 3 4	7 3 4	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	
Carcass ID Number	1 4 7	1 4 8	1 5 0	1 0 1	1 0 4	1 0 6	1 0 8	1 0 9	1 1 1	1 1 3	1 1 5	1 1 6	1 1 8	1 2 0	1 2 1	1 2 5	1 2 8	1 3 4	1 3 7	1 3 9	1 4 0	1 4 2	1 4 3	1 4 4	1 4 9	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Gallbladder	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Hepatocellular carcinoma		X																								4
Hepatocellular adenoma						X		X			X	X		X				X	X	X					X	12
Hepatocellular adenoma, multiple																						X	X	X		5
Histiocytic sarcoma																										1
Mesentery							+			+	+	+							+				+			10
Oral mucosa									+																	1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma																								X		1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma																										1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Blood vessel																										2
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign																				X						1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Parathyroid gland	+	M	M	M	+	+	+	+	+	+	+	M	M	M	+	+	+	+	+	M	+	M	M	+	+	35
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma																			X							4
Pars intermedia, adenoma																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, adenoma																			X							1
General Body System																										
Tissue NOS																										1
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	41
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	48
Cystadenoma												X														1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Polyp stromal				X																X						2

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

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

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

Number of Days on Study	7 3 4	7 3 4	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	
Carcass ID Number	1 4 7	1 4 8	1 5 0	1 0 1	1 0 4	1 0 6	1 0 8	1 0 9	1 1 1	1 1 3	1 1 5	1 1 6	1 1 8	1 2 0	1 2 1	1 2 5	1 2 8	1 3 4	1 3 7	1 3 9	1 4 0	1 4 2	1 4 3	1 4 4	1 4 9	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+																						+			4
Lymph node, bronchial	M	M	+	M	+	M	+	+	M	+	+	+	M	M	M	+	M	+	+	+	M	+	+	+	M	32
Lymph node, mandibular	+	M	+	+	M	+	+	M	M	+	M	+	M	+	M	+	I	+	+	+	+	+	+	M	M	32
Lymph node, mesenteric	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph node, mediastinal	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	M	+	+	M	M	+	M	+	+	M	38
Alveolar/bronchiolar carcinoma, metastatic, lung																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Histiocytic sarcoma																										1
Thymus	+	M	+	M	+	+	+	+	+	+	+	+	+	M	M	+	M	+	+	+	+	+	+	+	+	44
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma			X																							3
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Basal cell adenoma																										1
Subcutaneous tissue, hemangiosarcoma																										2
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Peripheral nerve																										1
Spinal cord																										1
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																										2
Alveolar/bronchiolar carcinoma																		X								2
Carcinoma, metastatic, harderian gland																										1
Hepatocellular carcinoma, metastatic, liver		X																								1
Histiocytic sarcoma																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye		+																								1
Harderian gland																										2
Adenoma																										1
Carcinoma																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Ureter																			+							1
Urethra																			+							1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Lymphoma malignant	X									X					X									X		7

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Chloroprene: 12.8 ppm

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

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Chloroprene: 12.8 ppm

Number of Days on Study	6 9 1	6 9 1	6 9 1	6 9 8	7 0 2	7 0 8	7 0 8	7 1 9	7 1 9	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	
Carcass ID Number	3 0 8	3 1 9	3 3 2	3 4 5	3 0 6	3 3 4	3 4 6	3 3 1	3 4 1	3 0 5	3 0 9	3 3 3	3 3 5	3 4 8	3 0 2	3 0 7	3 1 2	3 1 7	3 2 0	3 2 2	3 2 6	3 3 6	3 3 7	3 3 8	3 3 9	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Gallbladder	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, rectum	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, cecum	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine small, duodenum	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine small, jejunum	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, ileum	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatocellular carcinoma					X			X				X									X	X				10
Hepatocellular carcinoma, multiple																							X			1
Hepatocellular adenoma		X												X		X			X	X						12
Hepatocellular adenoma, multiple							X		X			X	X		X		X						X			7
Hepatocholangiocarcinoma																										1
Histiocytic sarcoma				X																						2
Sarcoma, metastatic, mesentery																										1
Mesentery			+		+	+			+		+			+			+									14
Hemangiosarcoma			X		X	X											X									4
Hepatocholangiocarcinoma, metastatic, liver																										1
Sarcoma									X		X															4
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatocholangiocarcinoma, metastatic, liver																										1
Sarcoma, metastatic, mesentery																										2
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Sarcoma, metastatic, mesentery																										1
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Hepatocholangiocarcinoma, metastatic, liver																										1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pheochromocytoma malignant																							X			1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma																										1
Parathyroid gland	+	+	M	+	+	+	+	M	M	+	+	+	+	M	+	+	M	+	M	M	+	+	M	+	+	35
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	48
Pars distalis, adenoma						X			X	X				X			X									6
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Follicular cell, adenoma																										1
Follicular cell, carcinoma									X					X												2
General Body System																										
None																										

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Chloroprene: 12.8 ppm

Number of Days on Study	2 8 5	3 1 8	3 2 1	4 4 0	4 4 7	4 8 2	5 2 3	5 3 1	5 4 0	5 4 8	5 5 1	5 5 1	6 0 7	6 2 1	6 2 3	6 2 4	6 3 1	6 3 1	6 3 6	6 7 3	6 7 4	6 7 7	6 8 0	6 9 0	6 9 0
Carcass ID Number	3 1 8	3 3 0	3 5 0	3 1 1	3 2 1	3 4 2	3 0 3	3 2 7	3 4 4	3 1 6	3 1 5	3 2 8	3 0 1	3 2 4	3 4 7	3 0 4	3 2 5	3 4 9	3 4 3	3 1 3	3 2 9	3 1 4	3 1 0	3 2 3	3 4 0
Genital System																									
Clitoral gland	M	+	A	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+
Ovary	+	+	A	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+
Cystadenoma																									
Histiocytic sarcoma											X														
Luteoma																						X			
Teratoma malignant									X																
Uterus	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma											X														
Leiomyosarcoma								X																	
Polyp stromal											X												X		
Hematopoietic System																									
Bone marrow	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma						X																			
Lymph node										+															
Lymph node, bronchial	M	+	A	+	+	+	M	M	+	M	+	M	M	+	M	M	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	A	+	+	M	M	+	+	+	+	+	+	M	+	+	+	M	+	M	+	M	+	M	+
Lymph node, mesenteric	+	M	A	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+
Hemangiosarcoma																									
Sarcoma, metastatic, mesentery							X																		
Sarcoma, metastatic, skin																				X					
Lymph node, mediastinal	M	+	M	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+
Hepatocholangiocarcinoma, metastatic liver												X													
Spleen	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma						X																			
Thymus	M	+	M	+	+	M	+	M	M	M	+	M	+	+	+	+	+	M	+	+	M	M	+	+	+
Integumentary System																									
Mammary gland	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoacanthoma				X																					
Adenoma																									
Carcinoma					X				X													X			
Skin	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, hemangiosarcoma						X																			
Subcutaneous tissue, histiocytic, sarcoma											X														
Subcutaneous tissue, sarcoma	X			X									X			X	X				X				
Subcutaneous tissue, sarcoma, multiple																									
Musculoskeletal System																									
Bone	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Chloroprene: 12.8 ppm

Number of Days on Study	6 9 1	6 9 1	6 9 1	6 9 8	7 0 2	7 0 8	7 0 8	7 1 9	7 1 9	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	
Carcass ID Number	3 0 8	3 1 9	3 3 2	3 4 5	3 0 6	3 3 4	3 4 6	3 3 1	3 4 1	3 0 5	3 0 9	3 3 3	3 3 5	3 4 8	3 0 2	3 0 7	3 1 2	3 1 7	3 2 0	3 2 2	3 2 6	3 3 6	3 3 7	3 3 8	3 3 9	Total Tissues/ Tumors
Genital System																										
Clitoral gland	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	40
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Cystadenoma																				X						1
Histiocytic sarcoma				X																						2
Luteoma																										1
Teratoma malignant																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma				X																						2
Leiomyosarcoma																										1
Polyp stromal														X		X										4
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma																										1
Lymph node																	+			+						3
Lymph node, bronchial	+	+	+	M	+	+	M	M	M	+	+	+	M	+	M	M	+	M	+	M	+	+	M	+	+	31
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	40
Lymph node, mesenteric	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Hemangiosarcoma			X																	X						2
Sarcoma, metastatic, mesentery																										1
Sarcoma, metastatic, skin																										1
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Hepatocholangiocarcinoma, metastatic, liver																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma																										1
Thymus	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	M	+	M	+	+	35
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoacanthoma																										1
Adenoma									X																	1
Carcinoma														X												4
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Subcutaneous tissue, hemangiosarcoma																										1
Subcutaneous tissue, histiocytic sarcoma																										1
Subcutaneous tissue, sarcoma	X	X						X						X												10
Subcutaneous tissue, sarcoma,multiple																						X				1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Chloroprene: 12.8 ppm

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

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Chloroprene: 12.8 ppm

Number of Days on Study	6 9 1	6 9 1	6 9 1	6 9 8	7 0 2	7 0 8	7 0 8	7 1 9	7 1 9	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	
Carcass ID Number	3 0 8	3 1 9	3 3 2	3 4 5	3 0 6	3 3 4	3 4 6	3 3 1	3 4 1	3 0 5	3 0 9	3 3 3	3 3 5	3 4 8	3 0 2	3 0 7	3 1 2	3 1 7	3 2 0	3 2 2	3 2 6	3 3 6	3 3 7	3 3 8	3 3 9	Total Tissues/ Tumors
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar adenoma		X	X		X	X			X				X													10
Alveolar/bronchiolar adenoma, multiple															X			X	X	X					X	6
Alveolar/bronchiolar carcinoma														X												8
Alveolar/bronchiolar carcinoma, multiple							X			X			X			X						X	X			6
Carcinoma, metastatic, harderian gland																										1
Hemangiosarcoma, metastatic, mesentery					X																					1
Hepatocellular carcinoma, metastatic, liver												X														1
Hepatocholangiocarcinoma, metastatic, liver																										1
Sarcoma, metastatic, skin								X																		2
Mediastinum, sarcoma, metastatic, skin								X																		1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Special Senses System																										
Eye																										1
Harderian gland							+					+		+									+			6
Adenoma												X											X			3
Carcinoma														X												2
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatocholangiocarcinoma, metastatic, liver																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma				X																						2
Lymphoma malignant								X			X						X									7

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Chloroprene: 32 ppm

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

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Chloroprene: 32 ppm

Number of Days on Study	5 8 2	5 8 8	5 9 6	6 0 4	6 0 7	6 0 8	6 2 0	6 2 3	6 2 4	6 2 9	6 2 9	6 3 1	6 3 4	6 3 5	6 4 4	6 4 9	6 5 2	6 5 6	6 5 6	6 6 7	6 7 1	6 7 4	6 9 1	7 1 7	7 3 5	
Carcass ID Number	5 2 2	5 2 0	5 3 6	5 2 5	5 2 6	5 0 7	5 3 9	5 2 7	5 4 4	5 4 1	5 4 2	5 0 1	5 1 6	5 0 9	5 3 7	5 0 8	5 5 0	5 1 7	5 3 8	5 4 9	5 3 4	5 1 3	5 1 5	5 4 3	5 1 4	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	M	+	+	+	+	+	A	+	+	+	+	+	+	+	+	M	+	+	42
Intestine large, colon	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Sarcoma																										1
Intestine large, rectum	+	+	+	M	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine large, cecum	+	+	+	+	+	+	+	A	+	+	+	+	A	I	+	+	+	+	+	+	+	+	+	+	+	45
Intestine small, duodenum	+	+	+	+	+	+	+	A	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	42
Intestine small, jejunum	+	+	+	+	+	+	+	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	44
Intestine small, ileum	+	+	+	+	+	+	+	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	46
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Hepatocellular carcinoma					X							X										X		X	X	7
Hepatocellular carcinoma, multiple			X					X					X								X		X			7
Hepatocellular adenoma			X		X							X						X	X	X		X			X	9
Hepatocellular adenoma, multiple														X		X										2
Hepatocholangiocarcinoma																										1
Histiocytic sarcoma																										3
Sarcoma, metastatic, mesentery																										1
Mesentery		+	+	+	+	+	+	+			+		+	+	+			+	+	+			+		+	27
Hemangioma					X																				X	2
Hemangiosarcoma		X				X	X	X						X									X			13
Histiocytic sarcoma																										1
Sarcoma			X								X		X		X			X	X							8
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Hemangiosarcoma, metastatic, mesentery		X																								1
Sarcoma, metastatic, mesentery											X				X											2
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma, metastatic, skin																										1
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Sarcoma, metastatic, mesentery															X											2
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma, metastatic, mesentery		X																								1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	48
Pheochromocytoma benign																		X								1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma													X													2
Parathyroid gland	M	M	M	+	+	+	+	+	+	M	M	M	M	+	+	+	M	+	M	+	+	+	+	+	M	31
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	48
Pars distalis, adenoma							X					X					X		X							4
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Follicular cell, adenoma																			X							1
Thyroglossal duct, adenoma																							X			1
General Body System																										
None																										

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Chloroprene: 32 ppm

Number of Days on Study	2 1 6	3 4 6	3 7 8	3 8 9	3 9 4	4 2 5	4 4 0	4 5 4	4 6 3	4 7 2	4 8 7	4 9 9	5 0 3	5 0 5	5 1 5	5 2 3	5 2 4	5 3 7	5 3 1	5 3 7	5 4 9	5 5 3	5 5 1	5 7 2
Carcass ID Number	5 0 5	5 3 2	5 4 5	5 3 5	5 4 0	5 3 0	5 0 2	5 4 8	5 1 0	5 2 9	5 2 1	5 1 2	5 0 6	5 2 4	5 2 3	5 4 7	5 3 1	5 1 8	5 1 9	5 0 3	5 0 4	5 1 1	5 2 8	5 4 6	5 3 3
Genital System																								
Clitoral gland	+	M	M	+	M	M	+	+	+	+	+	+	M	M	+	+	+	+	I	+	M	+	+	+ M
Ovary	+	+	+	+	+	+	+	A	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+ +
Cystadenoma																								
Histiocytic sarcoma			X																					
Sarcoma, metastatic, mesentery																X								
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+ +
Hemangiosarcoma															X									
Histiocytic sarcoma			X					X																
Polyp stromal																				X			X	
Vagina																								
Sarcoma																								
Hematopoietic System																								
Bone marrow	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+ +
Hemangiosarcoma																						X		
Lymph node																					+			
Iliac, hemangiosarcoma, metastatic, mesentery																								
Lymph node, bronchial	+	+	M	M	M	M	+	M	M	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+ +
Histiocytic sarcoma										X														
Lymph node, mandibular	+	+	+	+	+	+	+	+	M	+	+	M	+	M	+	+	+	M	+	+	I	+	+	M +
Lymph node, mesenteric	+	+	+	+	+	M	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+ +
Hemangiosarcoma	X																							
Hemangiosarcoma, metastatic, mesentery															X									
Histiocytic sarcoma			X							X														
Sarcoma																								
Sarcoma, metastatic, mesentery									X							X								
Sarcoma, metastatic, intestine large colon														X										
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+
Spleen	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+ +
Hemangiosarcoma																						X		
Histiocytic sarcoma										X														
Thymus	+	+	+	+	+	M	+	A	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+ +
Integumentary System																								
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+ +
Adenoacanthoma						X					X								X					
Adenoma																	X							
Carcinoma					X																		X	X
Carcinoma, multiple																								
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+ +
Subcutaneous tissue, hemangiosarcoma							X															X		
Subcutaneous tissue, sarcoma																	X	X						
Subcutaneous tissue, sarcoma, multiple																								
Subcutaneous tissue, sarcoma, metastatic, mesentery																								
Musculoskeletal System																								
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+ +
Skeletal muscle																+								
Sarcoma, metastatic, mesentery																X								
Sarcoma, metastatic, skin																								
Nervous System																								
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+ +

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Chloroprene: 32 ppm

Number of Days on Study	5 8 2	5 8 8	5 9 6	6 0 4	6 0 7	6 0 8	6 2 0	6 2 3	6 2 4	6 2 9	6 2 9	6 3 1	6 3 4	6 3 5	6 4 4	6 4 9	6 5 2	6 5 6	6 5 6	6 6 7	6 7 1	6 7 4	6 9 1	7 1 7	7 3 5	
Carcass ID Number	5 2 2	5 2 0	5 3 6	5 2 5	5 2 6	5 0 7	5 3 9	5 2 7	5 4 4	5 4 1	5 4 2	5 0 1	5 1 6	5 0 9	5 3 7	5 0 8	5 5 0	5 1 7	5 3 8	5 4 9	5 3 4	5 1 3	5 1 5	5 4 3	5 1 4	Total Tissues/ Tumors
Genital System																										
Clitoral gland	+	+	M	M	M	+	+	M	M	+	+	M	+	+	+	M	M	+	+	+	+	M	+	+	+	32
Ovary	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Cystadenoma																								X		1
Histiocytic sarcoma																										1
Sarcoma, metastatic, mesentery																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma						X																				2
Histiocytic sarcoma																										2
Polyp stromal																										2
Vagina								+																		1
Sarcoma								X																		1
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma																										1
Lymph node			+					+			+									+					5
Iliac, hemangiosarcoma, metastatic, mesentery								X																		1
Lymph node, bronchial	+	M	+	+	+	M	M	+	+	+	+	+	M	M	+	+	+	+	+	+	+	M	M	M	+	34
Histiocytic sarcoma																										1
Lymph node, mandibular	+	+	+	M	+	+	M	M	M	+	+	+	M	+	M	M	+	+	M	+	+	M	I	+	M	33
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Hemangiosarcoma																										1
Hemangiosarcoma, metastatic, mesentery		X						X																		3
Histiocytic sarcoma																										2
Sarcoma																		X								1
Sarcoma, metastatic, mesentery			X																X							4
Sarcoma, metastatic, intestine large colon																										1
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	M	+	45
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma																										1
Histiocytic sarcoma																										1
Thymus	+	M	M	+	+	+	M	+	+	+	M	+	+	+	M	+	+	M	M	+	M	+	+	+	+	39
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoacanthoma																										3
Adenoma																										1
Carcinoma					X			X							X											6
Carcinoma, multiple																			X							1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, hemangiosarcoma																										2
Subcutaneous tissue, sarcoma	X			X								X				X		X			X	X			X	10
Subcutaneous tissue, sarcoma, multiple									X																	1
Subcutaneous tissue, sarcoma, metastatic, mesentery													X													1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle	+																									2
Sarcoma, metastatic, mesentery																										1
Sarcoma, metastatic, skin	X																									1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Chloroprene: 32 ppm

Number of Days on Study	2 1 6	3 4 6	3 7 8	3 8 9	3 9 4	4 2 5	4 4 0	4 5 4	4 6 3	4 7 2	4 8 7	4 9 9	5 0 3	5 0 5	5 1 5	5 2 3	5 2 4	5 3 7	5 3 1	5 3 7	5 3 9	5 4 3	5 5 1	5 5 1	5 7 2
Carcass ID Number	5 0 5	5 3 2	5 4 5	5 3 5	5 4 0	5 3 0	5 0 2	5 4 8	5 1 0	5 2 9	5 2 1	5 1 2	5 0 6	5 2 4	5 2 3	5 4 7	5 3 1	5 1 8	5 1 9	5 0 3	5 0 4	5 1 1	5 2 8	5 4 6	5 3 3
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoacanthoma, metastatic, mammary gland						X						X							X						
Alveolar/bronchiolar adenoma		X					X	X				X						X	X				X		X
Alveolar/bronchiolar adenoma, multiple													X		X									X	
Alveolar/bronchiolar carcinoma																	X	X			X				
Alveolar/bronchiolar carcinoma, multiple																									
Carcinoma, metastatic, mammary gland																								X	X
Hemangiosarcoma, metastatic, mesentery				X																					
Hepatocellular carcinoma, metastatic, liver																						X			
Hepatocholangiocarcinoma, metastatic, liver													X												
Histiocytic sarcoma			X							X															
Sarcoma, metastatic, mesentery									X																
Sarcoma, metastatic, skin																									
Mediastinum, alveolar/bronchiolar carcinoma, metastatic, lung																									
Mediastinum, hemangiosarcoma																									
Mediastinum, sarcoma, metastatic, mesentery									X																
Nose	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory epithelium, adenoma																									
Trachea	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Harderian gland																	+								
Adenoma																	X								
Urinary System																									
Kidney	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma, metastatic, mesentery																									
Histiocytic sarcoma			X																						
Sarcoma, metastatic, mesentery																									
Urinary bladder	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Histiocytic sarcoma			X																						
Sarcoma, metastatic, mesentery																									
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma			X					X		X															
Lymphoma malignant																					X			X	

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Chloroprene: 32 ppm

Number of Days on Study	5 8 2	5 8 8	5 9 6	6 0 4	6 0 7	6 0 8	6 2 0	6 2 3	6 2 4	6 2 9	6 2 9	6 3 1	6 3 4	6 3 5	6 4 4	6 4 9	6 5 2	6 5 6	6 5 6	6 6 7	6 7 1	6 7 4	6 9 1	7 1 7	7 3 5	
Carcass ID Number	5 2 2	5 2 0	5 3 6	5 2 5	5 2 6	5 0 7	5 3 9	5 2 7	5 4 4	5 4 1	5 4 2	5 0 1	5 1 6	5 0 9	5 3 7	5 0 8	5 5 0	5 1 7	5 3 8	5 4 9	5 3 4	5 1 3	5 1 5	5 4 3	5 1 4	Total Tissues/ Tumors
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoacanthoma, metastatic, mammary gland																										3
Alveolar/bronchiolar adenoma		X	X			X	X				X					X		X						X	X	17
Alveolar/bronchiolar adenoma, multiple					X			X	X			X	X	X	X				X		X					12
Alveolar/bronchiolar carcinoma			X				X									X		X							X	8
Alveolar/bronchiolar carcinoma, multiple										X		X		X	X		X				X	X		X		8
Carcinoma, metastatic, mammary gland																										2
Hemangiosarcoma, metastatic, mesentery							X																			2
Hepatocellular carcinoma, metastatic, liver																										1
Hepatocholangiocarcinoma, metastatic, liver																										1
Histiocytic sarcoma																										2
Sarcoma, metastatic, mesentery															X											2
Sarcoma, metastatic, skin	X																									1
Mediastinum, alveolar/bronchiolar carcinoma, metastatic, lung																	X									1
Mediastinum, hemangiosarcoma																									X	1
Mediastinum, sarcoma, metastatic, mesentery																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Respiratory epithelium, adenoma																		X								1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Special Senses System																										
Harderian gland				+		+																		+		4
Adenoma				X		X																				3
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma, metastatic, mesentery		X																								1
Histiocytic sarcoma																										1
Sarcoma, metastatic, mesentery											X				X											2
Urinary bladder	+	+	+	+	+	+	+	+	+	M	+	+	A	+	+	+	+	M	+	+	+	+	+	+	+	46
Hemangiosarcoma																							X			1
Histiocytic sarcoma																										1
Sarcoma, metastatic, mesentery															X				X							2
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																				X						3
Lymphoma malignant																										3

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Chloroprene: 80 ppm

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

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Chloroprene: 80 ppm

Number of Days on Study	6 0 7	6 1 0	6 1 5	6 2 4	6 2 9	6 3 1	6 3 1	6 3 1	6 3 2	6 3 2	6 3 5	6 3 5	6 3 8	6 4 9	6 4 9	6 5 2	6 5 9	6 6 3	6 6 6	6 7 3	6 7 4	6 8 0	7 3 4	7 3 5	7 3 5	
Carcass ID Number	7 0 3	7 1 3	7 2 8	7 1 2	7 3 7	7 1 8	7 3 2	7 5 0	7 2 7	7 3 6	7 3 3	7 4 7	7 2 4	7 4 2	7 4 4	7 4 8	7 0 7	7 0 8	7 3 9	7 4 4	7 3 1	7 2 3	7 4 3	7 0 6	7 1 9	7 2 0	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	M	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	42
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	46
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma			X					X			X		X				X		X	X			X		X	15
Hepatocellular carcinoma, multiple									X					X									X			4
Hepatocellular adenoma			X		X											X					X			X		7
Hepatocellular adenoma, multiple		X												X	X			X	X	X		X				9
Sarcoma, metastatic, mesentery										X																2
Mesentery		+	+		+	+		+	+	+				+		+		+		+		+			+	21
Hemangioma																									X	1
Hemangiosarcoma								X	X																	4
Sarcoma						X				X																3
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma		X						X					X													4
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma, metastatic, mesentery																										1
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	M	+	M	+	+	+	+	M	+	37
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma															X							X				4
Pars intermedia, adenoma																			X							1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
General Body System																										
None																										
Genital System																										
Clitoral gland	M	+	M	+	M	+	M	M	+	M	+	+	+	+	M	M	+	+	M	+	+	M	+	+	+	35
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangioma				X		X																				2
Polyp stromal														X					X							3
Sarcoma, metastatic, mesentery						X																				1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Chloroprene: 80 ppm

Number of Days on Study	0 0 3	2 5 2	3 2 4	3 3 6	3 8 3	4 4 3	4 5 3	4 6 2	4 6 3	4 6 7	4 8 4	5 2 3	5 2 4	5 2 4	5 2 4	5 3 1	5 3 1	5 3 8	5 4 8	5 6 5	5 7 6	5 7 9	5 7 9	5 8 2	5 9 6
Carcass ID Number	7 3 8	7 1 1	7 2 5	7 3 4	7 2 9	7 2 1	7 0 5	7 4 1	7 1 6	7 0 1	7 3 5	7 0 9	7 1 7	7 2 2	7 4 9	7 1 5	7 2 6	7 4 5	7 4 0	7 1 0	7 0 4	7 0 2	7 4 6	7 1 4	7 3 0
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node																+									
Iliac, sarcoma, metastatic, mesentery																									
Lymph node, bronchial	M	+	+	+	+	+	+	+	+	+	M	+	M	M	+	+	M	+	M	+	M	+	+	M	+
Sarcoma, metastatic, mesentery																									
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	M	+	+	M	M	M	+
Lymph node, mesenteric	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																					X				
Lymph node, mediastinal	M	+	+	+	+	+	I	+	+	+	M	+	+	M	+	+	+	+	M	+	+	+	M	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung																									
Sarcoma, metastatic, mesentery																									
Sarcoma, metastatic, skin										X															
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	M	+	+	M	+	+	M
Alveolar/bronchiolar carcinoma, metastatic, lung																									
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoacanthoma																								X	
Carcinoma				X	X		X				X		X						X						X
Carcinoma, multiple																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Subcutaneous tissue, hemangiosarcoma																		X							
Subcutaneous tissue, sarcoma								X	X	X				X	X							X	X		
Subcutaneous tissue, sarcoma, multiple																X									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung																									
Skeletal muscle										+															
Sarcoma, metastatic, skin										X															
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma							X		X				X				X					X	X	X	
Alveolar/bronchiolar adenoma, multiple								X			X	X			X					X	X				X
Alveolar/bronchiolar carcinoma											X	X	X	X		X					X				X
Alveolar/bronchiolar carcinoma, multiple			X																X						
Carcinoma, metastatic, mammary gland				X									X												
Carcinoma, metastatic, Zymbal's gland																				X					
Hepatocellular carcinoma, metastatic, liver																	X								X
Sarcoma, metastatic, mesentery																									
Sarcoma, metastatic, skin										X															
Mediastinum, alveolar/bronchiolar carcinoma, metastatic, lung																									
Mediastinum, sarcoma, metastatic, mesentery																									
Mediastinum, sarcoma, metastatic, skin										X															
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Chloroprene: 80 ppm

Number of Days on Study	6 0 7	6 1 0	6 1 5	6 2 4	6 2 9	6 3 1	6 3 1	6 3 1	6 3 2	6 3 2	6 3 5	6 3 5	6 3 8	6 4 9	6 4 9	6 5 2	6 5 9	6 6 3	6 6 6	6 7 3	6 7 4	6 8 0	7 3 4	7 3 5	7 3 5	
Carcass ID Number	7 0 3	7 1 3	7 2 8	7 1 2	7 3 7	7 1 8	7 3 2	7 5 0	7 2 7	7 3 6	7 3 3	7 4 7	7 2 4	7 4 2	7 4 8	7 4 0 7	7 0 8	7 3 9	7 4 4	7 3 1	7 2 3	7 4 3	7 0 6	7 1 9	7 2 0	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node						+																				2
Iliac, sarcoma, metastatic, mesentery						X																				1
Lymph node, bronchial	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	M	+	+	+	+	M	38
Sarcoma, metastatic, mesentery										X																1
Lymph node, mandibular	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	M	40
Lymph node, mesenteric	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	46
Hemangiosarcoma																										1
Lymph node, mediastinal	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	40
Alveolar/bronchiolar carcinoma, metastatic, lung														X												1
Sarcoma, metastatic, mesentery										X																1
Sarcoma, metastatic, skin																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	M	+	M	+	+	+	+	M	+	+	+	M	+	+	+	I	M	+	+	+	+	+	+	+	+	39
Alveolar/bronchiolar carcinoma, metastatic, lung														X												1
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoacanthoma			X																							2
Carcinoma						X	X		X			X														11
Carcinoma, multiple																							X			1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma																						X				1
Subcutaneous tissue, hemangiosarcoma																										1
Subcutaneous tissue, sarcoma	X	X			X	X			X		X		X								X	X				16
Subcutaneous tissue, sarcoma, multiple							X																			2
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma, metastatic, lung																	X									1
Skeletal muscle																										1
Sarcoma, metastatic, skin																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma					X					X														X		10
Alveolar/bronchiolar adenoma, multiple			X				X	X				X				X		X		X			X		X	16
Alveolar/bronchiolar carcinoma			X		X					X						X										11
Alveolar/bronchiolar carcinoma, multiple		X		X		X			X		X		X	X	X		X	X	X		X	X		X	X	17
Carcinoma, metastatic, mammary gland																										2
Carcinoma, metastatic, Zymbal's gland				X																						2
Hepatocellular carcinoma, metastatic, liver											X								X							4
Sarcoma, metastatic, mesentery										X																1
Sarcoma, metastatic, skin		X																								2
Mediastinum, alveolar/bronchiolar carcinoma, metastatic, lung														X			X									2
Mediastinum, sarcoma, metastatic, mesentery										X																1
Mediastinum, sarcoma, metastatic, skin																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Chloroprene: 80 ppm

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

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Chloroprene: 80 ppm

Number of Days on Study	6 0 7	6 1 0	6 1 5	6 2 4	6 2 9	6 3 1	6 3 1	6 3 1	6 3 2	6 3 2	6 3 5	6 3 5	6 3 8	6 4 9	6 4 9	6 5 2	6 5 9	6 6 3	6 6 6	6 7 3	6 7 4	6 8 0	7 3 4	7 3 5	7 3 5	
Carcass ID Number	7 0 3	7 1 3	7 2 8	7 1 2	7 3 7	7 1 8	7 3 2	7 5 0	7 2 7	7 3 6	7 3 3	7 4 7	7 2 4	7 4 2	7 4 8	7 0 7	7 0 8	7 3 9	7 4 4	7 3 1	7 2 3	7 4 3	7 0 6	7 1 9	7 2 0	Total Tissues/ Tumors
Special Senses System																										
Ear																										1
Harderian gland	+	+							+	+						+								+	+	9
Adenoma	X	X							X	X														X	X	8
Carcinoma																X										1
Zymbal's gland				+																						3
Carcinoma				X																						3
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant																X										1

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

	Chamber Control	12.8 ppm	32 ppm	80 ppm
Harderian Gland: Adenoma				
Overall rate[a]	1/50 (2%)	3/50 (6%)	3/50 (6%)	8/50 (16%)
Adjusted rate[b]	2.9%	14.9%	12.0%	74.4%
Terminal rate[c]	1/35 (3%)	2/16 (13%)	0/1 (0%)	2/3 (67%)
First incidence (days)	734 (T)	621	524	467
Life table test[d]	P < 0.001	P = 0.120	P = 0.048	P < 0.001
Logistic regression test[d]	P = 0.001	P = 0.225	P = 0.293	P = 0.007
Cochran-Armitage test[d]	P = 0.006			
Fisher exact test[d]		P = 0.309	P = 0.309	P = 0.015
Harderian Gland: Adenoma or Carcinoma				
Overall rate	2/50 (4%)	5/50 (10%)	3/50 (6%)	9/50 (18%)
Adjusted rate	5.0%	23.8%	12.0%	77.0%
Terminal rate	1/35 (3%)	3/16 (19%)	0/1 (0%)	2/3 (67%)
First incidence (days)	527	621	524	467
Life table test	P < 0.001	P = 0.065	P = 0.157	P < 0.001
Logistic regression test	P = 0.004	P = 0.186	P = 0.577	P = 0.016
Cochran-Armitage test	P = 0.018			
Fisher exact test		P = 0.218	P = 0.500	P = 0.026
Liver: Hepatocellular Adenoma				
Overall rate	17/50 (34%)	19/49 (39%)	11/50 (22%)	16/50 (32%)
Adjusted rate	47.0%	69.1%	100.0%	85.1%
Terminal rate	16/35 (46%)	9/16 (56%)	1/1 (100%)	1/3 (33%)
First incidence (days)	637	523	505	383
Life table test	P < 0.001	P = 0.005	P < 0.001	P < 0.001
Logistic regression test	P = 0.070	P = 0.157	P = 0.064	P = 0.141
Cochran-Armitage test	P = 0.359N			
Fisher exact test		P = 0.388	P = 0.133N	P = 0.500N
Liver: Hepatocellular Carcinoma				
Overall rate	4/50 (8%)	11/49 (22%)	14/50 (28%)	19/50 (38%)
Adjusted rate	10.3%	41.8%	100.0%	91.5%
Terminal rate	2/35 (6%)	4/16 (25%)	1/1 (100%)	2/3 (67%)
First incidence (days)	493	440	503	524
Life table test	P < 0.001	P = 0.004	P < 0.001	P < 0.001
Logistic regression test	P < 0.001	P = 0.040	P = 0.002	P < 0.001
Cochran-Armitage test	P < 0.001			
Fisher exact test		P = 0.041	P = 0.009	P < 0.001
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rate	20/50 (40%)	26/49 (53%)	20/50 (40%)	30/50 (60%)
Adjusted rate	52.2%	81.8%	100.0%	100.0%
Terminal rate	17/35 (49%)	11/16 (69%)	1/1 (100%)	3/3 (100%)
First incidence (days)	493	440	503	383
Life table test	P < 0.001	P < 0.001	P < 0.001	P < 0.001
Logistic regression test	P < 0.001	P = 0.051	P = 0.011	P < 0.001
Cochran-Armitage test	P = 0.054			
Fisher exact test		P = 0.135	P = 0.581N	P = 0.036

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

	Chamber Control	12.8 ppm	32 ppm	80 ppm
Lung: Alveolar/bronchiolar Adenoma				
Overall rate	2/50 (4%)	16/49 (33%)	29/50 (58%)	26/50 (52%)
Adjusted rate	5.7%	57.9%	100.0%	100.0%
Terminal rate	2/35 (6%)	6/16 (38%)	1/1 (100%)	3/3 (100%)
First incidence (days)	734 (T)	447	346	453
Life table test	P < 0.001	P < 0.001	P < 0.001	P < 0.001
Logistic regression test	P < 0.001	P < 0.001	P < 0.001	P < 0.001
Cochran-Armitage test	P < 0.001			
Fisher exact test		P < 0.001	P < 0.001	P < 0.001
Lung: Alveolar/bronchiolar Carcinoma				
Overall rate	2/50 (4%)	14/49 (29%)	16/50 (32%)	28/50 (56%)
Adjusted rate	5.5%	51.9%	100.0%	95.4%
Terminal rate	1/35 (3%)	6/16 (38%)	1/1 (100%)	2/3 (67%)
First incidence (days)	706	447	524	324
Life table test	P < 0.001	P < 0.001	P < 0.001	P < 0.001
Logistic regression test	P < 0.001	P < 0.001	P < 0.001	P < 0.001
Cochran-Armitage test	P < 0.001			
Fisher exact test		P < 0.001	P < 0.001	P < 0.001
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rate	4/50 (8%)	28/49 (57%)	34/50 (68%)	42/50 (84%)
Adjusted rate	11.0%	83.5%	100.0%	100.0%
Terminal rate	3/35 (9%)	11/16 (69%)	1/1 (100%)	3/3 (100%)
First incidence (days)	706	447	346	324
Life table test	P < 0.001	P < 0.001	P < 0.001	P < 0.001
Logistic regression test	P < 0.001	P < 0.001	P < 0.001	P < 0.001
Cochran-Armitage test	P < 0.001			
Fisher exact test		P < 0.001	P < 0.001	P < 0.001
Mammary Gland: Adenoacanthoma				
Overall rate	0/50 (0%)	1/50 (2%)	3/50 (6%)	2/50 (4%)
Adjusted rate	0.0%	2.1%	7.7%	7.9%
Terminal rate	0/35 (0%)	0/16 (0%)	0/1 (0%)	0/3 (0%)
First incidence (days)	—[e]	440	425	582
Life table test	P = 0.147	P = 0.492	P = 0.091	P = 0.128
Logistic regression test	P = 0.355	P = 0.496	P = 0.205	P = 0.252
Cochran-Armitage test	P = 0.216			
Fisher exact test		P = 0.500	P = 0.121	P = 0.247
Mammary Gland: Carcinoma				
Overall rate	3/50 (6%)	4/50 (8%)	7/50 (14%)	12/50 (24%)
Adjusted rate	7.4%	13.6%	35.1%	56.4%
Terminal rate	1/35 (3%)	1/16 (6%)	0/1 (0%)	1/3 (33%)
First incidence (days)	527	447	394	336
Life table test	P < 0.001	P = 0.322	P = 0.003	P < 0.001
Logistic regression test	P = 0.008	P = 0.553	P = 0.207	P = 0.036
Cochran-Armitage test	P = 0.003			
Fisher exact test		P = 0.500	P = 0.159	P = 0.011

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

	Chamber Control	12.8 ppm	32 ppm	80 ppm
Mammary Gland: Adenoma or Carcinoma				
Overall rate	3/50 (6%)	5/50 (10%)	8/50 (16%)	12/50 (24%)
Adjusted rate	7.4%	18.4%	37.0%	56.4%
Terminal rate	1/35 (3%)	1/16 (6%)	0/1 (0%)	1/3 (33%)
First incidence (days)	527	447	394	336
Life table test	P < 0.001	P = 0.179	P = 0.001	P < 0.001
Logistic regression test	P = 0.013	P = 0.397	P = 0.152	P = 0.036
Cochran-Armitage test	P = 0.005			
Fisher exact test		P = 0.357	P = 0.100	P = 0.011
Mesentery: Hemangiosarcoma				
Overall rate	0/50 (0%)	4/50 (8%)	13/50 (26%)	4/50 (8%)
Adjusted rate	0.0%	18.6%	59.3%	15.8%
Terminal rate	0/35 (0%)	1/16 (6%)	0/1 (0%)	0/3 (0%)
First incidence (days)	—	691	389	523
Life table test	P = 0.008	P = 0.015	P < 0.001	P = 0.016
Logistic regression test	P = 0.525N	P = 0.032	P < 0.001	P = 0.072
Cochran-Armitage test	P = 0.206			
Fisher exact test		P = 0.059	P < 0.001	P = 0.059
Mesentery: Hemangioma or Hemangiosarcoma				
Overall rate	0/50 (0%)	4/50 (8%)	15/50 (30%)	5/50 (10%)
Adjusted rate	0.0%	18.6%	100.0%	43.9%
Terminal rate	0/35 (0%)	1/16 (6%)	1/1 (100%)	1/3 (33%)
First incidence (days)	—	691	389	523
Life table test	P < 0.001	P = 0.015	P < 0.001	P = 0.001
Logistic regression test	P = 0.132	P = 0.032	P < 0.001	P = 0.023
Cochran-Armitage test	P = 0.128			
Fisher exact test		P = 0.059	P < 0.001	P = 0.028
Mesentery: Sarcoma				
Overall rate	0/50 (0%)	4/50 (8%)	8/50 (16%)	3/50 (6%)
Adjusted rate	0.0%	16.3%	46.5%	12.6%
Terminal rate	0/35 (0%)	1/16 (6%)	0/1 (0%)	0/3 (0%)
First incidence (days)	—	523	463	443
Life table test	P = 0.018	P = 0.023	P < 0.001	P = 0.041
Logistic regression test	P = 0.308	P = 0.060	P = 0.004	P = 0.157
Cochran-Armitage test	P = 0.313			
Fisher exact test		P = 0.059	P = 0.003	P = 0.121
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	4/49 (8%)	6/48 (13%)	4/48 (8%)	4/50 (8%)
Adjusted rate	11.1%	30.5%	31.6%	34.7%
Terminal rate	3/35 (9%)	3/15 (20%)	0/1 (0%)	0/3 (0%)
First incidence (days)	729	636	620	443
Life table test	P = 0.006	P = 0.056	P = 0.002	P = 0.027
Logistic regression test	P = 0.299	P = 0.146	P = 0.124	P = 0.525
Cochran-Armitage test	P = 0.439N			
Fisher exact test		P = 0.357	P = 0.631	P = 0.631N

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

	Chamber Control	12.8 ppm	32 ppm	80 ppm
Skin (Subcutaneous Tissue): Sarcoma				
Overall rate	0/50 (0%)	11/50 (22%)	11/50 (22%)	18/50 (36%)
Adjusted rate	0.0%	35.3%	100.0%	69.6%
Terminal rate	0/35 (0%)	2/16 (13%)	1/1 (100%)	0/3 (0%)
First incidence (days)	—	285	524	462
Life table test	P < 0.001	P < 0.001	P < 0.001	P < 0.001
Logistic regression test	P < 0.001	P = 0.001	P < 0.001	P < 0.001
Cochran-Armitage test	P < 0.001			
Fisher exact test		P < 0.001	P < 0.001	P < 0.001
Stomach (Forestomach): Squamous Cell Papilloma				
Overall rate	0/50 (0%)	0/50 (0%)	0/50 (0%)	4/50 (8%)
Adjusted rate	0.0%	0.0%	0.0%	18.8%
Terminal rate	0/35 (0%)	0/16 (0%)	0/1 (0%)	0/3 (0%)
First incidence (days)	—	—[f]	—	576
Life table test	P < 0.001		—	P = 0.010
Logistic regression test	P = 0.001	—	—	P = 0.053
Cochran-Armitage test	P = 0.002			
Fisher exact test		—	—	P = 0.059
Stomach (Forestomach): Squamous Cell Papilloma or Squamous Cell Carcinoma				
Overall rate	1/50 (2%)	0/50 (0%)	0/50 (0%)	4/50 (8%)
Adjusted rate	2.9%	0.0%	0.0%	18.8%
Terminal rate	1/35 (3%)	0/16 (0%)	0/1 (0%)	0/3 (0%)
First incidence (days)	734 (T)	—	—	576
Life table test	P < 0.001	P = 0.656N	P = 0.998N	P = 0.015
Logistic regression test	P = 0.007	P = 0.656N	P = 0.998N	P = 0.120
Cochran-Armitage test	P = 0.018			
Fisher exact test		P = 0.500N	P = 0.500N	P = 0.181
Thyroid Gland (Follicular Cell): Adenoma or Carcinoma				
Overall rate	1/50 (2%)	3/49 (6%)	1/49 (2%)	0/50 (0%)
Adjusted rate	2.9%	14.3%	12.5%	0.0%
Terminal rate	1/35 (3%)	1/16 (6%)	0/1 (0%)	0/3 (0%)
First incidence (days)	734 (T)	673	656	—
Life table test	P = 0.566	P = 0.121	P = 0.222	P = 0.941N
Logistic regression test	P = 0.535N	P = 0.197	P = 0.543	P = 0.941N
Cochran-Armitage test	P = 0.179N			
Fisher exact test		P = 0.301	P = 0.747	P = 0.500N
Uterus: Stromal Polyp				
Overall rate	2/50 (4%)	4/50 (8%)	2/50 (4%)	3/50 (6%)
Adjusted rate	5.7%	17.7%	6.7%	23.2%
Terminal rate	2/35 (6%)	2/16 (13%)	0/1 (0%)	0/3 (0%)
First incidence (days)	734 (T)	551	537	443
Life table test	P = 0.037	P = 0.118	P = 0.187	P = 0.037
Logistic regression test	P = 0.438	P = 0.270	P = 0.668	P = 0.417
Cochran-Armitage test	P = 0.549			
Fisher exact test		P = 0.339	P = 0.691N	P = 0.500

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

	Chamber Control	12.8 ppm	32 ppm	80 ppm
Zymbal's Gland: Carcinoma				
Overall rate	0/50 (0%)	0/50 (0%)	0/50 (0%)	3/50 (6%)
Adjusted rate	0.0%	0.0%	0.0%	10.8%
Terminal rate	0/35 (0%)	0/16 (0%)	0/1 (0%)	0/3 (0%)
First incidence (days)	—	—	—	565
Life table test	P = 0.004	—	—	P = 0.054
Logistic regression test	P = 0.009	—	—	P = 0.137
Cochran-Armitage test	P = 0.010			
Fisher exact test		—	—	P = 0.121
All Organs: Hemangioma				
Overall rate	0/50 (0%)	0/50 (0%)	2/50 (4%)	3/50 (6%)
Adjusted rate	0.0%	0.0%	100.0%	39.5%
Terminal rate	0/35 (0%)	0/16 (0%)	1/1 (100%)	1/3 (33%)
First incidence (days)	—	—	607	624
Life table test	P < 0.001	—	P = 0.010	P = 0.007
Logistic regression test	P = 0.004	—	P = 0.072	P = 0.037
Cochran-Armitage test	P = 0.032			
Fisher exact test		—	P = 0.247	P = 0.121
All Organs: Hemangiosarcoma				
Overall rate	4/50 (8%)	6/50 (12%)	17/50 (34%)	5/50 (10%)
Adjusted rate	10.6%	25.7%	100.0%	18.3%
Terminal rate	3/35 (9%)	2/16 (13%)	1/1 (100%)	0/3 (0%)
First incidence (days)	541	482	216	523
Life table test	P = 0.017	P = 0.104	P < 0.001	P = 0.061
Logistic regression test	P = 0.493N	P = 0.330	P = 0.009	P = 0.486
Cochran-Armitage test	P = 0.504			
Fisher exact test		P = 0.370	P = 0.001	P = 0.500
All Organs: Hemangioma or Hemangiosarcoma				
Overall rate	4/50 (8%)	6/50 (12%)	18/50 (36%)	8/50 (16%)
Adjusted rate	10.6%	25.7%	100.0%	50.8%
Terminal rate	3/35 (9%)	2/16 (13%)	1/1 (100%)	1/3 (33%)
First incidence (days)	541	482	216	523
Life table test	P < 0.001	P = 0.104	P < 0.001	P = 0.002
Logistic regression test	P = 0.248	P = 0.330	P = 0.005	P = 0.110
Cochran-Armitage test	P = 0.189			
Fisher exact test		P = 0.370	P < 0.001	P = 0.178
All Organs: Histiocytic Sarcoma				
Overall rate	1/50 (2%)	2/50 (4%)	3/50 (6%)	0/50 (0%)
Adjusted rate	2.4%	6.9%	6.7%	0.0%
Terminal rate	0/35 (0%)	0/16 (0%)	0/1 (0%)	0/3 (0%)
First incidence (days)	637	551	378	—
Life table test	P = 0.508N	P = 0.392	P = 0.180	P = 0.733N
Logistic regression test	P = 0.169N	P = 0.528	P = 0.492	P = 0.521N
Cochran-Armitage test	P = 0.285N			
Fisher exact test		P = 0.500	P = 0.309	P = 0.500N

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

	Chamber Control	12.8 ppm	32 ppm	80 ppm
All Organs: Malignant Lymphoma				
Overall rate	7/50 (14%)	7/50 (14%)	3/50 (6%)	1/50 (2%)
Adjusted rate	18.0%	26.9%	22.3%	10.0%
Terminal rate	5/35 (14%)	2/16 (13%)	0/1 (0%)	0/3 (0%)
First incidence (days)	35	548	539	652
Life table test	P = 0.539N	P = 0.234	P = 0.216	P = 0.606N
Logistic regression test	P = 0.020N	P = 0.579N	P = 0.103N	P = 0.021N
Cochran-Armitage test	P = 0.014N			
Fisher exact test		P = 0.613N	P = 0.159N	P = 0.030N
All Organs: Benign Neoplasms				
Overall rate	22/50 (44%)	32/50 (64%)	38/50 (76%)	42/50 (84%)
Adjusted rate	57.8%	87.7%	100.0%	100.0%
Terminal rate	19/35 (54%)	12/16 (75%)	1/1 (100%)	3/3 (100%)
First incidence (days)	637	447	346	383
Life table test	P < 0.001	P < 0.001	P < 0.001	P < 0.001
Logistic regression test	P < 0.001	P = 0.003	P < 0.001	P < 0.001
Cochran-Armitage test	P < 0.001			
Fisher exact test		P = 0.035	P = 0.001	P < 0.001
All Organs: Malignant Neoplasms				
Overall rate	20/50 (40%)	42/50 (84%)	49/50 (98%)	48/50 (96%)
Adjusted rate	44.8%	89.3%	100.0%	100.0%
Terminal rate	11/35 (31%)	11/16 (69%)	1/1 (100%)	3/3 (100%)
First incidence (days)	35	285	216	324
Life table test	P < 0.001	P < 0.001	P < 0.001	P < 0.001
Logistic regression test	P < 0.001	P < 0.001	P < 0.001	P < 0.001
Cochran-Armitage test	P < 0.001			
Fisher exact test		P < 0.001	P < 0.001	P < 0.001
All Organs: Benign or Malignant Neoplasms				
Overall rate	34/50 (68%)	47/50 (94%)	50/50 (100%)	48/50 (96%)
Adjusted rate	77.0%	97.9%	100.0%	100.0%
Terminal rate	25/35 (71%)	15/16 (94%)	1/1 (100%)	3/3 (100%)
First incidence (days)	35	285	216	324
Life table test	P < 0.001	P < 0.001	P < 0.001	P < 0.001
Logistic regression test	P < 0.001	P < 0.001	P < 0.001	P < 0.001
Cochran-Armitage test	P < 0.001			
Fisher exact test		P < 0.001	P < 0.001	P < 0.001

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

TABLE D4a
Historical Incidence of Alveolar/bronchiolar Neoplasms in Chamber Control Female B6C3F$_1$ Mice[a]

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Battelle Pacific Northwest Laboratories			
1,3-Butadiene	4/50	0/50	4/50
Acetonitrile	7/49	1/49	8/49
Allyl Glycidyl Ether	0/50	0/50	0/50
2-Chloroacetophenone	4/50	3/50	6/50
l-Epinephrine Hydrochloride	3/50	2/50	5/50
Chloroethane	2/49	3/49	5/49
Hexachlorocyclopentadiene	4/48	3/48	7/48
o-Chlorobenzalmalononitrile	4/50	1/50	5/50
Ozone	4/50	2/50	6/50
Overall Historical Incidence			
Total	61/939 (6.5%)	38/939 (4.1%)	97/939 (10.3%)
Standard deviation	3.2%	3.2%	3.7%
Range	0%-14%	0%-12%	0%-16%

[a] Data as of 12 May 1995

TABLE D4b
Historical Incidence of Hemangioma and Hemangiosarcoma (All Sites) in Chamber Control Female B6C3F$_1$ Mice[a]

Study	Incidence in Controls		
	Hemangioma	Hemangiosarcoma	Hemangioma or Hemangiosarcoma
Historical Incidence at Battelle Pacific Northwest Laboratories			
1,3-Butadiene	2/50	3/50	5/50
Acetonitrile	2/49	3/49	5/49
Allyl Glycidyl Ether	0/50	2/50	2/50
2-Chloroacetophenone	0/50	0/50	0/50
l-Epinephrine Hydrochloride	2/50	2/50	4/50
Chloroethane	0/49	1/49	1/49
Hexachlorocyclopentadiene	1/49	0/49	1/49
o-Chlorobenzalmalononitrile	1/50	2/50	3/50
Ozone	0/50	2/50	2/50
Overall Historical Incidence			
Total	15/941 (1.6%)	28/941 (3.0%)	43/941 (4.6%)
Standard deviation	1.9%	2.3%	3.2%
Range	0%-4%	0%-6%	0%-10%

[a] Data as of 12 May 1995

TABLE D4c
Historical Incidence of Harderian Gland Neoplasms in Chamber Control Female B6C3F$_1$ Mice[a]

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Battelle Pacific Northwest Laboratories			
1,3-Butadiene	8/50	0/50	8/50
Acetonitrile	3/49	0/49	3/49
Allyl Glycidyl Ether	0/50	0/50	0/50
2-Chloroacetophenone	0/50	0/50	0/50
l-Epinephrine Hydrochloride	1/50	1/50	2/50
Chloroethane	2/49	0/49	2/49
Hexachlorocyclopentadiene	4/49	1/49	5/49
o-Chlorobenzalmalononitrile	2/50	2/50	4/50
Ozone	1/50	2/50	3/50
Overall Historical Incidence			
Total	26/941 (2.8%)	6/941 (0.6%)	32/941 (3.4%)
Standard deviation	4.1%	1.4%	4.4%
Range	0%-16%	0%-4%	0%-16%

[a] Data as of 12 May 1995

TABLE D4d
Historical Incidence of Mammary Gland Neoplasms in Chamber Control Female B6C3F$_1$ Mice[a]

Study	Incidence in Controls	
	Adenoacanthoma	Carcinoma
Historical Incidence at Battelle Pacific Northwest Laboratories		
1,3-Butadiene	0/50	0/50
Acetonitrile	0/49	3/49
Allyl Glycidyl Ether	0/50	4/50
2-Chloroacetophenone	0/50	4/50
l-Epinephrine Hydrochloride	0/50	1/50
Chloroethane	1/49	2/49
Hexachlorocyclopentadiene	0/49	1/49
o-Chlorobenzalmalononitrile	0/50	3/50
Ozone	0/50	1/50
Overall Historical Incidence		
Total	1/941 (0.1%)	29/941 (3.1%)
Standard deviation	0.5%	2.6%
Range	0%-2%	0%-8%

[a] Data as of 12 May 1995

TABLE D4e
Historical Incidence of Hepatocellular Neoplasms in Chamber Control Female B6C3F$_1$ Mice[a]

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Battelle Pacific Northwest Laboratories			
1,3-Butadiene	11/49	4/49	15/49
Acetonitrile	4/49	7/49	9/49
Allyl Glycidyl Ether	1/50	5/50	6/50
2-Chloroacetophenone	4/50	8/50	12/50
l-Epinephrine Hydrochloride	2/50	1/50	3/50
Chloroethane	0/49	3/49	3/49
Hexachlorocyclopentadiene	5/49	4/49	9/49
o-Chlorobenzalmalononitrile	4/50	7/50	11/50
Ozone	20/50	15/50	27/50
Overall Historical Incidence			
Total	114/937 (12.2%)	103/937 (11%)	200/937 (21.3%)
Standard deviation	9.7%	6.7%	11.9%
Range	0%-40%	0%-30%	3%-54%

[a] Data as of 12 May 1995

TABLE D4f
Historical Incidence of Skin Sarcoma in Chamber Control Female B6C3F$_1$ Mice[a]

Study	Incidence in Controls
Historical Incidence at Battelle Pacific Northwest Laboratories	
1,3-Butadiene	1/50
Acetonitrile	0/49
Allyl Glycidyl Ether	0/50
2-Chloroacetophenone	0/50
l-Epinephrine Hydrochloride	0/50
Chloroethane	1/49
Hexachlorocyclopentadiene	0/49
o-Chlorobenzalmalononitrile	1/50
Ozone	1/50
Overall Historical Incidence	
Total	5/941 (0.5%)
Standard deviation	0.9%
Range	0%-2%

[a] Data as of 12 May 1995

TABLE D4g
Historical Incidence of Mesentery Sarcoma in Chamber Control Female B6C3F$_1$ Mice[a]

Study	Incidence in Controls
Historical Incidence at Battelle Pacific Northwest Laboratories	
1,3-Butadiene	0/50
Acetonitrile	0/49
Allyl Glycidyl Ether	0/50
2-Chloroacetophenone	0/50
l-Epinephrine Hydrochloride	0/50
Chloroethane	0/49
Hexachlorocyclopentadiene	0/49
o-Chlorobenzalmalononitrile	0/50
Ozone	0/50
Overall Historical Incidence	
Total	0/941

[a] Data as of 12 May 1995

TABLE D4h
Historical Incidence of Forestomach Neoplasms in Chamber Control Female B6C3F$_1$ Mice[a]

Study	Incidence in Controls	
	Squamous Cell Papilloma	Squamous Cell Papilloma or Carcinoma
Historical Incidence at Battelle Pacific Northwest Laboratories		
1,3-Butadiene	0/50	0/50
Acetonitrile	1/49	1/49
Allyl Glycidyl Ether	1/50	1/50
2-Chloroacetophenone	0/50	1/50
l-Epinephrine Hydrochloride	0/50	0/50
Chloroethane	0/49	0/49
Hexachlorocyclopentadiene	0/49	0/49
o-Chlorobenzalmalononitrile	2/50	2/50
Ozone	0/50	0/50
Overall Historical Incidence		
Total	11/941 (1.2%)	13/941 (1.4%)
Standard deviation	1.8%	1.8%
Range	0%-6%	0%-6%

[a] Data as of 12 May 1995

TABLE D4i
Historical Incidence of Zymbal's Gland Carcinoma in Chamber Control Female B6C3F$_1$ Mice[a]

Study	Incidence in Controls
Historical Incidence at Battelle Pacific Northwest Laboratories	
1,3-Butadiene	0/50
Acetonitrile	0/49
Allyl Glycidyl Ether	0/50
2-Chloroacetophenone	0/50
l-Epinephrine Hydrochloride	0/50
Chloroethane	0/49
Hexachlorocyclopentadiene	0/49
o-Chlorobenzalmalononitrile	0/50
Ozone	0/50
Overall Historical Incidence	
Total	0/941

[a] Data as of 12 May 1995

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

	Chamber Control	12.8 ppm	32 ppm	80 ppm
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Accidental deaths		1		1
Moribund	13	27	38	41
Natural deaths	2	6	11	5
Survivors				
Died last week of study				1
Terminal sacrifice	35	16	1	2
Animals examined microscopically	50	50	50	50
Alimentary System				
Esophagus	(49)	(48)	(50)	(50)
Epithelium, hyperplasia		1 (2%)		
Gallbladder	(45)	(44)	(42)	(42)
Angiectasis	1 (2%)			
Cyst	1 (2%)			
Degeneration, hyaline			2 (5%)	
Inflammation, suppurative	3 (7%)	1 (2%)	2 (5%)	2 (5%)
Necrosis	1 (2%)			
Intestine large, colon	(50)	(47)	(48)	(49)
Inflammation, suppurative		1 (2%)		
Intestine large, cecum	(50)	(45)	(45)	(49)
Hemorrhage				1 (2%)
Lymphoid tissue, hyperplasia		1 (2%)	1 (2%)	
Intestine small, duodenum	(49)	(45)	(42)	(48)
Necrosis				1 (2%)
Epithelium, hyperplasia				1 (2%)
Intestine small, jejunum	(50)	(46)	(44)	(49)
Epithelium, hyperplasia	1 (2%)			
Peyer's patch, hyperplasia	1 (2%)		1 (2%)	
Liver	(50)	(49)	(50)	(50)
Angiectasis	2 (4%)	3 (6%)	4 (8%)	1 (2%)
Basophilic focus	4 (8%)			2 (4%)
Clear cell focus	1 (2%)			
Degeneration, fatty	1 (2%)		2 (4%)	
Eosinophilic focus	13 (26%)	12 (24%)	15 (30%)	28 (56%)
Fibrosis	1 (2%)			
Hematopoietic cell proliferation	1 (2%)	5 (10%)	9 (18%)	12 (24%)
Hyperplasia, lymphoid				1 (2%)
Inflammation, chronic		1 (2%)		
Mineralization			1 (2%)	1 (2%)
Necrosis	4 (8%)	5 (10%)	13 (26%)	7 (14%)
Regeneration				1 (2%)
Vacuolization cytoplasmic		2 (4%)		1 (2%)
Bile duct, cyst	1 (2%)			1 (2%)
Bile duct, hyperplasia	2 (4%)	1 (2%)	1 (2%)	3 (6%)
Centrilobular, degeneration			2 (4%)	3 (6%)
Centrilobular, necrosis		2 (4%)	2 (4%)	3 (6%)
Mesentery	(10)	(14)	(27)	(21)
Angiectasis	1 (10%)			1 (5%)
Hemorrhage			1 (4%)	
Fat, inflammation, chronic		1 (7%)		
Fat, necrosis	7 (70%)	3 (21%)	2 (7%)	18 (86%)

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

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Inhalation Study of Chloroprene

	Chamber Control	12.8 ppm	32 ppm	80 ppm
Alimentary System (continued)				
Oral mucosa	(1)			
Pharyngeal, hyperplasia	1 (100%)			
Pancreas	(49)	(49)	(48)	(50)
Angiectasis				1 (2%)
Atrophy	3 (6%)	6 (12%)	5 (10%)	3 (6%)
Hyperplasia				1 (2%)
Hypertrophy	2 (4%)	3 (6%)	3 (6%)	4 (8%)
Duct, cyst				1 (2%)
Salivary glands	(50)	(49)	(50)	(50)
Inflammation		1 (2%)		
Stomach, forestomach	(50)	(49)	(49)	(50)
Diverticulum		2 (4%)		
Hyperplasia				3 (6%)
Inflammation, suppurative	2 (4%)			8 (16%)
Mineralization	1 (2%)			
Ulcer		2 (4%)	3 (6%)	5 (10%)
Epithelium, hyperplasia	4 (8%)	3 (6%)	8 (16%)	27 (54%)
Stomach, glandular	(50)	(48)	(49)	(50)
Degeneration, hyaline				1 (2%)
Inflammation, suppurative				4 (8%)
Necrosis			3 (6%)	
Epithelium, hyperplasia				1 (2%)
Cardiovascular System				
Blood vessel	(2)			
Hyperplasia	1 (50%)			
Inflammation	1 (50%)			
Heart	(50)	(49)	(50)	(50)
Cardiomyopathy	35 (70%)	35 (71%)	34 (68%)	33 (66%)
Mineralization			1 (2%)	
Artery, inflammation				1 (2%)
Atrium, thrombosis		1 (2%)		
Endocrine System				
Adrenal cortex	(50)	(48)	(49)	(50)
Hematopoietic cell proliferation	1 (2%)		2 (4%)	1 (2%)
Hyperplasia	1 (2%)			
Hypertrophy	2 (4%)	2 (4%)	3 (6%)	2 (4%)
Inflammation, focal, granulomatous			1 (2%)	
Necrosis				1 (2%)
Capsule, hyperplasia		1 (2%)		
Adrenal medulla	(50)	(48)	(48)	(50)
Hyperplasia	3 (6%)	2 (4%)		1 (2%)
Necrosis				1 (2%)
Islets, pancreatic	(49)	(49)	(48)	(50)
Hyperplasia			1 (2%)	1 (2%)
Pituitary gland	(49)	(48)	(48)	(50)
Pars distalis, angiectasis		1 (2%)	1 (2%)	
Pars distalis, hyperplasia	18 (37%)	8 (17%)	7 (15%)	9 (18%)
Pars intermedia, hyperplasia		1 (2%)		1 (2%)
Thyroid gland	(50)	(49)	(49)	(50)
Follicular cell, hyperplasia	12 (24%)	15 (31%)	8 (16%)	4 (8%)

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Inhalation Study of Chloroprene

	Chamber Control	12.8 ppm	32 ppm	80 ppm
General Body System				
None				
Genital System				
Ovary	(48)	(47)	(47)	(49)
Angiectasis		1 (2%)		
Atrophy	7 (15%)	8 (17%)	7 (15%)	6 (12%)
Cyst	20 (42%)	18 (38%)	5 (11%)	6 (12%)
Fibrosis				1 (2%)
Hemorrhage		1 (2%)		1 (2%)
Corpus luteum, hyperplasia				1 (2%)
Granulosa cell, hyperplasia		2 (4%)	1 (2%)	
Uterus	(50)	(49)	(50)	(50)
Angiectasis	3 (6%)		2 (4%)	2 (4%)
Hemorrhage	1 (2%)			2 (4%)
Hydrometra	3 (6%)	6 (12%)	2 (4%)	8 (16%)
Hyperplasia, cystic	5 (10%)	3 (6%)	2 (4%)	3 (6%)
Inflammation, suppurative	1 (2%)		2 (4%)	
Endometrium, hyperplasia				1 (2%)
Hematopoietic System				
Bone marrow	(50)	(49)	(49)	(50)
Angiectasis				1 (2%)
Atrophy		1 (2%)		
Hyperplasia	2 (4%)	2 (4%)	3 (6%)	4 (8%)
Necrosis	1 (2%)			
Lymph node	(4)	(3)	(5)	(2)
Hyperplasia			1 (20%)	
Iliac, hyperplasia	1 (25%)		1 (20%)	1 (50%)
Pancreatic, hyperplasia	1 (25%)			
Renal, hyperplasia		1 (33%)		
Lymph node, bronchial	(32)	(31)	(34)	(38)
Congestion		1 (3%)		
Hematopoietic cell proliferation		1 (3%)	1 (3%)	
Hyperplasia	2 (6%)	3 (10%)	4 (12%)	3 (8%)
Lymph node, mandibular	(32)	(40)	(33)	(40)
Angiectasis		1 (3%)		
Hematopoietic cell proliferation				1 (3%)
Hyperplasia	2 (6%)	2 (5%)		4 (10%)
Infiltration cellular, mast cell		1 (3%)		
Lymph node, mesenteric	(48)	(45)	(48)	(46)
Angiectasis	1 (2%)	1 (2%)	1 (2%)	
Congestion				1 (2%)
Hematopoietic cell proliferation	1 (2%)	2 (4%)		1 (2%)
Hemorrhage				1 (2%)
Hyperplasia	6 (13%)	1 (2%)	2 (4%)	2 (4%)
Inflammation, chronic				1 (2%)
Lymph node, mediastinal	(38)	(44)	(45)	(40)
Hematopoietic cell proliferation			1 (2%)	
Hyperplasia		1 (2%)	7 (16%)	7 (18%)
Spleen	(50)	(49)	(49)	(50)
Angiectasis	1 (2%)			
Hematopoietic cell proliferation	13 (26%)	25 (51%)	42 (86%)	39 (78%)
Hyperplasia, lymphoid	9 (18%)	5 (10%)	1 (2%)	3 (6%)
Infiltration cellular, mononuclear cell	1 (2%)			

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Inhalation Study of Chloroprene

	Chamber Control	12.8 ppm	32 ppm	80 ppm
Hematopoietic System (continued)				
Thymus	(44)	(35)	(39)	(39)
Angiectasis	1 (2%)	1 (3%)		
Atrophy	1 (2%)		3 (8%)	1 (3%)
Hyperplasia, lymphoid	2 (5%)			
Integumentary System				
Mammary gland	(49)	(49)	(50)	(50)
Galactocele				1 (2%)
Hyperplasia		1 (2%)	1 (2%)	3 (6%)
Skin	(49)	(49)	(50)	(50)
Inflammation, chronic active	1 (2%)	3 (6%)	1 (2%)	
Sebaceous gland, hyperplasia				2 (4%)
Subcutaneous tissue, inflammation, suppurative	2 (4%)			
Musculoskeletal System				
Bone	(50)	(49)	(50)	(50)
Fibrous osteodystrophy	15 (30%)	11 (22%)	6 (12%)	9 (18%)
Fracture				1 (2%)
Nervous System				
Brain	(50)	(49)	(50)	(50)
Gliosis	1 (2%)			
Hemorrhage		1 (2%)		
Meninges, inflammation, chronic	3 (6%)			1 (2%)
Spinal cord	(1)			
Degeneration	1 (100%)			
Respiratory System				
Larynx	(50)	(49)	(50)	(50)
Hyperplasia	1 (2%)	1 (2%)	1 (2%)	5 (10%)
Inflammation, suppurative			1 (2%)	1 (2%)
Epiglottis, hyperplasia				1 (2%)
Lung	(50)	(49)	(50)	(50)
Angiectasis				1 (2%)
Hemorrhage		1 (2%)	1 (2%)	1 (2%)
Infiltration cellular, histiocyte	1 (2%)	14 (29%)	18 (36%)	23 (46%)
Inflammation, chronic, focal				1 (2%)
Thrombosis		1 (2%)		
Alveolar epithelium, hyperplasia	1 (2%)	1 (2%)	1 (2%)	4 (8%)
Bronchiole, hyperplasia		15 (31%)	12 (24%)	30 (60%)
Perivascular, infiltration cellular	1 (2%)		1 (2%)	
Nose	(50)	(49)	(49)	(50)
Infiltration cellular, mast cell		1 (2%)		
Inflammation, chronic				1 (2%)
Inflammation, suppurative		1 (2%)	3 (6%)	4 (8%)
Metaplasia				1 (2%)
Nasolacrimal duct, inflammation, suppurative			1 (2%)	
Olfactory epithelium, atrophy	6 (12%)	5 (10%)	4 (8%)	47 (94%)
Olfactory epithelium, degeneration, hyaline	3 (6%)			

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Inhalation Study of Chloroprene

	Chamber Control	12.8 ppm	32 ppm	80 ppm
Respiratory System (continued)				
Nose (continued)	(50)	(49)	(49)	(50)
Olfactory epithelium, hyperplasia, adenomatous	2 (4%)	3 (6%)		44 (88%)
Olfactory epithelium, metaplasia	2 (4%)	3 (6%)	1 (2%)	44 (88%)
Olfactory epithelium, glands, inflammation, acute		1 (2%)		
Respiratory epithelium, degeneration, hyaline	17 (34%)	9 (18%)	10 (20%)	25 (50%)
Respiratory epithelium, necrosis			1 (2%)	
Special Senses System				
Eye	(1)	(1)		
Inflammation		1 (100%)		
Urinary System				
Kidney	(50)	(49)	(49)	(50)
Hydronephrosis	1 (2%)	1 (2%)	4 (8%)	
Inflammation, chronic active	1 (2%)			
Metaplasia, osseous		1 (2%)		1 (2%)
Nephropathy	41 (82%)	35 (71%)	25 (51%)	20 (40%)
Pigmentation, hemosiderin		1 (2%)		3 (6%)
Artery, inflammation, chronic	1 (2%)			
Papilla, necrosis			1 (2%)	
Renal tubule, mineralization	1 (2%)			
Renal tubule, necrosis			4 (8%)	
Urinary bladder	(50)	(47)	(46)	(47)
Hemorrhage			1 (2%)	

APPENDIX E
GENETIC TOXICOLOGY

GENETIC TOXICOLOGY

SALMONELLA TYPHIMURIUM MUTAGENICITY TEST PROTOCOL

Testing was performed as reported by Zeiger *et al*. (1987). Chloroprene was sent to the laboratory as a coded aliquot from Radian Corporation (Austin, TX). It was incubated with the *Salmonella typhimurium* tester strains (TA98, TA100, TA1535, and TA1537) either in buffer or S9 mix (metabolic activation enzymes and cofactors from Aroclor 1254-induced male Sprague-Dawley rat or Syrian hamster liver) for 20 minutes at 37° C. Top agar supplemented with L-histidine and d-biotin was added, and the contents of the tubes were mixed and poured onto the surfaces of minimal glucose agar plates. Histidine-independent mutant colonies arising on these plates were counted following incubation for 2 days at 37° C.

Each trial consisted of triplicate plates of concurrent positive and negative controls and five doses of chloroprene. The high dose was limited by toxicity. All trials were repeated.

In this assay, a positive response is defined as a reproducible, dose-related increase in histidine-independent (revertant) colonies in any one strain/activation combination. An equivocal response is defined as an increase in revertants that is not dose related, not reproducible, or 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.

DROSOPHILA MELANOGASTER TEST PROTOCOL

The assay for induction of sex-linked recessive lethal (SLRL) mutations was performed with adult flies as described by Foureman *et al*. (1994). Chloroprene was supplied as a coded aliquot by Radian Corporation. It was assayed in the SLRL test by feeding for 3 days to adult Canton-S wild-type males no more than 24 hours old at the beginning of treatment. Because no response was obtained, chloroprene was retested by injection into adult males.

To administer chloroprene by injection, a glass Pasteur pipette was drawn out in a flame to a microfine filament and the tip was broken off to allow delivery of the test solution. Injection was performed either manually, by attaching a rubber bulb to the other end of the pipette and forcing through sufficient solution (0.2 to 0.3 μL) to slightly distend the abdomen of the fly or by attaching the pipette to a microinjector that automatically delivers a calibrated volume. Flies were anesthetized with ether and immobilized on a strip of tape. Injection into the thorax, under the wing, was performed with the aid of a dissecting microscope.

Toxicity tests were performed to set concentrations of chloroprene at a level that would induce approximately 30% mortality after 72 hours of feeding or 24 hours after injection, while keeping induced sterility at an acceptable level. Canton-S males were allowed to feed for 72 hours on a 5% sucrose solution of chloroprene dissolved in ethanol. In the injection experiments, 24- to 72-hour-old Canton-S males were administered a 0.7% sodium chloride solution of chloroprene and allowed to recover for 24 hours. Treated males were mated to three *Basc* females for 3 days and given fresh females at 2-day intervals to produce three matings of 3, 2, and 2 days (in each case, sample sperm from successive matings were treated at successively earlier postmeiotic stages). F_1 heterozygous females were mated with their siblings and then placed in individual vials. F_1 daughters from the same parental male were kept together to identify clusters. (A cluster occurs when a number of mutants from a given male result from a single spontaneous premeiotic mutation event and is identified when the number of mutants from that male exceeds the number predicted by a Poisson distribution). If a cluster was identified, all data from the male in question were discarded. Presumptive lethal mutations were identified as vials containing fewer than 5% of the expected number of wild-type males after 17 days; these were retested to confirm the response.

SLRL data were analyzed by simultaneous comparison with the concurrent and historical controls with a normal approximation to the binomial test (Margolin *et al.*, 1983). A test result was considered positive if the P value was less than or equal to 0.01 and the mutation frequency in the tested group was greater that 0.10%, or if the P value was less than or equal to 0.05 and the frequency in the treatment group was greater than 0.15%. A test was considered to be inconclusive if the P value was between 0.05 and 0.01 but the frequency in the treatment group was between 0.10% and 0.15% or the P value was between 0.10 and 0.05 but the frequency in the treatment group was greater than 0.10%. A test was considered negative if the P value was greater than or equal to 0.10 or if the frequency in the treatment group was less than 0.10%.

MOUSE BONE MARROW CHROMOSOMAL ABERRATIONS AND SISTER CHROMATID EXCHANGE TEST PROTOCOLS

The complete experimental protocols are described in detail by Tice *et al.* (1988). A dose range-finding study was performed. The highest experimental dose administered (80 ppm) was limited by toxicity. Male B6C3F$_1$ mice (15 animals per group) were exposed 6 hours per day for 12 days to ambient air or to chloroprene (12, 32, or 80 ppm). Approximately 1 hour before the twelfth exposure began, a 50-mg bromodeoxyuridine (BrdU) tablet coated partially (~ 70%) with paraffin (McFee *et al.*, 1983) was implanted subcutaneously into the abdominal area of each lightly anesthetized mouse. The use of BrdU allowed selection of the appropriate cell population for scoring. Chromosomal aberrations (Abs) induced by chemical administration are present in maximum number at the first metaphase following treatment; they decline in number during subsequent nuclear divisions due to cell death. Sister chromatid exchanges (SCEs) are properly scored in cells that are in the second division after treatment. Two hours before sacrifice, the mice received an intraperitoneal injection of colchicine in saline. Ten animals to be scored in each dose group for frequency of Abs were killed 17 to 20 hours after BrdU tablet implantation. For SCE analysis, five mice per dose group were killed 24 hours after BrdU implantation. One or both femurs were removed and the marrow was flushed out with phosphate-buffered saline (pH 7.0). Cells were treated with a hypotonic salt solution, fixed, and dropped onto chilled slides. After a 24-hour drying period, the slides were stained and scored. Fifty first-division metaphase cells were scored from each of eight animals per treatment for Abs. Responses were evaluated as the percentage of aberrant metaphase cells, excluding gaps. For SCE analysis, 25 second-division metaphase cells were scored from each of four animals per treatment. Responses were evaluated as SCEs/cell. For both the Abs and SCE tests, the data were analyzed by trend test (Margolin *et al.*, 1986).

MOUSE PERIPHERAL BLOOD MICRONUCLEUS TEST PROTOCOLS

16-Day Study

The mice used for micronucleus analysis were the same ones used in the bone marrow Abs and SCE analyses. Preliminary range-finding studies were performed and the exposure protocol is described in detail by Tice *et al.* (1988). Male B6C3F$_1$ mice were exposed 6 hours per day, 5 days per week for a total of 12 exposure days over a 16-day period to ambient air or to chloroprene (12, 32, or 80 ppm). For the micronucleus analysis, air-dried peripheral blood samples, obtained by tail-snip and immediately fixed in absolute methanol, were prepared at the end of the twelfth exposure day, at the time of colchicine injection (necessary for Abs and SCE analyses). Slides were coded and stained with acridine orange. Each slide was scanned at 800× magnification using epi-illuminated fluorescence microscopy (450 to 490 nm excitation, 520 nm emission). The frequency of micronucleated cells among 1,000 polychromatic erythrocytes (PCEs) and 1,000 normochromatic erythrocytes (NCEs) were scored. The results were tabulated as the mean of the pooled results from all animals within a treatment group, plus or minus the standard error of the mean. The frequency of micronucleated cells among PCEs and NCEs was analyzed over exposure groups using a one-tailed Cochran-Armitage trend test (Margolin and Risko, 1987), followed by pairwise comparisons between each exposure group and the control group.

13-Week Study

A detailed discussion of this assay is presented in MacGregor *et al.* (1990). At the end of the 13-week inhalation study, peripheral blood samples were obtained from male and female mice, and smears were immediately prepared and fixed in absolute methanol. The methanol-fixed slides were stained with a chromatin-specific fluorescent dye mixture of Hoechst 33258/pyronin Y (MacGregor *et al.*, 1983) and coded. Slides were scanned at 630× or 1,000× magnification using a semi-automated image analysis system to determine the frequency of micronuclei in 2,000 PCEs and 10,000 NCEs in each of 10 animals per exposure group. The criteria of Schmid (1976) were used in defining micronuclei, with the additional requirement that the micronuclei exhibit the characteristic fluorescent emissions of DNA (blue with 360 nm and orange with 540 nm UV illumination); the minimum size limit was approximately one-twentieth the diameter of the NCE cell. Log transformation of the NCE data, testing for normality by the Shapiro-Wilk test, and testing for heterogeneity of variance by Cochran's test were performed before statistical analyses. The frequency of micronucleated cells among NCEs was determined by analysis of variance with the SAS GLM procedure. The NCE data for each exposure group were compared with the concurrent control using Student's *t*-test. The frequency of micronucleated cells among PCEs was analyzed by the Cochran-Armitage trend test, and individual dose groups were compared to the concurrent control by Kastenbaum-Bowman's binomial test.

RESULTS

Chloroprene showed no evidence of mutagenicity in tests performed *in vitro* or *in vivo*. Chloroprene was not mutagenic in any of four strains of *S. typhimurium* (TA98, TA100, TA1535, or TA1537) when tested with a preincubation protocol at concentrations up to 3,333 µg/plate, with and without Aroclor-induced rat or hamster liver S9 (Zeiger *et al.*, 1987; Table E1). No induction of SLRL mutations was noted in germ cells of male *D. melanogaster* administered chloroprene via feeding or injection (Foureman *et al.*, 1994; Table E2). *In vivo* assays in male mice for induction of Abs, SCEs, and increases in the frequency of micronucleated erythrocytes after 12 inhalation exposures to chloroprene (12, 32, or 80 ppm) all gave negative results (Tice *et al.*, 1988; Tables E3, E4, and E5). In addition, no increase was observed in the frequency of micronucleated erythrocytes in peripheral blood of male and female mice exposed for 13 weeks to chloroprene (5 to 80 ppm) via inhalation (Table E6).

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

Strain	Dose (µg/plate)	Revertants/plate[b] -S9 Trial 1	-S9 Trial 2	+10% hamster S9 Trial 1	+10% hamster S9 Trial 2	+10% rat S9 Trial 1	+10% rat S9 Trial 2
TA100							
	0	145 ± 1.5	120 ± 4.7	160 ± 11.8	126 ± 9.1	154 ± 16.5	117 ± 7.8
	3	146 ± 7.6	139 ± 4.1				
	10	167 ± 7.9	124 ± 0.3		143 ± 1.3		146 ± 14.3
	33	164 ± 8.0	124 ± 6.6	140 ± 7.3	144 ± 2.8	149 ± 20.3	128 ± 3.5
	100	147 ± 6.1	98 ± 9.8	136 ± 10.3	141 ± 3.4	152 ± 5.1	149 ± 10.5
	333	92 ± 17.9	51 ± 16.6[c]	136 ± 11.4	130 ± 12.8	133 ± 6.2	158 ± 7.5
	1,000			94 ± 4.2[c]	145 ± 23.2	Toxic	126 ± 7.5
	3,333			0 ± 0.0[c]		Toxic	
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control[d]		321 ± 11.7	424 ± 16.2	2,113 ± 4.8	1,895 ± 83.7	1,055 ± 61.4	900 ± 15.3
TA1535							
	0	21 ± 3.7	15 ± 1.7	10 ± 1.7	12 ± 2.1	7 ± 2.5	10 ± 1.9
	3	24 ± 2.9	16 ± 5.0				
	10	22 ± 3.5	15 ± 1.5		7 ± 0.0		8 ± 2.2
	33	20 ± 3.2	19 ± 2.2	9 ± 1.5	9 ± 4.3	11 ± 4.9	6 ± 0.6
	100	18 ± 0.3	10 ± 2.2	12 ± 1.8	14 ± 1.5	7 ± 0.3	11 ± 2.3
	333	Toxic	6 ± 2.1[c]	20 ± 0.3	15 ± 3.1	7 ± 2.3	10 ± 2.5
	1,000			Toxic	11 ± 3.3[c]	Toxic	8 ± 1.5
	3,333			Toxic		Toxic	
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		384 ± 17.9	396 ± 2.3	429 ± 31.8	507 ± 35.4	255 ± 18.4	313 ± 77.0
TA1537							
	0	8 ± 0.6	5 ± 2.6	7 ± 3.0	8 ± 2.6	13 ± 2.9	6 ± 0.9
	3	7 ± 0.7	5 ± 1.2				
	10	13 ± 2.1	8 ± 3.2		10 ± 2.3		5 ± 2.3
	33	9 ± 2.3	5 ± 0.9	7 ± 1.0	5 ± 0.3	12 ± 4.2	7 ± 0.6
	100	11 ± 3.0[c]	7 ± 3.0	8 ± 1.5	7 ± 0.9	13 ± 1.9	9 ± 3.2
	333	Toxic	4 ± 0.9[c]	6 ± 0.9	5 ± 0.7	11 ± 4.3	8 ± 0.7
	1,000			Toxic	6 ± 0.9[c]	Toxic	6 ± 1.7
	3,333			Toxic		Toxic	
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		99 ± 3.5	100 ± 18.2	479 ± 6.1	353 ± 32.0	238 ± 4.4	283 ± 14.2
TA98							
	0	25 ± 0.9	22 ± 2.7	24 ± 3.7	28 ± 4.6	38 ± 6.7	24 ± 2.6
	3	23 ± 4.6	18 ± 2.8				
	10	25 ± 3.5	14 ± 3.3		26 ± 1.3		26 ± 3.8
	33	26 ± 0.9	20 ± 2.1	25 ± 3.5	34 ± 4.6	31 ± 3.6	26 ± 3.3
	100	17 ± 1.5	16 ± 1.9	29 ± 1.2	28 ± 2.1	33 ± 3.8	31 ± 3.5
	333	Toxic	12 ± 2.0	24 ± 2.9	33 ± 3.8	27 ± 4.1	28 ± 2.2
	1,000			30 ± 2.5	25 ± 0.9	Toxic	33 ± 4.5
	3,333			Toxic		Toxic	
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		830 ± 33.4	760 ± 8.0	1,779 ± 45.1	1,761 ± 147.7	613 ± 12.5	640 ± 8.7

[a] Study was performed at SRI International. The detailed protocol and these data are presented in Zeiger *et al*. (1987).
[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 (TA1537), and 4-nitro-*o*-phenylenediamine (TA98). The positive control for metabolic activation with all strains was 2-aminoanthracene.

TABLE E2
Induction of Sex-Linked Recessive Lethal Mutations in *Drosophila melanogaster* by Chloroprene[a]

Route of Exposure	Dose (ppm)	Incidence of Death (%)	Incidence of Sterility (%)	No. of Lethals/No. of X Chromosomes Tested			Total[b]
				Mating 1	Mating 2	Mating 3	
Feed	1,820	24	0	5/2,021	6/1,996	9/1,903	20/5,920 (0.34%)
	0			4/1,934	2/2,128	10/2,046	16/6,108 (0.26%)
Injection	1,820	16	2	5/2,471	1/1,587	0/1,374	6/5,432 (0.11%)
	0			1/2,115	0/1,720	8/1,895	9/5,730 (0.16%)

[a] Study was performed at the University of Wisconsin, Madison. A detailed description of the protocol and these data are presented in Foureman *et al*. (1994); results were not significant at the 5% level (Margolin *et al.*, 1983).
[b] Total number of lethal mutations/total number of X chromosomes tested for three mating trials

TABLE E3
Induction of Chromosomal Aberrations in Mouse Bone Marrow Cells by Chloroprene[a]

Compound	Dose (ppm)	Number of Mice	Total Abs	Abs/Cell	Cells with Abs (%)
Air[b]	0	8	0.8	0.01	1.09
Chloroprene					
	12	8	1.1	0.01	1.25
	32	8	1.8	0.02	2.00
	80	8	1.0	0.01	0.75
					P = 0.683[c]

[a] Study was performed at Brookhaven National Laboratories. The detailed protocol and these data are presented in Tice *et al*. (1988). Abs = aberrations
[b] Inhalation chamber control
[c] Significance tested by the one-tailed trend test (Margolin *et al*., 1986); significant at $P < 0.05$

TABLE E4
Induction of Sister Chromatid Exchanges in Mouse Bone Marrow Cells by Chloroprene[a]

Compound	Dose (ppm)	Number of Mice	Mean SCEs/Cell
Air[b]	0	4	5.06 ± 0.213
Chloroprene	12	4	6.37 ± 0.827
	32	4	4.61 ± 0.426
	80	4	3.94 ± 0.329
			P = 0.500[c]

[a] Study was performed at Brookhaven National Laboratories. The detailed protocol and these data are presented in Tice *et al*. (1988). Data for mean SCEs/cell are given as mean ± standard error. SCE = sister chromatid exchange
[b] Inhalation chamber control
[c] Significance tested by the one-tailed trend test (Margolin *et al*., 1986); significant at P < 0.05

TABLE E5
Frequency of Micronuclei in Peripheral Blood Erythrocytes of Male Mice Following Treatment with Chloroprene by Inhalation for 16 Days[a]

Compound	Dose (ppm)	Number of Mice	Micronucleated Cells/1,000 Cells[b]	
			PCEs	NCEs
Air[c]	0	15	2.07 ± 0.316	3.00 ± 0.414
Chloroprene	12	14	3.14 ± 0.501	2.57 ± 0.453
	32	15	2.20 ± 0.536	1.72 ± 0.284
	80	15	2.60 ± 0.456	2.80 ± 0.368
			P = 0.394[d]	P = 0.454

[a] Study was performed at Brookhaven National Laboratories. The detailed protocol and these data are presented in Tice *et al*. (1988). PCE = polychromatic erythrocyte; NCE = normochromatic erythrocyte
[b] Mean ± standard error
[c] Inhalation chamber control
[d] Significance of micronucleated cells/1,000 cells tested by the one-tailed trend test (Margolin *et al*., 1986); significant at P < 0.05

TABLE E6
Frequency of Micronuclei in Peripheral Blood Erythrocytes of Mice Following Treatment with Chloroprene by Inhalation for 13 Weeks[a]

Compound	Dose (ppm)	Number of Mice	Micronucleated Cells/1,000 Cells[b]	
			PCEs	NCEs
Males				
Air[c]	0	10	2.32 ± 0.36	1.36 ± 0.14
Chloroprene	5	10	2.36 ± 0.45	1.28 ± 0.08
	12	10	2.43 ± 0.63	1.32 ± 0.09
	32	10	1.40 ± 0.59	1.32 ± 0.12
	80	10	1.97 ± 0.39	1.39 ± 0.12
Females				
Air	0	10	2.09 ± 0.42	1.04 ± 0.07
Chloroprene	5	10	1.88 ± 0.53	0.98 ± 0.20
	12	10	1.99 ± 0.33	1.15 ± 0.07
	32	10	1.06 ± 0.42	0.94 ± 0.09
	80	10	1.32 ± 0.29	1.32 ± 0.09

[a] Study was performed at the USDA Western Regional Center. The detailed protocol are presented in MacGregor *et al*. (1990). PCE = polychromatic erythrocyte; NCE = normochromatic erythrocyte
[b] Mean ± standard error
[c] Inhalation chamber control

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

TABLE F1
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats in the 16-Day Inhalation Study of Chloroprene[a]

	Chamber Control	32 ppm	80 ppm	200 ppm	500 ppm
Male					
n	7	10	10	9	1[b]
Necropsy body wt	186 ± 7	183 ± 7	185 ± 6	173 ± 9	150
Brain					
Absolute	1.721 ± 0.028	1.700 ± 0.022	1.715 ± 0.020	1.703 ± 0.017	1.600
Relative	9.31 ± 0.20	9.41 ± 0.32	9.35 ± 0.23	10.04 ± 0.46	10.67
Heart					
Absolute	0.650 ± 0.022	0.647 ± 0.024	0.661 ± 0.023	0.609 ± 0.023	0.520
Relative	3.50 ± 0.07	3.55 ± 0.05	3.58 ± 0.04	3.55 ± 0.08	3.47
R. Kidney					
Absolute	0.834 ± 0.036	0.865 ± 0.025	0.867 ± 0.024	0.941 ± 0.041	0.890
Relative	4.49 ± 0.09	4.75 ± 0.07*	4.71 ± 0.08	5.47 ± 0.08**	5.93
Liver					
Absolute	8.800 ± 0.369	9.103 ± 0.327	9.342 ± 0.310	9.811 ± 0.534	9.750
Relative	47.36 ± 0.96	49.90 ± 0.64	50.64 ± 0.81*	56.75 ± 0.99**	65.00
Lung					
Absolute	1.143 ± 0.039	1.177 ± 0.069	1.234 ± 0.053	1.166 ± 0.068	1.180
Relative	6.16 ± 0.15	6.46 ± 0.33	6.75 ± 0.36	6.77 ± 0.26	7.87
Spleen					
Absolute	0.496 ± 0.014	0.489 ± 0.014	0.483 ± 0.014	0.478 ± 0.023	0.480
Relative	2.68 ± 0.10	2.69 ± 0.05	2.62 ± 0.05	2.81 ± 0.17	3.20
R. Testis					
Absolute	1.106 ± 0.036	1.064 ± 0.034	1.103 ± 0.034	1.094 ± 0.035	0.871
Relative	5.97 ± 0.17	5.85 ± 0.10	5.98 ± 0.04	6.39 ± 0.18	5.81
Thymus					
Absolute	0.475 ± 0.033	0.435 ± 0.016	0.475 ± 0.011	0.452 ± 0.022	0.362
Relative	2.56 ± 0.16	2.40 ± 0.10	2.60 ± 0.11	2.63 ± 0.10	2.41

TABLE F1
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats in the 16-Day Inhalation Study of Chloroprene

	Chamber Control	32 ppm	80 ppm	200 ppm	500 ppm
Female					
n	9	9	9	3	7
Necropsy body wt	130 ± 3	134 ± 4	137 ± 2	130 ± 3	130 ± 4
Brain					
Absolute	1.619 ± 0.024	1.633 ± 0.022	1.627 ± 0.018	1.543 ± 0.009	1.571 ± 0.025
Relative	12.49 ± 0.18	12.21 ± 0.24	11.91 ± 0.14	11.85 ± 0.23	12.17 ± 0.21
Heart					
Absolute	0.480 ± 0.012	0.492 ± 0.015	0.508 ± 0.010	0.463 ± 0.023	0.497 ± 0.014
Relative	3.70 ± 0.05	3.67 ± 0.05	3.72 ± 0.07	3.55 ± 0.16	3.84 ± 0.05
R. Kidney					
Absolute	0.638 ± 0.019	0.642 ± 0.019	0.709 ± 0.013*	0.697 ± 0.012	0.839 ± 0.028**
Relative	4.91 ± 0.09	4.79 ± 0.08	5.19 ± 0.07*	5.35 ± 0.04*	6.48 ± 0.13**
Liver					
Absolute	5.713 ± 0.206	6.047 ± 0.260	6.329 ± 0.125*	6.817 ± 0.098*	7.474 ± 0.273**
Relative	43.92 ± 0.94	44.96 ± 1.30	46.31 ± 0.68	52.40 ± 2.05**	57.65 ± 0.62**
Lung					
Absolute	0.901 ± 0.029	1.013 ± 0.059	0.934 ± 0.027	0.913 ± 0.088	0.883 ± 0.048
Relative	6.93 ± 0.12	7.49 ± 0.25	6.85 ± 0.24	7.02 ± 0.71	6.80 ± 0.23
Spleen					
Absolute	0.413 ± 0.046	0.386 ± 0.017	0.394 ± 0.007	0.353 ± 0.023	0.404 ± 0.025
Relative	3.19 ± 0.36	2.87 ± 0.10	2.89 ± 0.07	2.72 ± 0.23	3.13 ± 0.20
Thymus					
Absolute	0.334 ± 0.014	0.364 ± 0.022	0.360 ± 0.011	0.358 ± 0.007	0.361 ± 0.016
Relative	2.58 ± 0.10	2.71 ± 0.13	2.63 ± 0.07	2.75 ± 0.12	2.79 ± 0.11

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's test
** $P \leq 0.01$
[a] Organ weights (absolute weights) and body weights are given in grams; organ-weight-to-body-weight ratios (relative weights) are given as mg organ weight/g body weight (mean ± standard error).
[b] No standard error was calculated for the 500 ppm males due to high mortality in this exposure group.

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

	Chamber Control	5 ppm	12 ppm	32 ppm	80 ppm	200 ppm
Male						
n	10	10	10	10	10	9
Necropsy body wt	292 ± 9	306 ± 11	289 ± 8	309 ± 10	284 ± 8	284 ± 8
Brain						
Absolute	1.869 ± 0.014	1.866 ± 0.028	1.836 ± 0.021	1.876 ± 0.015	1.863 ± 0.014	1.846 ± 0.017
Relative	6.45 ± 0.17	6.14 ± 0.15	6.39 ± 0.17	6.13 ± 0.19	6.60 ± 0.15	6.52 ± 0.15
Heart						
Absolute	0.835 ± 0.029	0.875 ± 0.032	0.830 ± 0.037	0.905 ± 0.030	0.827 ± 0.021	0.871 ± 0.029
Relative	2.86 ± 0.04	2.86 ± 0.06	2.86 ± 0.07	2.93 ± 0.03	2.92 ± 0.05	3.07 ± 0.08*
R. Kidney						
Absolute	0.967 ± 0.037	1.064 ± 0.048	0.958 ± 0.041	1.077 ± 0.037	1.045 ± 0.026	1.247 ± 0.042**
Relative	3.31 ± 0.06	3.47 ± 0.07	3.30 ± 0.07	3.49 ± 0.05*	3.69 ± 0.04**	4.38 ± 0.07**
Liver						
Absolute	7.974 ± 0.341	8.423 ± 0.399	7.532 ± 0.281	8.408 ± 0.278	7.857 ± 0.381	8.926 ± 0.309
Relative	27.32 ± 0.88	27.43 ± 0.55	26.03 ± 0.47	27.25 ± 0.44	27.64 ± 0.93	31.42 ± 0.86**
Lung						
Absolute	1.548 ± 0.040	1.591 ± 0.070	1.429 ± 0.049	1.560 ± 0.085	1.461 ± 0.064	1.521 ± 0.043
Relative	5.33 ± 0.16	5.21 ± 0.18	4.97 ± 0.20	5.09 ± 0.32	5.15 ± 0.19	5.37 ± 0.19
Spleen						
Absolute	0.567 ± 0.019	0.610 ± 0.015	0.553 ± 0.016	0.593 ± 0.016	0.559 ± 0.018	0.546 ± 0.017
Relative	1.94 ± 0.04	2.00 ± 0.04	1.92 ± 0.04	1.93 ± 0.04	1.97 ± 0.05	1.92 ± 0.03
R. Testis						
Absolute	1.324 ± 0.034	1.344 ± 0.025	1.317 ± 0.035	1.375 ± 0.038	1.282 ± 0.027	1.351 ± 0.024
Relative	4.55 ± 0.12	4.42 ± 0.12	4.57 ± 0.12	4.46 ± 0.08	4.53 ± 0.09	4.77 ± 0.10
Thymus						
Absolute	0.283 ± 0.014	0.309 ± 0.012	0.307 ± 0.016	0.309 ± 0.016	0.282 ± 0.010	0.293 ± 0.014
Relative	0.97 ± 0.03	1.01 ± 0.02	1.06 ± 0.03	1.00 ± 0.04	0.99 ± 0.03	1.03 ± 0.04

TABLE F2
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats in the 13-Week Inhalation Study of Chloroprene

	Chamber Control	5 ppm	12 ppm	32 ppm	80 ppm	200 ppm
Female						
n	10	10	10	10	10	10
Necropsy body wt	176 ± 3	180 ± 3	187 ± 5	181 ± 4	180 ± 3	171 ± 3
Brain						
Absolute	1.746 ± 0.015	1.755 ± 0.021	1.731 ± 0.016	1.754 ± 0.030	1.718 ± 0.011	1.732 ± 0.007
Relative	9.94 ± 0.17	9.75 ± 0.14	9.31 ± 0.20*	9.68 ± 0.14	9.54 ± 0.13	10.17 ± 0.13
Heart						
Absolute	0.558 ± 0.014	0.574 ± 0.015	0.576 ± 0.009	0.566 ± 0.021	0.564 ± 0.012	0.556 ± 0.012
Relative	3.17 ± 0.05	3.18 ± 0.05	3.09 ± 0.05	3.11 ± 0.06	3.13 ± 0.04	3.26 ± 0.04
R. Kidney						
Absolute	0.626 ± 0.016	0.647 ± 0.017	0.648 ± 0.019	0.663 ± 0.023	0.701 ± 0.012**	0.810 ± 0.020**
Relative	3.56 ± 0.06	3.59 ± 0.05	3.47 ± 0.06	3.65 ± 0.07	3.89 ± 0.04**	4.75 ± 0.08**
Liver						
Absolute	4.508 ± 0.131	4.587 ± 0.193	4.743 ± 0.119	4.763 ± 0.222	4.638 ± 0.130	4.844 ± 0.133
Relative	25.62 ± 0.64	25.37 ± 0.71	25.42 ± 0.38	26.18 ± 0.91	25.70 ± 0.54	28.39 ± 0.55*
Lung						
Absolute	0.989 ± 0.030	1.014 ± 0.031	1.033 ± 0.028	1.028 ± 0.019	1.006 ± 0.023	0.973 ± 0.023
Relative	5.62 ± 0.15	5.62 ± 0.11	5.54 ± 0.11	5.68 ± 0.15	5.58 ± 0.11	5.70 ± 0.07
Spleen						
Absolute	0.374 ± 0.015	0.389 ± 0.014	0.367 ± 0.009	0.390 ± 0.015	0.355 ± 0.007	0.372 ± 0.013
Relative	2.13 ± 0.09	2.16 ± 0.07	1.97 ± 0.03	2.15 ± 0.07	1.97 ± 0.02	2.18 ± 0.06
Thymus						
Absolute	0.225 ± 0.005	0.233 ± 0.008	0.237 ± 0.007	0.246 ± 0.008	0.234 ± 0.007	0.211 ± 0.012
Relative	1.28 ± 0.03	1.30 ± 0.04	1.27 ± 0.03	1.36 ± 0.04	1.30 ± 0.03	1.23 ± 0.06

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

TABLE F3
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 16-Day Inhalation Study of Chloroprene[a]

	Chamber Control	12 ppm	32 ppm	80 ppm	200 ppm
Male					
n	10	10	10	10	0
Necropsy body wt	28.9 ± 0.7	28.9 ± 0.6	28.4 ± 0.4	28.2 ± 0.6	—[b]
Brain					
Absolute	0.487 ± 0.022	0.465 ± 0.006	0.473 ± 0.003	0.467 ± 0.003	—
Relative	16.87 ± 0.58	16.11 ± 0.22	16.67 ± 0.22	16.59 ± 0.26	—
Heart					
Absolute	0.132 ± 0.004	0.135 ± 0.005	0.138 ± 0.006	0.134 ± 0.007	—
Relative	4.58 ± 0.08	4.66 ± 0.10	4.84 ± 0.15	4.74 ± 0.20	—
R. Kidney					
Absolute	0.272 ± 0.009	0.279 ± 0.007	0.280 ± 0.007	0.280 ± 0.010	—
Relative	9.43 ± 0.22	9.65 ± 0.21	9.85 ± 0.19	9.90 ± 0.19	—
Liver					
Absolute	1.586 ± 0.056	1.621 ± 0.043	1.663 ± 0.043	1.699 ± 0.065	—
Relative	54.85 ± 0.80	56.03 ± 0.88	58.46 ± 0.97*	60.07 ± 1.44**	—
Lung					
Absolute	0.185 ± 0.004	0.194 ± 0.006	0.181 ± 0.005	0.188 ± 0.012	—
Relative	6.43 ± 0.14	6.71 ± 0.20	6.37 ± 0.15	6.68 ± 0.45	—
Spleen					
Absolute	0.079 ± 0.002	0.074 ± 0.006	0.074 ± 0.004	0.068 ± 0.003	—
Relative	2.74 ± 0.06	2.54 ± 0.19	2.59 ± 0.11	2.40 ± 0.08	—
R. Testis					
Absolute	0.105 ± 0.002	0.103 ± 0.002	0.106 ± 0.002	0.104 ± 0.002	—
Relative	3.64 ± 0.10	3.58 ± 0.09	3.72 ± 0.09	3.70 ± 0.06	—
Thymus					
Absolute	0.053 ± 0.002	0.051 ± 0.003	0.048 ± 0.003	0.041 ± 0.003**	—
Relative	1.85 ± 0.05	1.75 ± 0.09	1.67 ± 0.09	1.43 ± 0.09**	—

TABLE F3
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 16-Day Inhalation Study of Chloroprene

	Chamber Control	12 ppm	32 ppm	80 ppm	200 ppm
Female					
n	10	10	10	10	0
Necropsy body wt	23.6 ± 0.4	23.8 ± 0.5	23.2 ± 0.3	22.9 ± 0.3	—
Brain					
Absolute	0.468 ± 0.006	0.470 ± 0.004	0.470 ± 0.005	0.462 ± 0.004	—
Relative	19.83 ± 0.28	19.78 ± 0.40	20.28 ± 0.28	20.24 ± 0.28	—
Heart					
Absolute	0.116 ± 0.003	0.117 ± 0.003	0.111 ± 0.001	0.107 ± 0.002*	—
Relative	4.93 ± 0.19	4.91 ± 0.06	4.79 ± 0.07	4.68 ± 0.09	—
R. Kidney					
Absolute	0.182 ± 0.005	0.192 ± 0.004	0.189 ± 0.003	0.188 ± 0.004	—
Relative	7.69 ± 0.15	8.06 ± 0.08*	8.15 ± 0.12*	8.22 ± 0.13**	—
Liver					
Absolute	1.204 ± 0.027	1.307 ± 0.047	1.279 ± 0.021	1.390 ± 0.029**	—
Relative	50.92 ± 0.66	54.70 ± 1.03**	55.12 ± 0.53**	60.78 ± 0.65**	—
Lung					
Absolute	0.182 ± 0.006	0.186 ± 0.003	0.175 ± 0.003	0.190 ± 0.009	—
Relative	7.69 ± 0.19	7.82 ± 0.15	7.56 ± 0.20	8.32 ± 0.40	—
Spleen					
Absolute	0.090 ± 0.004	0.092 ± 0.003	0.090 ± 0.003	0.082 ± 0.003	—
Relative	3.81 ± 0.14	3.86 ± 0.09	3.88 ± 0.12	3.58 ± 0.10	—
Thymus					
Absolute	0.064 ± 0.003	0.064 ± 0.003	0.062 ± 0.002	0.052 ± 0.003**	—
Relative	2.72 ± 0.14	2.70 ± 0.12	2.66 ± 0.07	2.27 ± 0.10**	—

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's test
** $P \leq 0.01$
[a] Organ weights (absolute weights) and body weights are given in grams; organ-weight-to-body-weight ratios (relative weights) are given as mg organ weight/g body weight (mean ± standard error).
[b] No data were calculated for the 200 ppm males or females due to 100% mortality in these exposure groups.

TABLE F4
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 13-Week Inhalation Study of Chloroprene[a]

	Chamber Control	5 ppm	12 ppm	32 ppm	80 ppm
Male					
n	10	10	10	10	10
Necropsy body wt	36.0 ± 0.9	35.8 ± 1.0	35.1 ± 0.6	36.8 ± 0.9	33.4 ± 0.6
Brain					
Absolute	0.453 ± 0.006	0.452 ± 0.004	0.451 ± 0.004	0.452 ± 0.005	0.447 ± 0.004
Relative	12.66 ± 0.38	12.69 ± 0.30	12.87 ± 0.17	12.34 ± 0.32	13.42 ± 0.23
Heart					
Absolute	0.150 ± 0.004	0.155 ± 0.006	0.152 ± 0.004	0.158 ± 0.005	0.142 ± 0.002
Relative	4.18 ± 0.13	4.32 ± 0.11	4.33 ± 0.08	4.30 ± 0.13	4.26 ± 0.07
R. Kidney					
Absolute	0.286 ± 0.010	0.291 ± 0.009	0.289 ± 0.008	0.301 ± 0.009	0.279 ± 0.007
Relative	7.95 ± 0.21	8.17 ± 0.33	8.23 ± 0.18	8.21 ± 0.30	8.36 ± 0.13
Liver					
Absolute	1.589 ± 0.042	1.700 ± 0.056	1.638 ± 0.047	1.642 ± 0.042	1.522 ± 0.037
Relative	44.21 ± 1.04	47.47 ± 0.92*	46.60 ± 0.78	44.64 ± 0.55	45.58 ± 0.64
Lung					
Absolute	0.204 ± 0.006	0.211 ± 0.008	0.203 ± 0.005	0.214 ± 0.005	0.202 ± 0.009
Relative	5.68 ± 0.18	5.90 ± 0.20	5.79 ± 0.14	5.83 ± 0.13	6.04 ± 0.18
Spleen					
Absolute	0.070 ± 0.002	0.072 ± 0.003	0.074 ± 0.002	0.071 ± 0.002	0.067 ± 0.002
Relative	1.95 ± 0.06	2.01 ± 0.07	2.11 ± 0.04	1.94 ± 0.05	2.01 ± 0.06
R. Testis					
Absolute	0.114 ± 0.004	0.120 ± 0.002	0.116 ± 0.002	0.122 ± 0.004	0.123 ± 0.004
Relative	3.20 ± 0.17	3.37 ± 0.10	3.32 ± 0.05	3.33 ± 0.10	3.68 ± 0.09*
Thymus					
Absolute	0.046 ± 0.004	0.043 ± 0.004	0.041 ± 0.002	0.047 ± 0.003	0.042 ± 0.004
Relative	1.27 ± 0.09	1.21 ± 0.11	1.16 ± 0.06	1.27 ± 0.08	1.25 ± 0.11

TABLE F4
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 13-Week Inhalation Study of Chloroprene

	Chamber Control	5 ppm	12 ppm	32 ppm	80 ppm
Female					
n	10	10	10	10	10
Necropsy body wt	31.5 ± 1.1	33.5 ± 0.8	31.2 ± 0.7	33.5 ± 0.7	30.2 ± 1.5
Brain					
Absolute	0.465 ± 0.005	0.470 ± 0.003	0.463 ± 0.006	0.469 ± 0.004	0.458 ± 0.006
Relative	14.92 ± 0.55	14.10 ± 0.37	14.94 ± 0.43	14.05 ± 0.27	15.42 ± 0.60
Heart					
Absolute	0.127 ± 0.002	0.136 ± 0.002	0.131 ± 0.004	0.134 ± 0.003	0.121 ± 0.002
Relative	4.06 ± 0.12	4.07 ± 0.10	4.22 ± 0.14	4.01 ± 0.09	4.05 ± 0.11
R. Kidney					
Absolute	0.194 ± 0.005	0.210 ± 0.004*	0.195 ± 0.004	0.202 ± 0.006	0.200 ± 0.004
Relative	6.20 ± 0.19	6.29 ± 0.14	6.28 ± 0.17	6.04 ± 0.13	6.71 ± 0.24
Liver					
Absolute	1.471 ± 0.037	1.583 ± 0.038	1.469 ± 0.023	1.622 ± 0.041*	1.499 ± 0.050
Relative	46.87 ± 0.81	47.31 ± 1.00	47.30 ± 0.95	48.48 ± 0.93	49.90 ± 0.75
Lung					
Absolute	0.192 ± 0.005	0.203 ± 0.004	0.187 ± 0.005	0.215 ± 0.007**	0.203 ± 0.004
Relative	6.14 ± 0.20	6.10 ± 0.22	6.05 ± 0.27	6.42 ± 0.17	6.85 ± 0.31
Spleen					
Absolute	0.098 ± 0.004	0.101 ± 0.003	0.094 ± 0.003	0.108 ± 0.002	0.092 ± 0.003
Relative	3.13 ± 0.14	3.03 ± 0.13	3.04 ± 0.14	3.23 ± 0.09	3.10 ± 0.17
Thymus					
Absolute	0.057 ± 0.005	0.058 ± 0.004	0.047 ± 0.004	0.056 ± 0.003	0.054 ± 0.005
Relative	1.78 ± 0.09	1.71 ± 0.10	1.51 ± 0.12	1.66 ± 0.08	1.76 ± 0.12

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

APPENDIX G
HEMATOLOGY, CLINICAL CHEMISTRY, AND URINALYSIS RESULTS

TABLE G1
Day 4 Hematology, Clinical Chemistry, and Urinalysis Data for Rats in the 16-Day Inhalation Study of Chloroprene[a]

	Chamber Control	32 ppm	80 ppm	200 ppm	500 ppm
Male					
n	10	10	10	10	7
Hematology					
Hematocrit (%)	46.2 ± 0.6	46.5 ± 0.4	46.5 ± 0.4	46.6 ± 0.8	29.8 ± 4.3*
Hemoglobin (g/dL)	15.0 ± 0.2	15.0 ± 0.1	15.0 ± 0.1	15.0 ± 0.2	9.3 ± 1.4*
Erythrocytes (10^6/µL)	8.00 ± 0.09	7.90 ± 0.12	8.08 ± 0.10	8.21 ± 0.14	5.06 ± 0.78*
Reticulocytes (10^6/µL)	0.30 ± 0.02	0.27 ± 0.03	0.20 ± 0.03	0.21 ± 0.03	0.92 ± 0.07*
Nucleated erythrocytes (10^3/µL)	0.10 ± 0.03	0.06 ± 0.03	0.05 ± 0.03	0.04 ± 0.02	3.81 ± 1.31*
Mean cell volume (fL)	57.8 ± 0.4	58.9 ± 0.9	57.6 ± 0.4	56.8 ± 0.4	59.7 ± 0.9
Mean cell hemoglobin (pg)	18.7 ± 0.1	19.0 ± 0.3	18.6 ± 0.1	18.3 ± 0.1	18.5 ± 0.1
Mean cell hemoglobin concentration (g/dL)	32.4 ± 0.1	32.2 ± 0.1	32.3 ± 0.2	32.3 ± 0.1	31.0 ± 0.4**
Platelets (10^3/µL)	865.5 ± 38.3	852.4 ± 30.2	878.3 ± 34.4	782.6 ± 59.8	516.6 ± 126.8*
Leukocytes (10^3/µL)	7.21 ± 0.31	8.17 ± 0.54	8.14 ± 0.20	8.29 ± 0.38	15.60 ± 3.06**
Segmented neutrophils (10^3/µL)	0.53 ± 0.09	0.73 ± 0.17	0.81 ± 0.08*	0.74 ± 0.09	3.29 ± 0.71**
Lymphocytes (10^3/µL)	6.43 ± 0.29	7.07 ± 0.38	6.99 ± 0.18	7.19 ± 0.36	11.61 ± 2.58
Monocytes (10^3/µL)	0.25 ± 0.05	0.36 ± 0.08	0.30 ± 0.07	0.31 ± 0.06	0.74 ± 0.21*
Eosinophils (10^3/µL)	0.02 ± 0.02	0.02 ± 0.01	0.04 ± 0.02	0.05 ± 0.02	0.00 ± 0.00
Clinical Chemistry					
Urea nitrogen (mg/dL)	19.9 ± 0.7	19.4 ± 0.8	19.3 ± 0.5	18.3 ± 1.0	24.6 ± 4.9
Creatinine (mg/dL)	1.00 ± 0.04	1.02 ± 0.04	0.95 ± 0.03	1.04 ± 0.04	0.74 ± 0.07*
Alanine aminotransferase (IU/L)	33 ± 3	33 ± 2	31 ± 1	55 ± 15	113 ± 19**
Glutamate dehydrogenase (IU/L)	4.3 ± 0.5	4.6 ± 0.4	3.9 ± 0.5	10.1 ± 4.0	62.5 ± 10.1**
Sorbitol dehydrogenase (IU/L)	8 ± 1	9 ± 0	8 ± 0	10 ± 1	11 ± 1
n	9	10	10	10	7
Urinalysis					
Creatinine (mg/dL)	23.3 ± 2.6	14.5 ± 2.0	16.5 ± 1.7	16.1 ± 2.4	11.1 ± 2.1*
Glucose (µg/mg creatinine)	150 ± 8	131 ± 14	123 ± 18	133 ± 17	178 ± 39
Protein (µg/mg creatinine)	665 ± 85	644 ± 45	565 ± 41	472 ± 20*	730 ± 202
Alkaline phosphatase (mU/mg creatinine)	210 ± 26	282 ± 55	618 ± 426	214 ± 18	336 ± 42
Aspartate aminotransferase (mU/mg creatinine)	14 ± 2	14 ± 3	25 ± 11	19 ± 3	26 ± 4
Volume (mL/16 hr)	13.0 ± 2.0	21.1 ± 3.2	18.2 ± 2.3	16.5 ± 2.9	17.0 ± 3.7
Specific gravity	1.011 ± 0.001	1.007 ± 0.001	1.008 ± 0.001	1.008 ± 0.001	1.009 ± 0.003
Urea (mg/mg creatinine)	26 ± 1	28 ± 2	29 ± 1	31 ± 2	45 ± 8**
Thioethers (mM/mg creatinine)	0.044 ± 0.011	0.074 ± 0.015	0.062 ± 0.016	0.062 ± 0.024	0.113 ± 0.024

TABLE G1
Day 4 Hematology, Clinical Chemistry, and Urinalysis Data for Rats in the 16-Day Inhalation Study of Chloroprene

	Chamber Control	32 ppm	80 ppm	200 ppm	500 ppm
Female					
n	10	10	10	10	10
Hematology					
Hematocrit (%)	49.0 ± 0.7	48.0 ± 0.5	49.0 ± 0.5	42.7 ± 3.6	44.1 ± 2.6
Hemoglobin (g/dL)	15.7 ± 0.2	15.9 ± 0.2	15.8 ± 0.2	13.6 ± 1.2	14.3 ± 0.9
Erythrocytes (10^6/µL)	8.56 ± 0.10	8.40 ± 0.16	8.45 ± 0.08	7.35 ± 0.63	7.67 ± 0.49
Reticulocytes (10^6/µL)	0.18 ± 0.02	0.15 ± 0.02	0.15 ± 0.01	0.44 ± 0.05**	0.38 ± 0.11*
Nucleated erythrocytes (10^3/µL)	0.06 ± 0.02	0.04 ± 0.02	0.09 ± 0.03	0.78 ± 0.38*	0.06 ± 0.03[b]
Mean cell volume (fL)	57.4 ± 0.3	57.4 ± 0.8	58.1 ± 0.4	58.4 ± 0.5	58.0 ± 0.8
Mean cell hemoglobin (pg)	18.3 ± 0.1	18.9 ± 0.2	18.6 ± 0.1	18.5 ± 0.3	18.7 ± 0.2
Mean cell hemoglobin concentration (g/dL)	32.0 ± 0.2	33.0 ± 0.1**	32.2 ± 0.1	31.7 ± 0.3	32.3 ± 0.3
Platelets (10^3/µL)	835.8 ± 61.6	851.0 ± 37.9	890.6 ± 24.7	395.4 ± 61.3**	684.9 ± 72.1*
Leukocytes (10^3/µL)	8.95 ± 0.33	9.12 ± 0.38	8.83 ± 0.31	10.03 ± 1.27	9.17 ± 0.46[b]
Segmented neutrophils (10^3/µL)	1.02 ± 0.11	0.68 ± 0.12	0.62 ± 0.09	1.18 ± 0.44	0.84 ± 0.13[b]
Lymphocytes (10^3/µL)	7.77 ± 0.38	8.05 ± 0.40	7.91 ± 0.27	8.51 ± 0.92	7.91 ± 0.38[b]
Monocytes (10^3/µL)	0.15 ± 0.04	0.38 ± 0.09	0.28 ± 0.05	0.32 ± 0.06	0.39 ± 0.03*[b]
Eosinophils (10^3/µL)	0.02 ± 0.01	0.01 ± 0.01	0.04 ± 0.01	0.03 ± 0.02	0.02 ± 0.02[b]
Clinical Chemistry					
Urea nitrogen (mg/dL)	21.4 ± 0.4	20.5 ± 0.6	20.9 ± 0.6	17.9 ± 1.1**	19.3 ± 0.7*
Creatinine (mg/dL)	0.99 ± 0.03	1.03 ± 0.03	0.98 ± 0.07	1.13 ± 0.07	1.32 ± 0.08**
Alanine aminotransferase (IU/L)	32 ± 2	28 ± 1	27 ± 2	165 ± 44**	59 ± 11*
Glutamate dehydrogenase (IU/L)	5.6 ± 0.6	4.3 ± 0.3	3.8 ± 0.5	31.3 ± 10.2**	17.1 ± 4.3*
Sorbitol dehydrogenase (IU/L)	9 ± 1	9 ± 0	9 ± 1	15 ± 2**	11 ± 1*
n	10	10	10	10	10
Urinalysis					
Creatinine (mg/dL)	20.5 ± 1.7	11.4 ± 1.4**	14.0 ± 1.5**	12.6 ± 2.6**	11.2 ± 1.4**
Glucose (µg/mg creatinine)	181 ± 7	158 ± 11	178 ± 9	180 ± 12	200 ± 23
Protein (µg/mg creatinine)	452 ± 53	512 ± 76	476 ± 57	848 ± 108**	694 ± 58**
Alkaline phosphatase (mU/mg creatinine)	3,084 ± 1599	2,649 ± 861	1,340 ± 587	788 ± 66	2,137 ± 890
Aspartate aminotransferase (mU/mg creatinine)	50 ± 17	128.3 ± 48	43 ± 12	69 ± 80**	77 ± 39**
Volume (mL/16 hr)	9.3 ± 1.1	17.8 ± 2.4*	13.3 ± 2.1	14.7 ± 2.0	15.2 ± 2.1
Specific gravity	1.012 ± 0.001	1.006 ± 0.001**	1.008 ± 0.001**	1.007 ± 0.001**	1.006 ± 0.001**
Urea (mg/mg creatinine)	37.3 ± 1.3	36.5 ± 1.0	37.8 ± 1.4	31.9 ± 1.7	34.6 ± 1.7
Thioethers (mM/mg creatinine)	0.025 ± 0.009	0.062 ± 0.020	0.057 ± 0.015	0.048 ± 0.016	0.051 ± 0.016

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

TABLE G2
Hematology, Clinical Chemistry, and Urinalysis Data for Rats in the 13-Week Inhalation Study of Chloroprene[a]

	Chamber Control	5 ppm	12 ppm	32 ppm	80 ppm	200 ppm
Male						
n						
Day 2	9	0	0	9	9	10
Day 22	10	10	10	10	10	10
Week 13	10	10	10	10	10	9
Hematology						
Hematocrit (%)						
Day 2	39.4 ± 0.8	—[b]	—	40.7 ± 0.5	41.6 ± 0.4**	40.6 ± 2.5**
Day 22	48.7 ± 0.4	48.4 ± 0.5	48.9 ± 0.3	48.6 ± 0.4	49.2 ± 0.5	47.2 ± 0.4
Week 13	47.7 ± 0.6	46.3 ± 0.7	47.0 ± 0.5	46.9 ± 0.5	46.9 ± 0.5	44.8 ± 1.8
Hemoglobin (g/dL)						
Day 2	12.6 ± 0.2	—	—	13.2 ± 0.2	13.2 ± 0.1*	13.2 ± 0.8**
Day 22	16.0 ± 0.1	15.9 ± 0.2	16.2 ± 0.1	16.0 ± 0.1	16.2 ± 0.1	15.6 ± 0.1
Week 13	16.1 ± 0.2	15.6 ± 0.3	15.9 ± 0.1	15.8 ± 0.2	15.7 ± 0.2	15.1 ± 0.6
Erythrocytes (10^6/µL)						
Day 2	7.36 ± 0.15	—	—	7.68 ± 0.14	7.76 ± 0.15	7.67 ± 0.47**
Day 22	9.58 ± 0.11	9.64 ± 0.12	9.66 ± 0.08	9.70 ± 0.07	9.81 ± 0.08	9.64 ± 0.09
Week 13	10.31 ± 0.11	9.97 ± 0.18	10.12 ± 0.11	10.13 ± 0.13	10.06 ± 0.10	9.85 ± 0.37
Reticulocytes (10^6/µL)						
Day 22	0.14 ± 0.01	0.13 ± 0.01	0.10 ± 0.01	0.15 ± 0.02	0.17 ± 0.03	0.14 ± 0.02
Week 13	0.14 ± 0.01	0.19 ± 0.02	0.16 ± 0.01	0.15 ± 0.02	0.19 ± 0.01	0.20 ± 0.05
Nucleated erythrocytes (10^3/µL)						
Day 22	0.01 ± 0.01	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Week 13	0.00 ± 0.00	0.00 ± 0.00	0.01 ± 0.01	0.00 ± 0.00	0.01 ± 0.01	0.00 ± 0.00[c]
Mean cell volume (fL)						
Day 2	53.4 ± 0.4	—	—	53.2 ± 0.5	53.9 ± 0.8	53.0 ± 0.3
Day 22	51.0 ± 0.3	50.3 ± 0.3	50.6 ± 0.4	50.1 ± 0.3	50.2 ± 0.4	48.9 ± 0.3**
Week 13	46.3 ± 0.3	46.5 ± 0.3	46.6 ± 0.3	46.3 ± 0.2	46.4 ± 0.2	45.7 ± 0.2
Mean cell hemoglobin (pg)						
Day 2	17.1 ± 0.1	—	—	17.2 ± 0.2	17.1 ± 0.3	17.1 ± 0.1
Day 22	16.7 ± 0.1	16.5 ± 0.1	16.8 ± 0.1	16.4 ± 0.1*	16.5 ± 0.1*	16.2 ± 0.1**
Week 13	15.6 ± 0.1	15.6 ± 0.1	15.7 ± 0.1	15.6 ± 0.0	15.6 ± 0.1	15.4 ± 0.1*
Mean cell hemoglobin concentration (g/dL)						
Day 2	31.9 ± 0.2	—	—	32.3 ± 0.2	31.8 ± 0.2	32.3 ± 0.2
Day 22	32.9 ± 0.2	32.9 ± 0.2	33.1 ± 0.2	32.8 ± 0.2	32.9 ± 0.2	33.0 ± 0.2
Week 13	33.8 ± 0.1	33.7 ± 0.1	33.7 ± 0.1	33.7 ± 0.1	33.4 ± 0.2	33.8 ± 0.2
Platelets (10^3/µL)						
Day 2	662.3 ± 25.0	—	—	704.7 ± 20.7	682.4 ± 22.3	479.7 ± 73.2
Day 22	631.3 ± 12.8	596.4 ± 11.8	585.7 ± 13.1	619.0 ± 11.5	629.1 ± 17.7	509.0 ± 46.6
Week 13	510.8 ± 13.1	486.7 ± 19.6	533.4 ± 7.8	531.7 ± 13.5	565.0 ± 10.8**	617.6 ± 42.7**
Leukocytes (10^3/µL)						
Day 2	2.11 ± 0.19	—	—	2.30 ± 0.12	1.83 ± 0.18	1.65 ± 0.15
Day 22	6.12 ± 0.23	6.18 ± 0.37	6.21 ± 0.29	6.59 ± 0.32	6.60 ± 0.33	6.36 ± 0.32
Week 13	6.79 ± 0.44	6.74 ± 0.37	6.70 ± 0.29	7.27 ± 0.41	6.77 ± 0.43	6.72 ± 0.47
Segmented neutrophils (10^3/µL)						
Day 2	0.22 ± 0.04	—	—	0.24 ± 0.02	0.25 ± 0.03	0.31 ± 0.05
Day 22	0.68 ± 0.07	0.67 ± 0.07	0.54 ± 0.07	0.63 ± 0.07	0.51 ± 0.04	0.83 ± 0.13
Week 13	1.11 ± 0.08	0.96 ± 0.08	1.06 ± 0.06	0.91 ± 0.14	0.80 ± 0.07*	0.73 ± 0.09**

TABLE G2
Hematology, Clinical Chemistry, and Urinalysis Data for Rats in the 13-Week Inhalation Study of Chloroprene

	Chamber Control	5 ppm	12 ppm	32 ppm	80 ppm	200 ppm
Male (continued)						
n						
Day 2	9	0	0	9	9	10
Day 22	10	10	10	10	10	10
Week 13	10	10	10	10	10	9
Hematology (continued)						
Lymphocytes (10^3/μL)						
Day 2	1.85 ± 0.16	—	—	2.03 ± 0.12	1.56 ± 0.15	1.32 ± 0.15*
Day 22	5.15 ± 0.21	5.30 ± 0.36	5.46 ± 0.25	5.64 ± 0.31	5.78 ± 0.33	5.22 ± 0.31
Week 13	5.42 ± 0.44	5.55 ± 0.40	5.39 ± 0.27	6.11 ± 0.39	5.81 ± 0.44	5.80 ± 0.50
Monocytes (10^3/μL)						
Day 2	0.03 ± 0.01	—	—	0.02 ± 0.01	0.02 ± 0.00	0.02 ± 0.01
Day 22	0.24 ± 0.04	0.19 ± 0.03	0.17 ± 0.05	0.28 ± 0.05	0.27 ± 0.05	0.28 ± 0.04
Week 13	0.21 ± 0.04	0.22 ± 0.06	0.21 ± 0.05	0.21 ± 0.03	0.14 ± 0.05	0.14 ± 0.04
Eosinophils (10^3/μL)						
Day 2	0.00 ± 0.00	—	—	0.01 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Day 22	0.05 ± 0.02	0.03 ± 0.01	0.04 ± 0.02	0.04 ± 0.02	0.04 ± 0.02	0.03 ± 0.02
Week 13	0.05 ± 0.02	0.01 ± 0.01	0.03 ± 0.02	0.05 ± 0.02	0.01 ± 0.01	0.06 ± 0.03
Euglobulin lysis time (minutes)						
Day 2	65.9 ± 4.6[d]	—	—	90.7 ± 21.4	119.0 ± 28.7[d]	147.5 ± 21.3
Fibrinogen (mg/dL)						
Day 2	228.6 ± 5.3[d]	—	—	223.6 ± 14.2	252.2 ± 30.1[e]	209.1 ± 15.2
Activated partial thromboplastin time (seconds)						
Day 2	16.6 ± 0.6[d]	—	—	18.6 ± 0.7[f]	17.6 ± 0.7[g]	24.1 ± 3.2**
Prothrombin time (seconds)						
Day 2	14.0 ± 0.1[f]	—	—	14.2 ± 0.2	14.1 ± 0.1[f]	17.3 ± 2.3*
n						
Day 22	9	9	10	10	10	9
Week 13	10	10	10	10	10	9
Clinical Chemistry						
Urea nitrogen (mg/dL)						
Day 22	14.5 ± 0.3	14.1 ± 0.3	13.9 ± 0.4	14.5 ± 0.2	13.7 ± 0.4	14.5 ± 2.1
Week 13	17.5 ± 0.5	16.7 ± 0.6	16.3 ± 0.4	16.4 ± 0.6	15.8 ± 0.6	16.3 ± 0.6
Creatinine						
Day 22	0.94 ± 0.03	0.91 ± 0.03	0.94 ± 0.04	0.95 ± 0.03	1.00 ± 0.04	1.09 ± 0.05*
Week 13	1.23 ± 0.05	1.16 ± 0.03	1.19 ± 0.05	1.19 ± 0.04	1.10 ± 0.04	1.08 ± 0.07
Alanine aminotransferase (IU/L)						
Day 22	33 ± 3	30 ± 2	28 ± 1	29 ± 1	33 ± 2	279 ± 67**
Week 13	41 ± 1	43 ± 3	40 ± 2	43 ± 1	38 ± 1	36 ± 1*
Glutamate dehydrogenase (IU/L)						
Day 22	3.7 ± 0.5	3.8 ± 0.8	2.9 ± 0.4	3.0 ± 0.3	2.9 ± 0.6	19.0 ± 4.4*
Week 13	1.9 ± 0.3	1.9 ± 0.2	1.9 ± 0.3	2.0 ± 0.2	1.8 ± 0.2	2.3 ± 0.5
Sorbitol dehydrogenase (IU/L)						
Day 22	13 ± 1	13 ± 1	13 ± 1	14 ± 1	13 ± 1	56 ± 12**
Week 13	14 ± 0	17 ± 2	15 ± 1	17 ± 1	14 ± 1	13 ± 1

TABLE G2
Hematology, Clinical Chemistry, and Urinalysis Data for Rats in the 13-Week Inhalation Study of Chloroprene

	Chamber Control	5 ppm	12 ppm	32 ppm	80 ppm	200 ppm
Male (continued)						
n						
Day 22	9	9	10	10	10	9
Week 13	10	10	10	10	10	9
Urinalysis						
Creatinine (mg/dL)						
Day 22	29.52 ± 3.68	35.41 ± 4.22	33.87 ± 3.71	31.87 ± 3.19	20.62 ± 1.23	13.77 ± 1.17**
Week 13	87.9 ± 11.7	80.2 ± 9.6	74.0 ± 11.3	62.0 ± 8.1	55.7 ± 4.9	40.1 ± 4.2**
Glucose (µg/mg creatinine)						
Day 22	125 ± 4	141 ± 5	137 ± 4	131 ± 4	127 ± 5	126 ± 6
Week 13	110 ± 3	103 ± 3	108 ± 2	105 ± 4	108 ± 4	110 ± 4
Protein (µg/mg creatinine)						
Day 22	1,574 ± 231	1,472 ± 123	1,313 ± 147	1,750 ± 148	1,565 ± 177	1,511 ± 119
Week 13	864 ± 31	736 ± 82	818 ± 39	822 ± 39	886 ± 50	1,134 ± 71*
Alkaline phosphatase (mU/mg creatinine)						
Day 22	371 ± 32	351 ± 21	339 ± 15	448 ± 36	421 ± 37	423 ± 90
Week 13	195 ± 16	209 ± 16	237 ± 15*	259 ± 14**	266 ± 17**	353 ± 23**
Aspartate aminotransferase (mU/mg creatinine)						
Day 22	6 ± 2	5 ± 2	8 ± 2	10 ± 3	10 ± 3	28 ± 19
Week 13	13 ± 1	10 ± 1	13 ± 1	13 ± 1	16 ± 2	14 ± 2
Volume (mL/16 hr)						
Day 22	19.1 ± 3.4	14.8 ± 2.1	14.0 ± 1.7	15.3 ± 2.0	19.4 ± 2.0	36.2 ± 3.1**
Week 13	10.0 ± 1.6	10.8 ± 1.8	11.8 ± 2.1	13.9 ± 1.5	14.3 ± 1.5	22.0 ± 3.2**
Specific gravity						
Day 22	1.010 ± 0.001	1.012 ± 0.001	1.012 ± 0.001	1.011 ± 0.001	1.007 ± 0.000	1.005 ± 0.001**
Week 13	1.022 ± 0.003	1.019 ± 0.002	1.018 ± 0.003	1.015 ± 0.002	1.013 ± 0.001*	1.011 ± 0.001**
Urea (mg/mg creatinine)						
Day 22	20.8 ± 0.7	20.9 ± 0.9	21.3 ± 0.6	20.8 ± 0.3	21.5 ± 0.7	24.3 ± 0.8*
Week 13	16.1 ± 0.4	14.6 ± 0.3	15.2 ± 0.6	15.3 ± 0.5	15.3 ± 0.4	17.2 ± 0.3

TABLE G2
Hematology, Clinical Chemistry, and Urinalysis Data for Rats in the 13-Week Inhalation Study of Chloroprene

	Chamber Control	5 ppm	12 ppm	32 ppm	80 ppm	200 ppm
Female						
n						
Day 2	10	0	0	10	10	9
Day 22	10	10	10	10	10	10
Week 13	10	10	10	10	10	10
Hematology						
Hematocrit (%)						
Day 2	42.8 ± 0.8	—	—	41.7 ± 1.4	43.5 ± 0.6	46.7 ± 0.5**
Day 22	50.4 ± 0.8	52.0 ± 0.5	52.0 ± 0.4	51.6 ± 0.7	51.8 ± 0.6	50.5 ± 0.4
Week 13	48.1 ± 0.4	47.2 ± 0.4	48.2 ± 0.4	47.0 ± 0.4	48.1 ± 0.2	44.6 ± 0.8**
Hemoglobin (g/dL)						
Day 2	14.2 ± 0.3	—	—	13.9 ± 0.4	14.2 ± 0.2	15.4 ± 0.2**
Day 22	15.9 ± 0.2	16.5 ± 0.2	16.5 ± 0.1	16.3 ± 0.2	16.4 ± 0.2	16.0 ± 0.1
Week 13	15.9 ± 0.1	15.7 ± 0.2	16.1 ± 0.1	15.6 ± 0.1	16.0 ± 0.1	14.7 ± 0.2**
Erythrocytes (10^6/µL)						
Day 2	8.24 ± 0.20	—	—	8.05 ± 0.26	8.19 ± 0.17	9.06 ± 0.15*
Day 22	9.35 ± 0.16	9.66 ± 0.09	9.65 ± 0.07	9.56 ± 0.13	9.58 ± 0.14	9.60 ± 0.11
Week 13	9.60 ± 0.07	9.46 ± 0.10	9.64 ± 0.07	9.39 ± 0.09	9.69 ± 0.04	9.01 ± 0.19*
Reticulocytes (10^6/µL)						
Day 22	0.09 ± 0.01	0.06 ± 0.01	0.10 ± 0.01	0.09 ± 0.01	0.07 ± 0.01	0.13 ± 0.01
Week 13	0.16 ± 0.01	0.16 ± 0.01	0.13 ± 0.02	0.13 ± 0.01	0.14 ± 0.01	0.20 ± 0.03
Nucleated erythrocytes (10^3/µL)						
Day 22	0.01 ± 0.01	0.01 ± 0.01	0.01 ± 0.01	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Week 13	0.00 ± 0.00	0.00 ± 0.00	0.01 ± 0.01	0.01 ± 0.01	0.01 ± 0.01	0.01 ± 0.01
Mean cell volume (fL)						
Day 2	52.0 ± 0.5	—	—	51.9 ± 0.7	53.2 ± 0.5	51.7 ± 0.4
Day 22	53.7 ± 0.3	53.9 ± 0.2	53.9 ± 0.2	54.0 ± 0.3	54.0 ± 0.4	52.6 ± 0.3
Week 13	50.2 ± 0.1	49.9 ± 0.2	50.1 ± 0.1	50.1 ± 0.2	49.7 ± 0.2*	49.5 ± 0.3**
Mean cell hemoglobin (pg)						
Day 2	17.3 ± 0.1	—	—	17.3 ± 0.1	17.4 ± 0.2	17.0 ± 0.1
Day 22	17.0 ± 0.1	17.0 ± 0.1	17.1 ± 0.0	17.1 ± 0.1	17.2 ± 0.1	16.6 ± 0.1
Week 13	16.6 ± 0.0	16.6 ± 0.1	16.7 ± 0.1	16.7 ± 0.1	16.5 ± 0.0	16.4 ± 0.1
Mean cell hemoglobin concentration (g/dL)						
Day 2	33.3 ± 0.3	—	—	33.4 ± 0.3	32.7 ± 0.1	33.1 ± 0.1
Day 22	31.6 ± 0.1	31.7 ± 0.1	31.7 ± 0.1	31.6 ± 0.1	31.7 ± 0.1	31.6 ± 0.1
Week 13	33.1 ± 0.2	33.2 ± 0.1	33.4 ± 0.2	33.2 ± 0.2	33.3 ± 0.1	33.1 ± 0.1
Platelets (10^3/µL)						
Day 2	633.9 ± 24.9	—	—	669.8 ± 22.5	668.9 ± 22.5	336.3 ± 52.5**
Day 22	640.8 ± 19.9	586.3 ± 9.2	581.9 ± 15.7	585.6 ± 22.0	577.0 ± 15.4*	491.2 ± 18.5**
Week 13	570.5 ± 13.6	607.3 ± 12.9*	547.3 ± 7.5	604.8 ± 35.5	582.7 ± 10.8	787.7 ± 73.6**
Leukocytes (10^3/µL)						
Day 2	3.15 ± 0.24	—	—	2.06 ± 0.21**	2.22 ± 0.10*	2.35 ± 0.18
Day 22	5.55 ± 0.27	5.66 ± 0.34	5.50 ± 0.27	5.63 ± 0.20	5.27 ± 0.24	6.13 ± 0.42
Week 13	6.19 ± 0.26	5.48 ± 0.33	5.06 ± 0.19*	6.24 ± 0.35	5.40 ± 0.43	6.36 ± 0.31
Segmented neutrophils (10^3/µL)						
Day 2	0.34 ± 0.06	—	—	0.18 ± 0.02	0.20 ± 0.02	0.51 ± 0.16
Day 22	0.71 ± 0.07	0.58 ± 0.06	0.46 ± 0.05	0.57 ± 0.09	0.48 ± 0.08*	0.68 ± 0.10
Week 13	0.75 ± 0.07	0.94 ± 0.10	0.82 ± 0.09	1.14 ± 0.10*	0.80 ± 0.10	0.75 ± 0.08
Lymphocytes (10^3/µL)						
Day 2	2.74 ± 0.20	—	—	1.82 ± 0.21**	1.97 ± 0.11*	1.74 ± 0.26*
Day 22	4.63 ± 0.22	4.83 ± 0.30	4.83 ± 0.26	4.81 ± 0.18	4.59 ± 0.25	5.23 ± 0.34
Week 13	5.21 ± 0.28	4.36 ± 0.29	4.02 ± 0.16*	4.85 ± 0.30	4.44 ± 0.41	5.37 ± 0.33

TABLE G2
Hematology, Clinical Chemistry, and Urinalysis Data for Rats in the 13-Week Inhalation Study of Chloroprene

	Chamber Control	5 ppm	12 ppm	32 ppm	80 ppm	200 ppm
Female (continued)						
n						
Day 2	10	0	0	10	10	9
Day 22	10	10	10	10	10	10
Week 13	10	10	10	10	10	10
Hematology (continued)						
Monocytes (10^3/µL)						
Day 2	0.04 ± 0.01	—	—	0.03 ± 0.01	0.03 ± 0.01	0.05 ± 0.01
Day 22	0.18 ± 0.04	0.19 ± 0.05	0.18 ± 0.04	0.21 ± 0.03	0.15 ± 0.03	0.20 ± 0.06
Week 13	0.18 ± 0.02	0.15 ± 0.03	0.20 ± 0.03	0.22 ± 0.05	0.15 ± 0.04	0.19 ± 0.04
Eosinophils (10^3/µL)						
Day 2	0.03 ± 0.01	—	—	0.02 ± 0.01	0.02 ± 0.00	0.01 ± 0.01
Day 22	0.03 ± 0.02	0.06 ± 0.02	0.03 ± 0.01	0.04 ± 0.02	0.05 ± 0.03	0.03 ± 0.01
Week 13	0.06 ± 0.02	0.03 ± 0.01	0.02 ± 0.01	0.03 ± 0.01	0.02 ± 0.01	0.05 ± 0.02
Euglobulin lysis time (minutes)						
Day 2	89.8 ± 10.2[e]	—	—	139.7 ± 21.9[d]	93.4 ± 14.4[f]	220.7 ± 24.5**[h]
Fibrinogen (mg/dL)						
Day 2	197.8 ± 4.8[e]	—	—	200.3 ± 6.2[i]	206.0 ± 7.5[g]	154.0 ± 10.7*[h]
Activated partial thromboplastin time (seconds)						
Day 2	16.5 ± 0.5[i]	—	—	18.7 ± 0.8	18.5 ± 0.5[i]	21.2 ± 1.2**[f]
Prothrombin time (seconds)						
Day 2	14.1 ± 0.1[i]	—	—	14.0 ± 0.2	14.1 ± 0.1	16.3 ± 0.8[i]
n						
Day 22	10	10	10	10	10	10
Week 13	10	10	10	10	10	10
Clinical Chemistry						
Urea nitrogen (mg/dL)						
Day 22	16.3 ± 0.4	15.6 ± 0.3	15.7 ± 0.4	16.2 ± 0.3	14.7 ± 0.4**	13.2 ± 0.2**
Week 13	20.1 ± 0.5	19.7 ± 1.1	19.5 ± 0.5	19.7 ± 0.8	19.8 ± 0.7	19.7 ± 0.8
Creatinine (mg/dL)						
Day 22	1.00 ± 0.03	0.98 ± 0.03	1.03 ± 0.04	0.95 ± 0.03	1.01 ± 0.02	1.17 ± 0.05
Week 13	1.12 ± 0.04	1.09 ± 0.02	1.07 ± 0.02	1.19 ± 0.13	1.04 ± 0.03	1.02 ± 0.03
Alanine aminotransferase (IU/L)						
Day 22	30 ± 1	30 ± 1	32 ± 1	31 ± 1	30 ± 1	95 ± 15**
Week 13	37 ± 1	35 ± 2	35 ± 1	34 ± 1	35 ± 1	33 ± 1
Glutamate dehydrogenase (IU/L)						
Day 22	3.3 ± 0.7	4.5 ± 0.9	4.3 ± 0.5	4.4 ± 0.9	4.2 ± 0.7	6.4 ± 1.1*
Week 13	1.9 ± 0.3	2.2 ± 0.3	2.0 ± 0.3	1.7 ± 0.2	1.8 ± 0.1	1.4 ± 0.3
Sorbitol dehydrogenase (IU/L)						
Day 22	15 ± 1	14 ± 1	16 ± 1	14 ± 1	13 ± 1	17 ± 1
Week 13	11 ± 1	11 ± 1	10 ± 1	11 ± 1	10 ± 1	11 ± 1

TABLE G2
Hematology, Clinical Chemistry, and Urinalysis Data for Rats in the 13-Week Inhalation Study of Chloroprene

	Chamber Control	5 ppm	12 ppm	32 ppm	80 ppm	200 ppm
Female (continued)						
n						
Day 22	10	10	10	10	10	10
Week 13	10	10	10	10	10	10
Urinalysis						
Creatinine (mg/dL)						
Day 22	18.7 ± 3.1	19.2 ± 4.0	16.9 ± 2.1	18.0 ± 2.8	19.1 ± 3.5	8.4 ± 0.9**
Week 13	45.1 ± 4.9	31.4 ± 2.2*	45.7 ± 3.2	26.8 ± 4.0**	28.5 ± 2.9**	29.0 ± 3.2**
Glucose (µg/mg creatinine)						
Day 22	142 ± 8	199 ± 24	146 ± 7	149 ± 10	167 ± 6	151 ± 21
Week 13	97 ± 4	100 ± 3	105 ± 2	98 ± 4	102 ± 4	99 ± 3
Protein (µg/mg creatinine)						
Day 22	431 ± 51	390 ± 41	416 ± 34	343 ± 31	383 ± 21	694 ± 73*
Week 13	173 ± 13	200 ± 13	217 ± 40	203 ± 18	188 ± 14	201 ± 15
Alkaline phosphatase (mU/mg creatinine)						
Day 22	296 ± 35	397 ± 66	337 ± 64	285 ± 30	357 ± 19	524 ± 79**
Week 13	144 ± 7	147 ± 8	146 ± 5	141 ± 14	163 ± 10	267 ± 19**
Aspartate aminotransferase (mU/mg creatinine)						
Day 22	11 ± 1	21 ± 12	36 ± 28	13 ± 3	27 ± 13	26 ± 9
Week 13	4 ± 1	8 ± 2	6 ± 1[i]	5 ± 1	7 ± 1	9 ± 2*
Volume (mL/16 hr)						
Day 22	19.5 ± 2.4	16.5 ± 1.9	17.4 ± 1.9	19.1 ± 2.9	18.0 ± 2.8	30.6 ± 3.0
Week 13	10.9 ± 1.6	15.4 ± 1.6	10.7 ± 1.2	18.6 ± 2.7	18.4 ± 2.9	15.8 ± 1.5
Specific gravity						
Day 22	1.008 ± 0.001	1.010 ± 0.002	1.008 ± 0.001	1.008 ± 0.001	1.009 ± 0.002	1.004 ± 0.000**
Week 13	1.013 ± 0.001	1.010 ± 0.001*	1.014 ± 0.001	1.008 ± 0.001**	1.009 ± 0.001**	1.009 ± 0.001**
Urea (mg/mg creatinine)						
Day 22	25.4 ± 0.7	27.5 ± 0.5	28.0 ± 0.7	28.4 ± 0.9	25.8 ± 0.5	27.4 ± 1.2
Week 13	20.3 ± 0.5	20.9 ± 0.5	20.6 ± 0.4	21.8 ± 0.8	21.5 ± 0.5	21.5 ± 0.6

* Significantly different ($P \leq 0.05$) from the control group by Dunn's or Shirley's test
** $P \leq 0.01$
[a] Mean ± standard error. Statistical tests were performed on unrounded data.
[b] Not measured at this exposure concentration
[c] n = 10
[d] n = 7
[e] n = 6
[f] n = 8
[g] n = 5
[h] n = 3
[i] n = 9

TABLE G3
Day 5 Hematology and Clinical Chemistry Data for Mice in the 16-Day Inhalation Study of Chloroprene[a]

	Chamber Control	12 ppm	32 ppm	80 ppm	200 ppm
Male					
n	10	10	10	10	0[b]
Hematology					
Hematocrit (%)	49.4 ± 0.5	48.3 ± 0.5	47.2 ± 0.8	48.4 ± 0.6	—
Hemoglobin (g/dL)	16.3 ± 0.2	16.0 ± 0.1	15.6 ± 0.3[c]	15.9 ± 0.2	—
Erythrocytes (10^6/μL)	9.95 ± 0.13	9.64 ± 0.12	9.40 ± 0.20	9.65 ± 0.13	—
Reticulocytes (10^6/μL)	0.14 ± 0.02	0.15 ± 0.02	0.13 ± 0.03	0.19 ± 0.02	—
Nucleated erythrocytes (10^3/μL)	0.00 ± 0.00	0.01 ± 0.01	0.01 ± 0.01	0.00 ± 0.00	—
Howell-Jolly bodies (% erythrocytes)	0.2 ± 0.1	0.1 ± 0.0	0.1 ± 0.0	0.1 ± 0.0	—
Mean cell volume (fL)	49.7 ± 0.4	50.2 ± 0.4	50.4 ± 0.3	50.1 ± 0.4	—
Mean cell hemoglobin (pg)	16.4 ± 0.1	16.6 ± 0.1	16.5 ± 0.1[c]	16.4 ± 0.1	—
Mean cell hemoglobin concentration (g/dL)	33.0 ± 0.1	33.1 ± 0.1	32.7 ± 0.2[c]	32.8 ± 0.2	—
Platelets (10^3/μL)	930.2 ± 22.7	893.2 ± 26.7	959.1 ± 41.2	985.1 ± 62.7	—
Leukocytes (10^3/μL)	3.40 ± 0.24	4.33 ± 0.53	4.51 ± 0.66	3.40 ± 0.34	—
Segmented neutrophils (10^3/μL)	0.37 ± 0.05	0.39 ± 0.06	0.51 ± 0.10	0.38 ± 0.07	—
Lymphocytes (10^3/μL)	2.99 ± 0.20	3.87 ± 0.52	3.93 ± 0.56	2.99 ± 0.30	—
Monocytes (10^3/μL)	0.04 ± 0.01	0.06 ± 0.02	0.05 ± 0.02	0.03 ± 0.01	—
Eosinophils (10^3/μL)	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.01 ± 0.01	—
Clinical Chemistry					
Urea nitrogen (mg/dL)	41.2 ± 3.8[c]	35.4 ± 2.5[c]	40.3 ± 4.9[c]	45.5 ± 4.6[d]	—
Creatinine (mg/dL)	0.64 ± 0.08[c]	0.59 ± 0.07[c]	0.68 ± 0.06[d]	0.79 ± 0.06[d]	—
Alanine aminotransferase (IU/L)	306 ± 73	333 ± 70	193 ± 50[c]	325 ± 52[c]	—
Glutamate dehydrogenase (IU/L)	12.0 ± 0.9	11.9 ± 1.1	11.1 ± 1.0	14.4 ± 0.9	—
Sorbitol dehydrogenase (IU/L)	38 ± 3	37 ± 2	36 ± 2	35 ± 2	—

TABLE G3
Day 5 Hematology and Clinical Chemistry Data for Mice in the 16-Day Inhalation Study of Chloroprene

	Chamber Control	12 ppm	32 ppm	80 ppm	200 ppm
Female					
n	9	10	10	10	0[b]
Hematology					
Hematocrit (%)	48.5 ± 0.7	49.4 ± 0.2	48.6 ± 0.4	47.9 ± 0.4	—
Hemoglobin (g/dL)	15.6 ± 0.3	16.1 ± 0.1	15.8 ± 0.1	15.5 ± 0.1	—
Erythrocytes (10^6/µL)	9.40 ± 0.18	9.74 ± 0.09	9.47 ± 0.11	9.37 ± 0.09	—
Reticulocytes (10^6/µL)	0.09 ± 0.03	0.10 ± 0.01	0.10 ± 0.03	0.06 ± 0.01	—
Nucleated erythrocytes (10^3/µL)	0.00 ± 0.00	0.01 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	—
Howell-Jolly bodies (% erythrocytes)	0.1 ± 0.0	0.1 ± 0.0	0.1 ± 0.1	0.1 ± 0.0	—
Mean cell volume (fL)	51.8 ± 0.4	50.8 ± 0.2	51.4 ± 0.4	51.1 ± 0.3	—
Mean cell hemoglobin (pg)	16.7 ± 0.1	16.5 ± 0.1	16.7 ± 0.1	16.6 ± 0.1	—
Mean cell hemoglobin concentration (g/dL)	32.3 ± 0.1	32.6 ± 0.1	32.4 ± 0.1	32.4 ± 0.1	—
Platelets (10^3/µL)	804.2 ± 20.3	792.5 ± 22.7	847.1 ± 12.5	945.4 ± 24.9**	—
Leukocytes (10^3/µL)	3.30 ± 0.20	3.29 ± 0.25	3.20 ± 0.20	3.02 ± 0.23	—
Segmented neutrophils (10^3/µL)	0.42 ± 0.05	0.41 ± 0.07	0.40 ± 0.05	0.39 ± 0.05	—
Lymphocytes (10^3/µL)	2.79 ± 0.19	2.80 ± 0.23	2.72 ± 0.16	2.54 ± 0.18	—
Monocytes (10^3/µL)	0.09 ± 0.02	0.07 ± 0.03	0.09 ± 0.02	0.09 ± 0.02	—
Eosinophils (10^3/µL)	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	—
Clinical Chemistry					
Urea nitrogen (mg/dL)	34.5 ± 2.5	29.4 ± 2.3	29.3 ± 1.8	32.9 ± 2.6[c]	—
Creatinine (mg/dL)	0.79 ± 0.05	0.69 ± 0.05	0.65 ± 0.03	0.73 ± 0.06[c]	—
Alanine aminotransferase (IU/L)	87 ± 13	167 ± 51	142 ± 43	238 ± 68	—
Glutamate dehydrogenase (IU/L)	10.0 ± 0.5	10.5 ± 0.8	9.4 ± 1.0	14.3 ± 1.8	—
Sorbitol dehydrogenase (IU/L)	30 ± 3	24 ± 1	26 ± 1	28 ± 1	—

** Significantly different ($P \leq 0.01$) from the control group by Dunn's or Shirley's test
[a] Mean ± standard error. Statistical tests were performed on unrounded data.
[b] Not measured at this exposure concentration due to high mortality
[c] n = 9
[d] n = 8

TABLE G4
Hematology and Clinical Chemistry Data for Mice in the 13-Week Inhalation Study of Chloroprene[a]

	Chamber Control	5 ppm	12 ppm	32 ppm	80 ppm
Male					
n	10	10	9	10	10
Hematology					
Hematocrit (%)	45.3 ± 0.8	45.5 ± 0.6	44.3 ± 2.0	46.1 ± 0.4	44.9 ± 0.2
Hemoglobin (g/dL)	16.2 ± 0.2	16.3 ± 0.2	16.1 ± 0.7	16.7 ± 0.1	16.3 ± 0.1
Erythrocytes (10^6/µL)	10.19 ± 0.15	10.23 ± 0.11	10.06 ± 0.46	10.41 ± 0.08	10.21 ± 0.06
Reticulocytes (10^6/µL)	0.23 ± 0.01	0.21 ± 0.01	0.24 ± 0.02	0.23 ± 0.02	0.20 ± 0.01
Howell-Jolly bodies (% erythrocytes)	0.1 ± 0.0	0.1 ± 0.1	0.2 ± 0.0[b]	0.2 ± 0.0	0.1 ± 0.0
Mean cell volume (fL)	44.5 ± 0.2	44.5 ± 0.2	43.9 ± 0.4	44.3 ± 0.3	43.9 ± 0.2
Mean cell hemoglobin (pg)	15.9 ± 0.1	16.0 ± 0.1	16.0 ± 0.1	16.0 ± 0.1	16.0 ± 0.0
Mean cell hemoglobin concentration (g/dL)	35.9 ± 0.2	35.8 ± 0.2	36.3 ± 0.2	36.2 ± 0.2	36.4 ± 0.2
Platelets (10^3/µL)	913.6 ± 18.5	881.4 ± 17.5	847.9 ± 44.1	929.8 ± 17.4	914.4 ± 30.6
Leukocytes (10^3/µL)	3.96 ± 0.47	3.46 ± 0.27	4.20 ± 0.58	4.35 ± 0.46	4.63 ± 0.54
Segmented neutrophils (10^3/µL)	0.45 ± 0.04	0.48 ± 0.06	0.51 ± 0.06	0.53 ± 0.06	0.77 ± 0.14
Lymphocytes (10^3/µL)	3.37 ± 0.45	2.83 ± 0.22	3.56 ± 0.53	3.70 ± 0.40	3.71 ± 0.46
Monocytes (10^3/µL)	0.11 ± 0.02	0.12 ± 0.03	0.07 ± 0.02	0.08 ± 0.02	0.12 ± 0.03
Eosinophils (10^3/µL)	0.04 ± 0.01	0.035 ± 0.01	0.06 ± 0.02	0.04 ± 0.02	0.04 ± 0.02
Clinical Chemistry					
Urea nitrogen (mg/dL)	31.0 ± 2.3	32.4 ± 2.1	32.0 ± 2.0	32.5 ± 3.6	25.0 ± 1.8
Creatinine (mg/dL)	0.51 ± 0.03[c]	0.44 ± 0.05	0.47 ± 0.04	0.47 ± 0.09	0.36 ± 0.04*[c]
Alanine aminotransferase (IU /L)	71 ± 19	91 ± 17	108 ± 26	176 ± 56	122 ± 29
Glutamate dehydrogenase (IU/L)	4.5 ± 0.6	6.0 ± 0.9	5.9 ± 1.1	7.3 ± 1.1	6.6 ± 1.3
Sorbitol dehydrogenase (IU/L)	35 ± 3	32 ± 1	32 ± 3[b]	31 ± 1	33 ± 2

TABLE G4
Hematology and Clinical Chemistry Data for Mice in the 13-Week Inhalation Study of Chloroprene

	Chamber Control	5 ppm	12 ppm	32 ppm	80 ppm
Female					
n	10	10	10	10	10
Hematology					
Hematocrit (%)	45.9 ± 0.4	45.6 ± 0.4	45.3 ± 0.3	44.7 ± 0.3*	44.3 ± 0.3**
Hemoglobin (g/dL)	16.4 ± 0.1	16.4 ± 0.1	16.4 ± 0.1	16.3 ± 0.1	16.2 ± 0.1
Erythrocytes (10^6/µL)	10.16 ± 0.05	10.08 ± 0.07	10.20 ± 0.05	10.09 ± 0.05	9.93 ± 0.06*
Reticulocytes (10^6/µL)	0.22 ± 0.03	0.24 ± 0.03	0.23 ± 0.01	0.22 ± 0.02	0.23 ± 0.03
Howell-Jolly bodies (% erythrocytes)	0.12 ± 0.04	0.13 ± 0.04	0.09 ± 0.03	0.09 ± 0.03	0.11 ± 0.03
Mean cell volume (fL)	45.1 ± 0.3	45.3 ± 0.4	44.5 ± 0.2	44.2 ± 0.2	44.5 ± 0.2
Mean cell hemoglobin (pg)	16.1 ± 0.1	16.2 ± 0.0	16.1 ± 0.1	16.2 ± 0.1	16.3 ± 0.0*
Mean cell hemoglobin concentration (g/dL)	35.8 ± 0.3	36.0 ± 0.3	36.1 ± 0.1	36.5 ± 0.1	36.6 ± 0.2*
Platelets (10^3/µL)	866.2 ± 18.0	861.4 ± 15.0	890.0 ± 11.4	924.9 ± 18.0*	964.9 ± 24.5**
Leukocytes (10^3/µL)	3.24 ± 0.25	3.27 ± 0.43	3.10 ± 0.33	3.81 ± 0.41	3.21 ± 0.25
Segmented neutrophils (10^3/µL)	0.35 ± 0.05	0.45 ± 0.08	0.34 ± 0.03	0.68 ± 0.27	0.36 ± 0.04
Lymphocytes (10^3/µL)	2.77 ± 0.21	2.67 ± 0.33	2.68 ± 0.32	2.97 ± 0.20	2.72 ± 0.21
Monocytes (10^3/µL)	0.08 ± 0.02	0.12 ± 0.05	0.06 ± 0.01	0.12 ± 0.03	0.09 ± 0.03
Eosinophils (10^3/µL)	0.04 ± 0.01	0.04 ± 0.02	0.02 ± 0.01	0.04 ± 0.02	0.04 ± 0.01
Clinical Chemistry					
Urea nitrogen (mg/dL)	24.8 ± 1.4	21.7 ± 1.3*	20.0 ± 0.8**	19.5 ± 0.9**	18.1 ± 0.6**
Creatinine (mg/dL)	0.63 ± 0.09	0.57 ± 0.03	0.57 ± 0.03[c]	0.54 ± 0.04	0.51 ± 0.04[c]
Alanine aminotransferase (IU/L)	46 ± 12	32 ± 3	31 ± 3	41 ± 4	48 ± 13
Glutamate dehydrogenase (IU/L)	5.2 ± 0.8	4.0 ± 0.4	3.8 ± 0.3	4.3 ± 0.3	4.6 ± 0.5
Sorbitol dehydrogenase (IU/L)	23 ± 3	27 ± 1	26 ± 3	30 ± 2	26 ± 1

* Significantly different ($P \leq 0.05$) from the control group by Dunn's or Shirley's test
** $P \leq 0.01$
[a] Mean ± standard error. Statistical tests were performed on unrounded data.
[b] n = 10
[c] n = 9

APPENDIX H
TISSUE NONPROTEIN SULFHYDRYL CONCENTRATION RESULTS

TABLE H1
Tissue Nonprotein Sulfhydryl Concentrations in Rats in the 13-Week Inhalation Study of Chloroprene[a]

	Chamber Control	5 ppm	32 ppm	200 ppm
Male				
n	5	5	5	5
Kidney nonprotein sulfhydryl				
Day 1	1.10 ± 0.12	1.22 ± 0.23	1.38 ± 0.25[b]	1.30 ± 0.16
Week 12	0.72 ± 0.22	1.46 ± 0.44	1.62 ± 0.14	1.48 ± 0.40
Liver nonprotein sulfhydryl				
Day 1	1.70 ± 0.28	1.56 ± 0.25	1.88 ± 0.18	0.50 ± 0.17*
Week 12	5.04 ± 0.39	4.58 ± 0.34	3.90 ± 0.86	2.90 ± 0.22*
Lung nonprotein sulfhydryl				
Day 1	0.180 ± 0.058	0.100 ± 0.000	0.080 ± 0.020	0.075 ± 0.025[b]
Week 12	0.24 ± 0.07	0.14 ± 0.05	0.10 ± 0.03	0.34 ± 0.12
Thymus nonprotein sulfhydryl				
Day 1	1.52 ± 0.06	1.34 ± 0.17	1.42 ± 0.20	1.60 ± 0.12[b]
Week 12	1.80 ± 0.26[b]	1.84 ± 0.15	1.70 ± 0.18	1.78 ± 0.13
Kidney total sulfhydryl/ nonprotein sulfhydryl				
Day 1	12.58 ± 1.33	12.32 ± 1.62	10.68 ± 1.42[b]	11.94 ± 1.26
Week 12	26.44 ± 6.36	14.28 ± 4.92	9.20 ± 0.96	13.56 ± 4.05
Liver total sulfhydryl/ nonprotein sulfhydryl				
Day 1	11.00 ± 2.05	11.46 ± 1.77	8.38 ± 0.96	50.42 ± 20.57
Week 12	2.68 ± 0.25	2.70 ± 0.21	4.40 ± 1.32	4.66 ± 0.24
Lung total sulfhydryl/ nonprotein sulfhydryl				
Day 1	42.8 ± 14.5	60.3 ± 5.1	69.4 ± 7.1	82.6 ± 18.4[b]
Week 12	48.9 ± 16.8	69.0 ± 20.8	108.1 ± 42.8	27.5 ± 5.1
Thymus total sulfhydryl/ nonprotein sulfhydryl				
Day 1	5.70 ± 0.31	6.44 ± 0.99	6.84 ± 1.12	5.48 ± 0.61[b]
Week 12	5.28 ± 0.72[b]	5.42 ± 0.42	5.84 ± 0.91	4.98 ± 0.18

TABLE H1
Tissue Nonprotein Sulfhydryl Concentrations in Rats in the 13-Week Inhalation Study of Chloroprene

	Chamber Control	5 ppm	32 ppm	200 ppm
Female				
n	5	5	5	5
Kidney nonprotein sulfhydryl				
Day 1	1.38 ± 0.16	1.50 ± 0.27	1.42 ± 0.26	1.10 ± 0.19
Week 12	1.32 ± 0.27	1.76 ± 0.29	1.88 ± 0.14	2.70 ± 0.31**
Liver nonprotein sulfhydryl				
Day 1	1.58 ± 0.24	1.90 ± 0.40	1.62 ± 0.30	0.96 ± 0.37
Week 12	4.76 ± 0.30	4.48 ± 0.23	4.02 ± 0.19	1.46 ± 0.07**
Lung nonprotein sulfhydryl				
Day 1	0.160 ± 0.060	0.160 ± 0.087	0.060 ± 0.024	0.020 ± 0.020*
Week 12	0.16 ± 0.06	0.20 ± 0.08	0.46 ± 0.14	0.34 ± 0.10
Thymus nonprotein sulfhydryl				
Day 1	1.98 ± 0.10	1.70 ± 0.15	2.02 ± 0.11	1.74 ± 0.09
Week 12	1.88 ± 0.16	1.96 ± 0.12	1.90 ± 0.20	1.76 ± 0.09
Kidney total sulfhydryl/ nonprotein sulfhydryl				
Day 1	8.96 ± 0.88	8.82 ± 1.23	10.08 ± 1.30	12.82 ± 2.88
Week 12	12.50 ± 2.68	9.08 ± 1.92	7.46 ± 0.40	6.10 ± 0.65*
Liver total sulfhydryl/ nonprotein sulfhydryl				
Day 1	9.98 ± 1.63	8.90 ± 1.43	10.60 ± 2.11	54.94 ± 28.14
Week 12	3.80 ± 0.25	4.28 ± 0.22	3.86 ± 0.66	11.32 ± 0.64**
Lung total sulfhydryl/ nonprotein sulfhydryl				
Day 1	53.0 ± 10.7	59.5 ± 16.6	92.0 ± 11.3	119.7 ± 29.7*
Week 12	47.4 ± 7.4	49.3 ± 14.2	28.7 ± 14.6	34.3 ± 14.7
Thymus total sulfhydryl/ nonprotein sulfhydryl				
Day 1	4.54 ± 0.14	5.02 ± 0.32	4.58 ± 0.11	4.60 ± 0.25
Week 12	4.64 ± 0.12	4.28 ± 0.11	4.30 ± 0.15	4.70 ± 0.17

* Significantly different ($P \leq 0.05$) from the control group by Dunn's or Shirley's test
** $P \leq 0.01$
[a] Mean ± standard error in units of µmole/g tissue. Statistical tests were performed on unrounded data.
[b] n = 4

TABLE H2
Tissue Nonprotein Sulfhydryl Concentrations in Mice in the 13-Week Inhalation Study of Chloroprene[a]

	Chamber Control	12 ppm	32 ppm	80 ppm
Male				
n	5	5	5	5
Kidney nonprotein sulfhydryl				
Day 1	1.74 ± 0.36	1.62 ± 0.26	1.66 ± 0.27	1.64 ± 0.34
Week 12	1.98 ± 0.07	2.28 ± 0.25	2.10 ± 0.27	2.36 ± 0.20
Liver nonprotein sulfhydryl				
Day 1	2.46 ± 0.17	2.36 ± 0.25	2.30 ± 0.18	2.54 ± 0.30
Week 12	4.38 ± 0.35	4.90 ± 0.25	4.58 ± 0.25	3.00 ± 0.13
Lung nonprotein sulfhydryl				
Day 1	0.68 ± 0.14	0.72 ± 0.20	0.72 ± 0.15	0.58 ± 0.09
Week 12	1.04 ± 0.13	1.06 ± 0.12	0.86 ± 0.07	0.64 ± 0.15
Thymus nonprotein sulfhydryl				
Day 1	1.58 ± 0.26	1.92 ± 0.12	1.56 ± 0.17	1.68 ± 0.21
Week 12	2.06 ± 0.23	1.50 ± 0.30	1.84 ± 0.41	1.60 ± 0.15
Kidney total sulfhydryl/ nonprotein sulfhydryl				
Day 1	9.28 ± 1.83	9.02 ± 1.67	8.60 ± 1.19	9.98 ± 2.19
Week 12	6.72 ± 0.34	6.98 ± 1.20	6.94 ± 1.09	5.26 ± 0.80
Liver total sulfhydryl/ nonprotein sulfhydryl				
Day 1	5.06 ± 0.32	5.44 ± 0.34	5.76 ± 0.63	5.08 ± 0.64
Week 12	2.32 ± 0.14	2.22 ± 0.11	2.38 ± 0.17	3.32 ± 0.18**
Lung total sulfhydryl/ nonprotein sulfhydryl				
Day 1	12.16 ± 2.46	11.46 ± 2.69	11.62 ± 2.34	12.92 ± 1.53
Week 12	7.90 ± 1.50	7.14 ± 0.74	7.98 ± 0.47	14.68 ± 6.31
Thymus total sulfhydryl/ nonprotein sulfhydryl				
Day 1	4.96 ± 0.36	3.92 ± 0.16	4.52 ± 0.34	5.04 ± 0.96
Week 12	2.58 ± 0.42	2.96 ± 0.43	4.22 ± 2.01	3.12 ± 0.43

TABLE H2
Tissue Nonprotein Sulfhydryl Concentrations in Mice in the 13-Week Inhalation Study of Chloroprene

	Chamber Control	12 ppm	32 ppm	80 ppm
Female				
n	5	5	5	5
Kidney nonprotein sulfhydryl				
Day 1	1.38 ± 0.10	1.86 ± 0.10*	1.76 ± 0.17	1.74 ± 0.10
Week 12	1.58 ± 0.22	2.08 ± 0.27	1.54 ± 0.11	1.58 ± 0.19
Liver nonprotein sulfhydryl				
Day 1	2.12 ± 0.33	2.56 ± 0.19	2.82 ± 0.16	2.96 ± 0.19
Week 12	4.00 ± 0.21	4.24 ± 0.34	4.04 ± 0.32	2.62 ± 0.20
Lung nonprotein sulfhydryl				
Day 1	0.56 ± 0.09	0.82 ± 0.05	0.62 ± 0.19	0.52 ± 0.06
Week 12	0.74 ± 0.06	0.60 ± 0.22	0.64 ± 0.16	0.50 ± 0.06
Thymus nonprotein sulfhydryl				
Day 1	1.70 ± 0.17	1.90 ± 0.22	2.36 ± 0.34	1.94 ± 0.10
Week 12	1.64 ± 0.08	2.16 ± 0.21	1.82 ± 0.13	1.62 ± 0.16
Kidney total sulfhydryl/ nonprotein sulfhydryl				
Day 1	9.34 ± 0.46	7.38 ± 0.40	7.26 ± 0.62	8.20 ± 0.57
Week 12	8.74 ± 1.01	7.02 ± 0.70	8.86 ± 0.70	9.22 ± 0.97
Liver total sulfhydryl/ nonprotein sulfhydryl				
Day 1	6.50 ± 0.76	5.26 ± 0.47	4.66 ± 0.28	4.48 ± 0.39
Week 12	2.78 ± 0.05	2.70 ± 0.27	2.74 ± 0.14	4.08 ± 0.29
Lung total sulfhydryl/ nonprotein sulfhydryl				
Day 1	13.80 ± 2.49	9.06 ± 0.47	10.25 ± 1.39[b]	14.68 ± 1.15
Week 12	9.70 ± 0.51	17.36 ± 6.01	13.28 ± 4.64	12.72 ± 1.43
Thymus total sulfhydryl/ nonprotein sulfhydryl				
Day 1	4.74 ± 0.39	4.14 ± 0.46	3.30 ± 0.54	4.50 ± 0.33
Week 12	4.20 ± 0.31	3.68 ± 0.43	3.94 ± 0.34	3.50 ± 0.18

* Significantly different ($P \leq 0.05$) from the control group by Dunn's or Shirley's test
** $P \leq 0.01$
[a] Mean ± standard error in units of µmole/g tissue. Statistical tests were performed on unrounded data.
[b] n = 4

APPENDIX I
REPRODUCTIVE TISSUE EVALUATIONS AND CYCLE CHARACTERIZATION

TABLE I1
Summary of Reproductive Tissue Evaluations and Estrous Cycle Characterization for Rats in the 13-Week Study of Chloroprene[a]

	Chamber Control	5 ppm	32 ppm	200 ppm
Male				
n	10	10	9	9
Weights (g)				
Necropsy body wt	292 ± 9	306 ± 11	309 ± 10[b]	284 ± 8
R. cauda	0.1578 ± 0.0057	0.1620 ± 0.0077	0.1568 ± 0.0073	0.1547 ± 0.0048
R. epididymis	0.4524 ± 0.0166	0.4298 ± 0.0159	0.4467 ± 0.0106	0.4328 ± 0.0117
R. testis	1.324 ± 0.034	1.344 ± 0.025	1.375 ± 0.038	1.351 ± 0.024
Epididymal spermatozoal parameters				
Motility (%)	86.73 ± 1.04	83.62 ± 1.93	82.16 ± 1.84	80.04 ± 1.99**
Abnormal sperm (%)	0.70 ± 0.05	0.78 ± 0.11	0.73 ± 0.11	1.02 ± 0.14
Concentration (10^6/g cauda epididymal tissue)	698 ± 40	722 ± 62	689 ± 46	683 ± 25
Female				
n	10	10	10	10
Necropsy body wt (g)	176 ± 3	180 ± 3	181 ± 4	171 ± 3
Estrous cycle length (days)	5.00 ± 0.15	4.67 ± 0.17[c]	5.00 ± 0.27[d]	5.33 ± 0.17[c]
Estrous stages (% of cycle)				
Diestrus	42.9	35.7	44.3	45.7
Proestrus	15.7	18.6	11.4	17.1
Estrus	18.6	22.9	20.0	15.7
Metestrus	22.9	22.9	24.3	20.0
Uncertain diagnoses	0.0	0.0	0.0	1.4

** Significantly different ($P \leq 0.01$) from the control group by Shirley's test

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

[b] n = 10

[c] Estrous cycle was longer than 12 days or unclear in 1 of 10 animals.

[d] Estrous cycle was longer than 12 days or unclear in 2 of 10 animals.

TABLE I2
Summary of Reproductive Tissue Evaluations and Estrous Cycle Characterization for Mice in the 13-Week Study of Chloroprene[a]

	Chamber Control	12 ppm	32 ppm	80 ppm
Male				
n	7	8	10	10
Weights (g)				
Necropsy body wt	36.0 ± 0.9[b]	35.1 ± 0.6[b]	36.8 ± 0.9	33.4 ± 0.6
R. cauda	0.0172 ± 0.0006	0.0164 ± 0.0011	0.0164 ± 0.0014	0.0158 ± 0.0005
R. epididymis	0.0492 ± 0.0021	0.0488 ± 0.0019	0.0510 ± 0.0043	0.0470 ± 0.0011
R. testis	0.114 ± 0.004	0.116 ± 0.002	0.122 ± 0.004	0.123 ± 0.004
Epididymal spermatozoal parameters				
Motility (%)	79.09 ± 1.20	81.07 ± 1.13	80.08 ± 1.19	80.04 ± 1.47
Abnormal sperm (%)	1.49 ± 0.42	1.30 ± 0.22	0.98 ± 0.10	1.36 ± 0.22
Concentration (10^6/g cauda epididymal tissue)	1,632 ± 138	1,447 ± 122	1,575 ± 104	1,672 ± 134
Female				
n	10	10	10	10
Necropsy body wt (g)	31.5 ± 1.1	31.2 ± 0.7	33.5 ± 0.7	30.2 ± 1.5
Estrous cycle length (days)	4.00 ± 0.00	4.30 ± 0.21	4.22 ± 0.15[c]	4.13 ± 0.13[d]
Estrous stages (% of cycle)				
Diestrus	31.4	31.4	30.0	35.7
Proestrus	20.0	20.0	22.9	25.7
Estrus	24.3	24.3	25.7	20.0
Metestrus	24.3	24.3	21.4	18.6

[a] Weights, epididymal spermatozoal parameters, and estrous cycle lengths are presented as mean ± standard error. Differences from the control group are not significant by Dunn's test (epididymal spermatozoal parameters, estrous cycle length) or Dunnett's test (organ and body weights). By multivariate analysis of variance, exposed females do not differ significantly from the chamber control females in relative length of time spent in the estrous stages.
[b] n = 10
[c] Estrous cycle was longer than 12 days or unclear in 1 of 10 animals.
[d] Estrous cycle was longer than 12 days or unclear in 2 of 10 animals.

APPENDIX J
NEUROBEHAVIORAL STUDIES

TABLE J1
Neurobehavioral Data for Rats at 11 Weeks in the 13-Week Inhalation Study of Chloroprene[a]

	0 ppm	5 ppm	12 ppm	32 ppm	80 ppm	200 ppm
Male						
n	10	10	10	10	10	9
Forelimb grip strength[b] (g)	515.8 ± 24.9	526.5 ± 29.0	506.7 ± 18.2	558.8 ± 27.4	525.9 ± 28.1	467.4 ± 23.7
Hindlimb grip strength[b] (g)	409.6 ± 29.0	397.5 ± 28.0	396.5 ± 16.4	440.6 ± 15.9	410.1 ± 19.2	393.2 ± 24.5
Horizontal activity count (1 hour)	163.5 ± 13.9	196.4 ± 20.5	182.2 ± 7.9	201.2 ± 15.5*	207.7 ± 14.4*	218.9 ± 9.6**
Rearing activity count (1 hour)	31.5 ± 4.4	38.7 ± 4.5	36.0 ± 5.3	42.2 ± 6.4	33.9 ± 3.9	41.1 ± 4.3
Total activity count (1 hour)	195.0 ± 15.1	235.1 ± 23.6	218.2 ± 12.5	243.4 ± 19.4*	241.6 ± 16.6	260.0 ± 10.3**
Tailflick latency test (seconds)	4.18 ± 0.31	4.81 ± 0.44	4.47 ± 0.57	5.70 ± 1.02	4.37 ± 0.50	4.66 ± 0.76
Startle response latency[c] (milliseconds)	47.6 ± 2.1	43.3 ± 1.2	42.5 ± 2.3	47.5 ± 3.3	44.0 ± 2.7	40.7 ± 1.8
Startle response amplitude[c] (volts)	93.4 ± 9.4	89.4 ± 9.3	96.1 ± 10.2	118.0 ± 18.7	104.4 ± 14.3	60.3 ± 8.6
Female						
n	10	10	10	10	10	10
Forelimb grip strength test (g)	460.5 ± 15.0	475.2 ± 15.5	509.2 ± 15.1	482.1 ± 18.9	490.1 ± 21.2	463.2 ± 28.2
Hindlimb grip strength test (g)	369.8 ± 17.8	395.8 ± 15.0	394.2 ± 17.2	370.4 ± 17.0	395.4 ± 14.2	358.2 ± 15.5
Horizontal activity count (1 hour)	244.6 ± 28.2	260.1 ± 31.4	234.4 ± 18.6	258.8 ± 19.2	270.4 ± 20.5	257.7 ± 16.8
Rearing activity count (1 hour)	41.8 ± 3.8	37.8 ± 5.6	38.6 ± 5.9	47.0 ± 6.4	55.5 ± 7.3	50.0 ± 4.6
Total activity count (1 hour)	286.4 ± 30.0	297.9 ± 35.9	273.0 ± 23.3	305.8 ± 22.7	325.9 ± 23.4	307.7 ± 20.0
Tailflick latency test (seconds)	4.40 ± 0.29	6.42 ± 0.87	4.07 ± 0.34	4.43 ± 0.41	5.10 ± 0.69	4.31 ± 0.23
Startle response latency (milliseconds)	43.0 ± 2.9	38.0 ± 1.9	39.6 ± 1.8	40.9 ± 2.4	40.9 ± 2.0	42.8 ± 1.9
Startle response amplitude (volts)	40.4 ± 9.7	42.5 ± 4.9	45.1 ± 8.2	34.4 ± 3.9	48.2 ± 8.0	36.6 ± 3.7

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

APPENDIX K
CHEMICAL CHARACTERIZATION AND GENERATION OF CHAMBER CONCENTRATIONS

CHEMICAL CHARACTERIZATION AND GENERATION OF CHAMBER CONCENTRATIONS

PROCUREMENT AND CHARACTERIZATION OF CHLOROPRENE

Chloroprene was obtained for the 16-day and 13-week studies from Denka Chemical Company (Houston, TX) in 5 lots. Chloroprene for the 2-year study was supplied by Mobay Synthetic Corporation (Houston, TX) in 12 lots. Identity, purity, and stability studies of lot 12103-4-1, from the first lot of material procured for these studies, were performed by the analytical chemistry laboratory, Midwest Research Institute (Kansas City, MO). Reports on the analyses performed by the analytical chemistry laboratory in support of the chloroprene studies are on file at the National Institute of Environmental Health Sciences. Subsequent purity and identity analyses of chloroprene lots were performed by the study laboratory.

The chemical, a clear colorless liquid, was identified as chloroprene by infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopy. The infrared and nuclear magnetic resonance spectra were consistent with the literature spectra (Bothner-By and Harris, 1953; Szasz and Sheppard, 1953) of chloroprene; all spectra were consistent with the structure of chloroprene. The infrared and nuclear magnetic resonance spectra are presented in Figures K1 and K2. The boiling point and density of the chemical were also consistent with literature references (*CRC Handbook of Chemistry and Physics*, 1982).

The purity of lot 12103-4-1 was determined by elemental analysis, Karl Fischer water analysis, approximation of *t*-butylcatechol, thin layer chromatography (TLC), and gas chromatography. To approximate the concentration of *t*-butylcatechol inhibitor, 1.0 N sodium hydroxide was added to a chloroprene sample and the resultant color was compared to *t*-butylcatechol standards. TLC was performed on Silica Gel 60, F-254 plates with a methanol solvent system. Plates were examined under iodine vapor. Gas chromatography was performed using a flame ionization detector. Two systems were used:

A) 0.1% SP-1000 on 80/100 Carbopack glass column, with a nitrogen carrier gas at a flow rate of 70 mL per minute, and an oven temperature program of 50° C for 5 minutes, then 50° C to 225° C at 10° C per minute.

B) DB-5 fused silica column, with a helium carrier gas at a flow rate of 50 cm^3 per second, a nitrogen make-up gas at a flow rate of 30 mL per minute, and an oven temperature program of 30° C for 5 minutes, and then 30° C to 250° C at 10° C per minute.

Peroxide concentrations were analyzed for lot 12103-4-1. To determine peroxide concentrations a sample of chloroprene was dissolved in glacial acetic acid:chloroform (3:2). Saturated potassium iodide solution was added and the sample was allowed to stand for 1 minute. Distilled water was then added; liberated iodine was titrated with 0.01 sodium thiosulfate to a colorimetric endpoint using a starch indicator.

Chloroprene procured for the 16-day and 13-week studies was fortified with 0.1% phenothiazine and *t*-butylcatechol. Chloroprene procured for the 2-year study had 0.1% phenothiazine and *t*-butylcatechol added by the producer before shipment to the study laboratory.

Elemental analyses for carbon, hydrogen, and chlorine agreed with the theoretical values for chloroprene. Karl Fisher water analysis indicated less than 0.01% water. Approximation of *t*-butylcatechol inhibitor indicated 40 to 50 ppm with flame ionization detection, a DB-5 megabore capillary column, and an oven program from an initial temperature of 35° C for 5 minutes then ramped at 10° C/minute to a final temperature of 175° C using helium as the carrier gas. TLC indicated one major spot. TLC of a second sample left at room temperature overnight revealed another spot in addition to the major spot. Gas

chromatography by system A indicated four impurities with a cumulative peak area of 0.96% relative to the major peak; gas chromatography by system B indicated six impurities with a total area of 3.30% relative to the major peak area. Gas chromatography/mass spectrometry identified six impurities: chlorobutene, chlorobutadiene, toluene, and three chloroprene dimers. Five additional impurity peaks with areas less than 0.1% were also observed. Titration for peroxide indicated 1.96 ± 0.06 mEq peroxide per kilogram of sample. The cumulative analytical data from the analysis of lot 12103-4-1 indicated a purity of approximately 96%.

During the studies, the bulk chemical was stored under a nitrogen headspace in the original containers at approximately –20° C. Stability was monitored by the study laboratory throughout the studies with gas chromatography with flame ionization detection and titration for peroxides. The concentrations of the stabilizers phenothiazine and *t*-butylcatechol were also determined with gas chromatography. No degradation of the bulk chemical was detected; all lots used during the studies had less than 1 mEq peroxide per kilogram. The stabilizer concentrations were acceptable.

VAPOR GENERATION AND EXPOSURE SYSTEM

Diagrams of the chloroprene vapor generation and delivery systems used in the 16-day, 13-week, and 2-year studies are shown in Figures K3 through K5. The vapor generation system consisted of an evaporation flask in a hot-water bath (72° C, 16-day studies; 66° C, 13-week and 2-year studies) and a temperature-controlled, cooled condenser column. For the 16-day studies and the first 6 weeks of the 13-week studies, a rotating evaporation flask (Buchi Rotavapor Model EL-1315) was used; thereafter, a nonrotating flask was used to prevent deterioration of the flask seals. The chloroprene vapor was pumped at a steady rate from a dry-ice-chilled reservoir into the rotating flask (16-day studies) or was held in the flask, under pressure, with a nitrogen headspace (13-week and 2-year studies). A calibrated flow of nitrogen was metered into the base of the condenser column, which was attached to the flask, and carried vapor rising from the flask through the condenser. Test article containing any materials boiling at a higher temperature than chloropene, which was controlled at 1° C by a thermostat, was condensed and returned to the flask. The temperature of the remaining chloroprene-saturated nitrogen vapor was monitored by a sensor at the top of the column; the vapor pressure was calculated and used to determine the vapor output.

Vapor entering the distribution manifold was diluted with HEPA- and charcoal-filtered air (16-day and 13-week studies) or with additional nitrogen (2-year studies). Flow to each chamber was controlled by compressed-air-driven vacuum pumps; vapor flowed through separate metering valves for each exposure chamber and was diluted with air before entering the chamber. The vapor concentrations were regulated by adjusting the amount of air entering the distribution lines from the compressor and by adjusting the amount of vapor entering the chambers through the metering valves.

Diagrams of the inhalation chamber suites for all studies are shown in Figure K6 through K8. The study laboratory designed the stainless-steel inhalation exposure chambers (Hazleton H-2000®; Harford Systems Division of Lab Products, Inc., Aberdeen, MD) so that uniform vapor concentrations could be maintained throughout the chamber when catch pans were in place. The total volume of each chamber was 2.3 m^3; the active mixing volume of each chamber was 1.7 m^3. A small particle detector (Type CN, Gardner Associates, Schenectady, NY) was used with and without animals in the exposure chambers to ensure that chloroprene vapor, and not aerosol, was produced. No particle counts above the minimum resolvable level (approximately 200 particles/cm^3) were detected.

VAPOR CONCENTRATION MONITORING

Chamber concentrations of chloroprene were monitored by a Hewlett Packard Model 5840 (16-day and 13-week studies) or Model 5890 (2-year) on-line gas chromatograph (Hewlett Packard, Palo Alto, CA). Samples were drawn from the exposure chambers at least once every hour by a 12-port stream selection valve. During the 16-day and 2-year studies, samples from the distribution line were monitored for purity with a second gas chromatograph; during the 13-week studies, distribution line samples were monitored by the same gas chromatograph that was used to monitor the exposure chambers.

The on-line exposure chamber monitoring system was calibrated based on quantitative analysis of grab samples collected in dimethylformaldehyde-filled bubblers. Chamber monitor results were compared to those of an off-line gas chromatograph (Model HP 5830 or HP 5840), calibrated with a gravimetrically prepared chloroprene standard in dimethylformaldehyde. An on-line standard of chloroprene in nitrogen (MG Industries Scientific Gases, Los Angeles, CA) was used to monitor instrument drift throughout the day. Summaries of the chamber concentrations for the 16-day, 13-week, and 2-year studies are in Tables K1 through K5.

CHAMBER ATMOSPHERE CHARACTERIZATION

The times for the exposure concentration to build up to 90% of the final exposure concentration (T_{90}) and to decay to 10% of the exposure concentration (T_{10}) were measured. In all studies, the T_{90} and T_{10} were measured in all exposure chambers with and without animals present. At a chamber airflow rate of 15 air changes per hour, the theoretical value for the T_{90} was calculated to be 11 minutes (16-day and 13-week studies) or 12.5 minutes (2-year studies). The T_{90} used throughout all studies was 12 minutes.

Without animals present, T_{90} values range from 9 to 14 minutes and the T_{10} values ranged from 9 to 12 minutes during the 16-day studies; with animals present, T_{90} values ranged from 9 to 11 minutes and T_{10} values ranged from 9 to 13 minutes. In the 13-week study, without animals present, T_{90} values ranged from 7.5 to 12 minutes for rats and from 7 to 12 minutes for mice; T_{10} values ranged from 8.5 to 11 minutes for rats and 8 to 11 minutes for mice. With animals present T_{90} values ranged from 10 to 13 minutes for rats and for mice; T_{10} values ranged from 10 to 15 minutes for rats and 10 to 13 minutes for mice. In the 2-year studies, without animals present, T_{90} values ranged from 10 to 11 minutes for rats and mice; T_{10} values ranged from 10 to 11 minutes for rats, and the mouse study had a T_{10} value of 11 minutes. With animals present, T_{90} values ranged from 9 to 12 minutes for rats and 11 to 13 minutes for mice; T_{10} values ranged from 10 to 12 minutes for rats and 10 to 11 minutes for mice.

Vapor concentration uniformity in the exposure chambers without animals in the chambers was measured before each of the studies began. Concentration uniformity with animals present was measured once during the 16-day and 13-week studies and at 90-day intervals during the 2-year studies. Vapor concentration was measured using the on-line gas chromatograph with the automatic 12-port sample valve disabled to allow continuous monitoring from a single input line. Samples taken from several positions within each exposure chamber were analyzed. Chamber concentration uniformity was maintained throughout the studies.

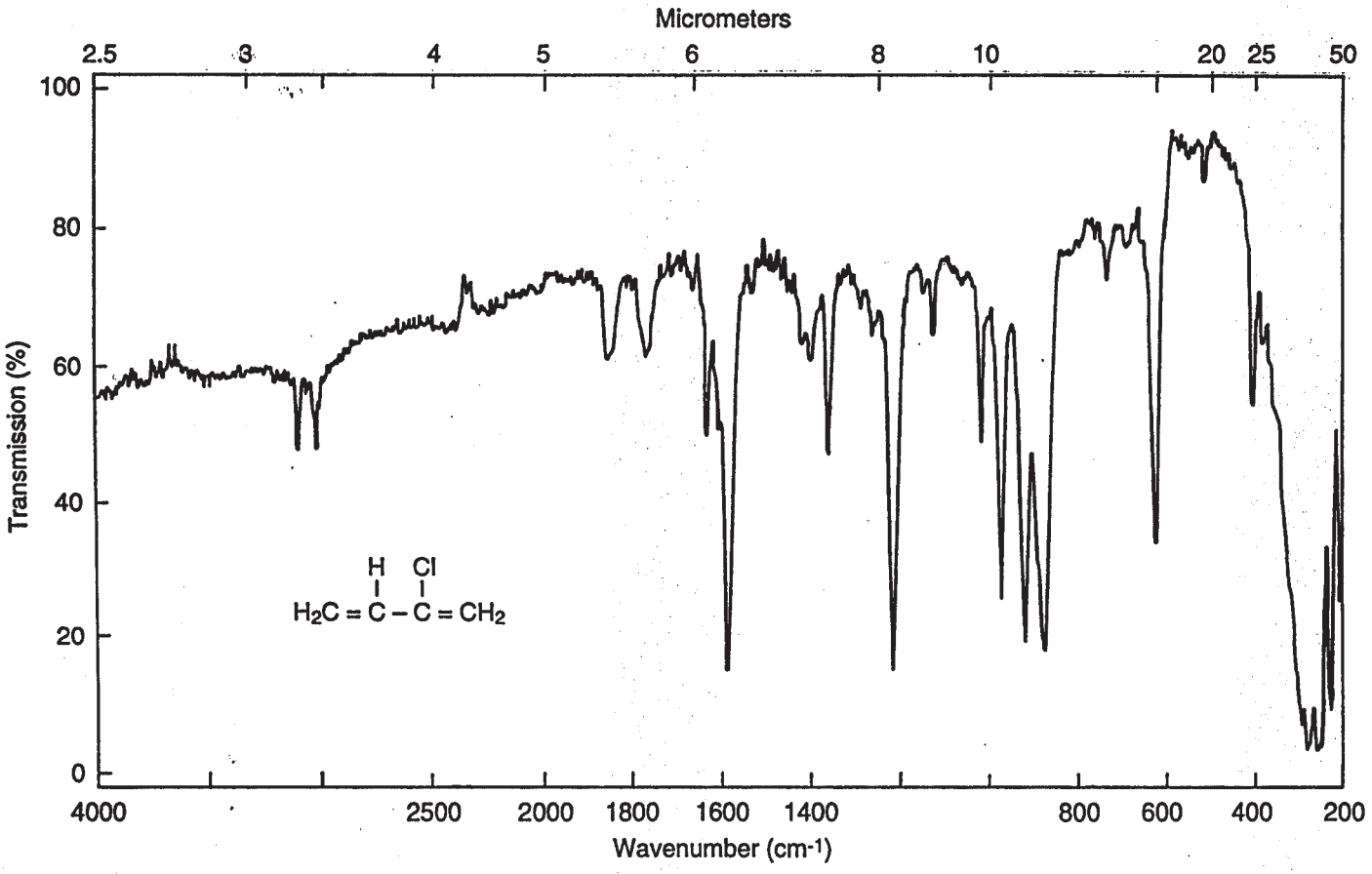
During the 2-year studies, the persistence of chloroprene after exposure ceased was monitored by gas chromatography in the 80 ppm chambers, with and without animals present, at the beginning of the exposures and at 90 day intervals afterward. The concentration decreased to less than 1% of the target concentration within 22 to 29 minutes. No chloroprene was detectable after 2 hours.

Chloroprene from the generator flask was tested for stability during the 2-year studies with gas chromatography and with potentiometric titration with standardized sodium thiosulfate to determine peroxide content. Samples were collected at the beginning and the end of an exposure period. The sample taken at the beginning of exposure was determined to be 99% pure; at the end of the exposure period, the sample was

95% pure. The total dimer content was approximately 3%, with the most concentrated dimer isomer present at approximately 2%. The peroxide concentration increased from 0.15 mEq/kg at the beginning of the exposure period to 0.25 mEq/kg at the end of the exposure period. The stabilizers in the bulk chloroprene, most of the expected impurities, and most of the degradation products caused by thermal decomposition of chloroprene are less volatile or have lower boiling points than chloroprene; therefore, the evaporation flask method of exposure removed most of these materials. The more volatile impurities, which could not be removed from the chloroprene vapor by the generation system, included the chlorobutenes and 1-chlorobutadienes. Stability was monitored during the 2-year studies by analyzing chloroprene vapor samples collected in dimethylformamide-filled bubblers from the distribution line for *t*-butylcatechol and phenothiazine inhibitors with gas chromatography; additional distribution line samples and exposure chamber samples were collected in standard charcoal gas sampling tubes at the beginning and end of an exposure period, desorbed with methylene chloride, and analyzed for monomer impurities by gas chromatography. Distribution line samples contained approximately 0.5% chlorobutene and 0.1% 1-chlorobutadiene at the beginning of the exposure period and 0.6% chlorobutene and 0.2% 1-chlorobutadiene by area at the end of the exposure period. Samples from the 12.8 ppm chamber contained 0.4% chlorobutene; samples from the 80 ppm chamber contained 0.5% chlorobutene at the beginning of the exposure period. All other impurities present in the distribution line and exposure chambers had concentrations at or below 0.1%.

Peroxide formation in the distribution line and exposure chambers was analyzed with a Hewlett-Packard 1046A fluorescence detector. Samples were collected with bubblers filled with peroxide reagents obtained from Sigma Chemical Company (St. Louis, MO). Fluorescence from excitation at 320 nm was measured at a 400 nm emission wavelength. The detector was calibrated with standard chloroprene peroxide solutions. No peroxides were detected in the distribution line or exposure chamber samples.

Chloroprene vapor concentrations were monitored before and during each exposure in the 13-week and 2-year studies using a separate on-line gas chromatograph (Model HP-5890) which sampled from the distribution line. No decomposition or degradation products exceeding 1% of the chloroprene concentration were detected during the 13-week studies. At the point of sampling, the chloroprene concentration in the 2-year studies was approximately 25,000 ppm, which allowed the detection of even small amounts of impurities. The system permitted the detection of volatile and non-volatile (e.g., dimers) impurities. The gas chromatograph allowed the detection of at least seven impurities more volatile than chloroprene that had total peak areas 0.13% of the chloroprene peak at the start of exposure and 0.04% at the end of exposure. The major volatile impurity was believed to be chloromethylpropene. Less volatile impurities that were detected were isomers of chlorobutene and 1-chlorobutadiene. The chlorobutene impurity had a peak area approximately 0.46% that of chloroprene at the start of exposure and approximately 0.52% at the end of exposure. The 1-chlorobutadiene impurity peak area was approximately 0.11% that of chloroprene at the start of exposure and approximately 0.15% at the end of exposure. No chloroprene dimer peaks were observed. These results were in excellent agreement with the results of analyses of charcoal tube samples.



Abscissa Expansion: 1 Suppression: Off Chloroprene Lot No.: 12103-4-1 Batch No.: 01 Task: SB-1730	Ordinate Expansion: 1 %T: 0-100 ABS: – Remarks: 8401-32	Scan Time: 12 min Response: 1 Slit Program: N Solvent:: – Concentration: Neat	Rep. Scan: – Single Beam: – Time Drive: – Presample Chop: – Operator: M. Ross Date: 4-3-86 Cell Path: Thin film between silver chloride plates Reference: 351N

FIGURE K1
Infrared Absorption Spectrum of Chloroprene

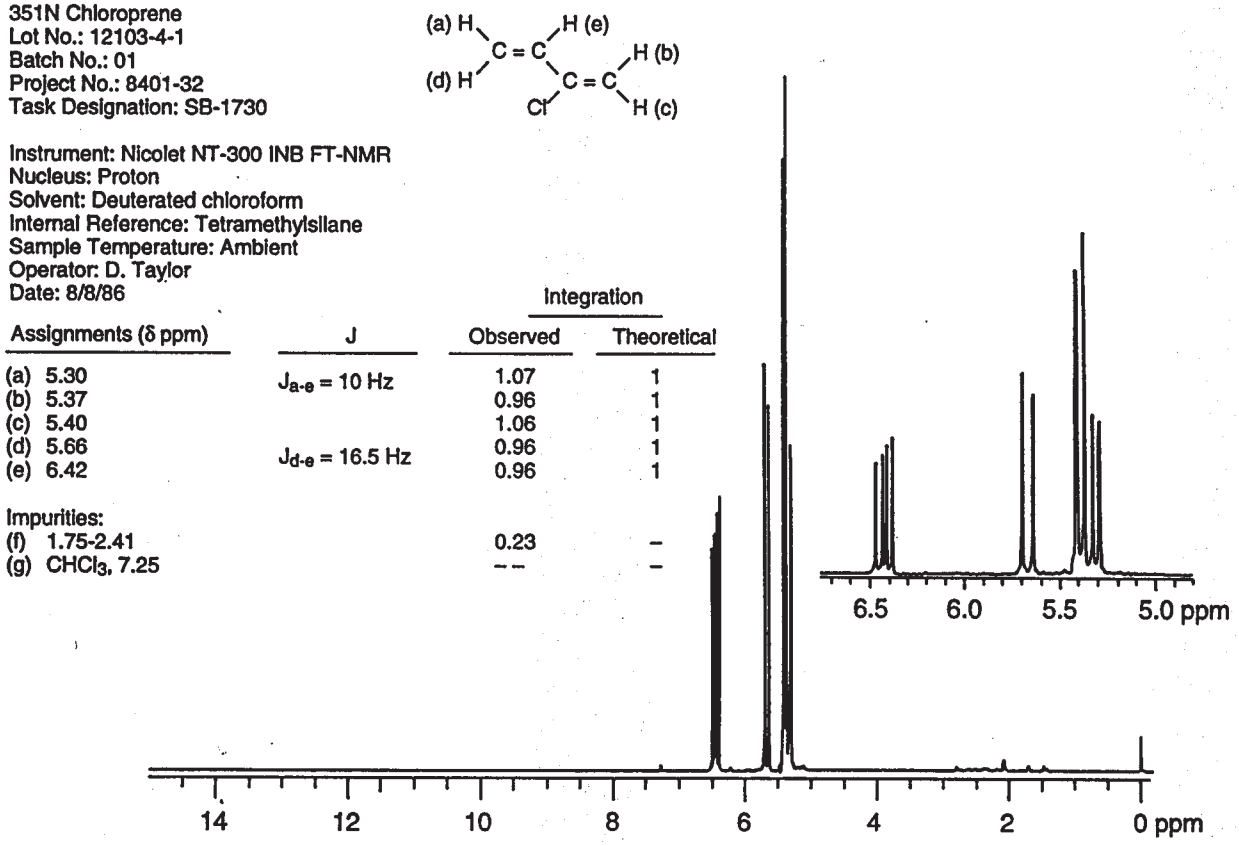


FIGURE K2
Nuclear Magnetic Resonance Spectrum of Chloroprene

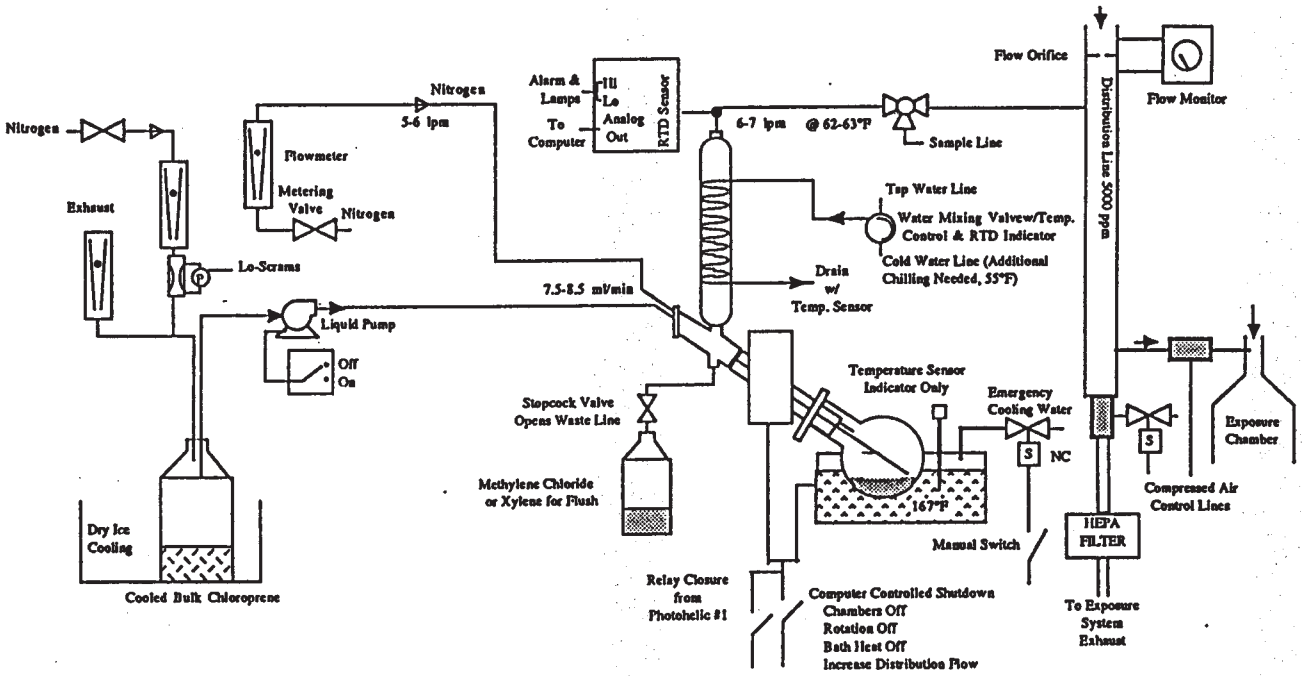


FIGURE K3
Schematic of Generation and Delivery System for the 16-Day Studies

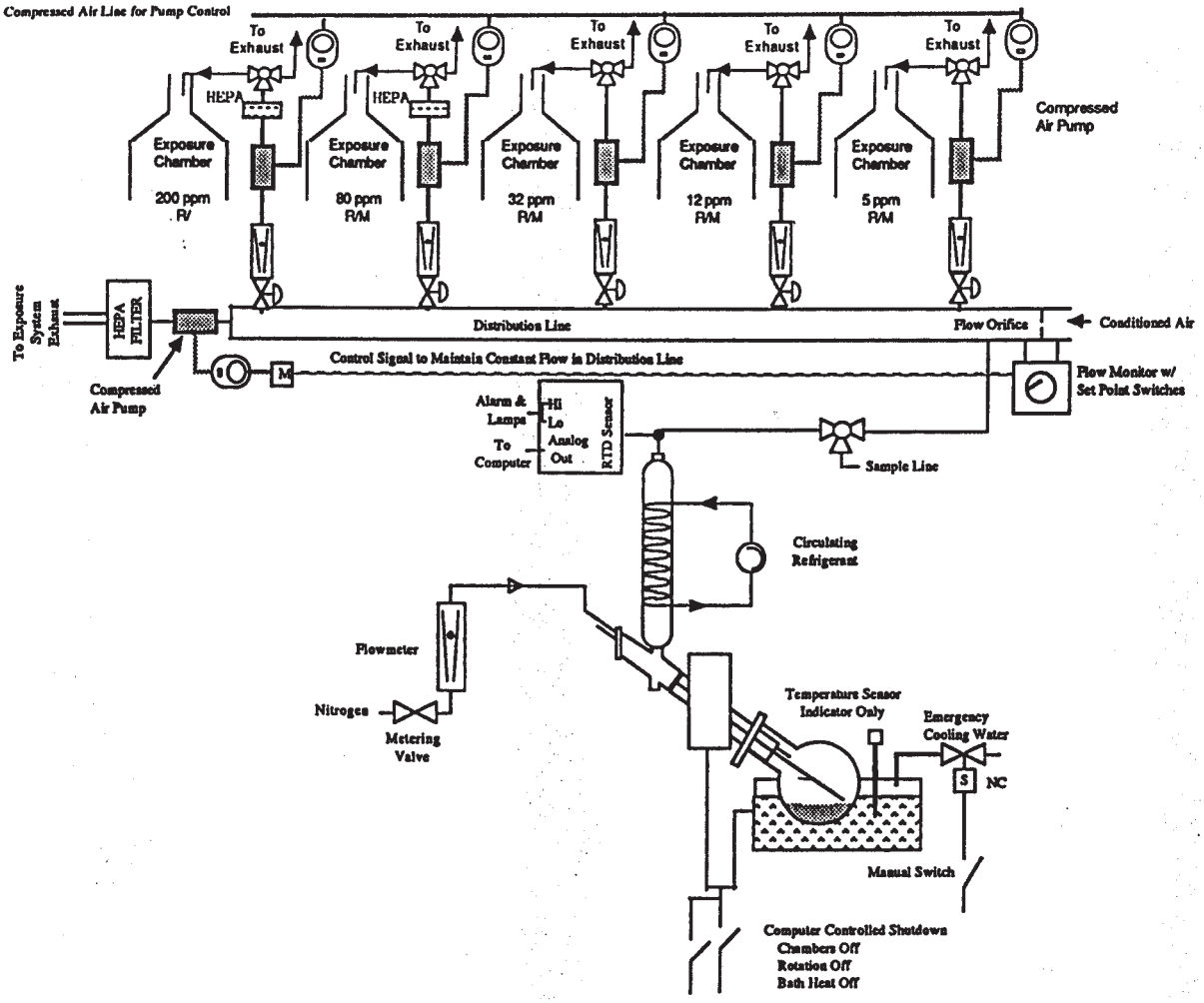


FIGURE K4
Schematic of Generation and Delivery System for the 13-Week Studies

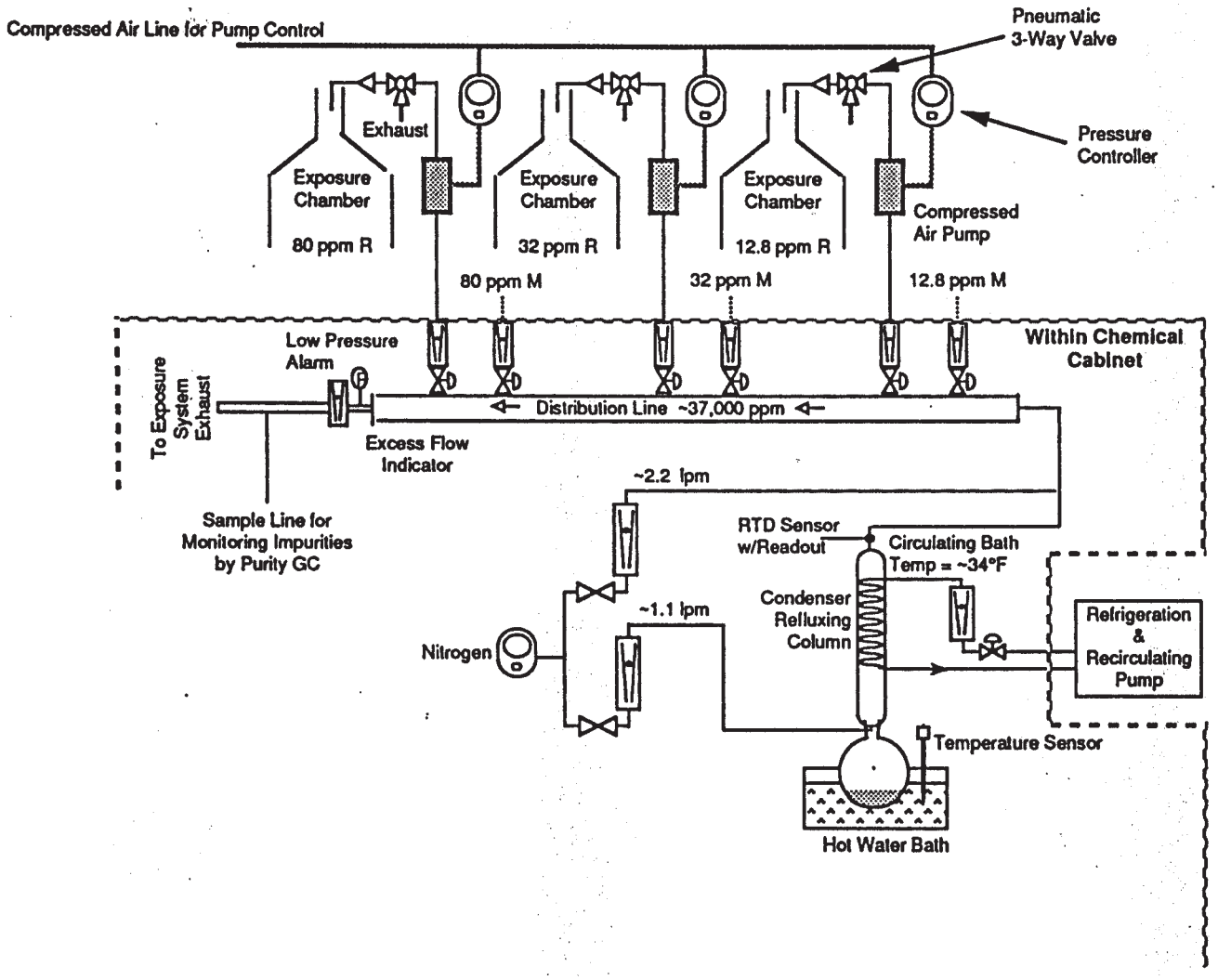


FIGURE K5
Schematic of Generation and Delivery System for the 2-Year Studies

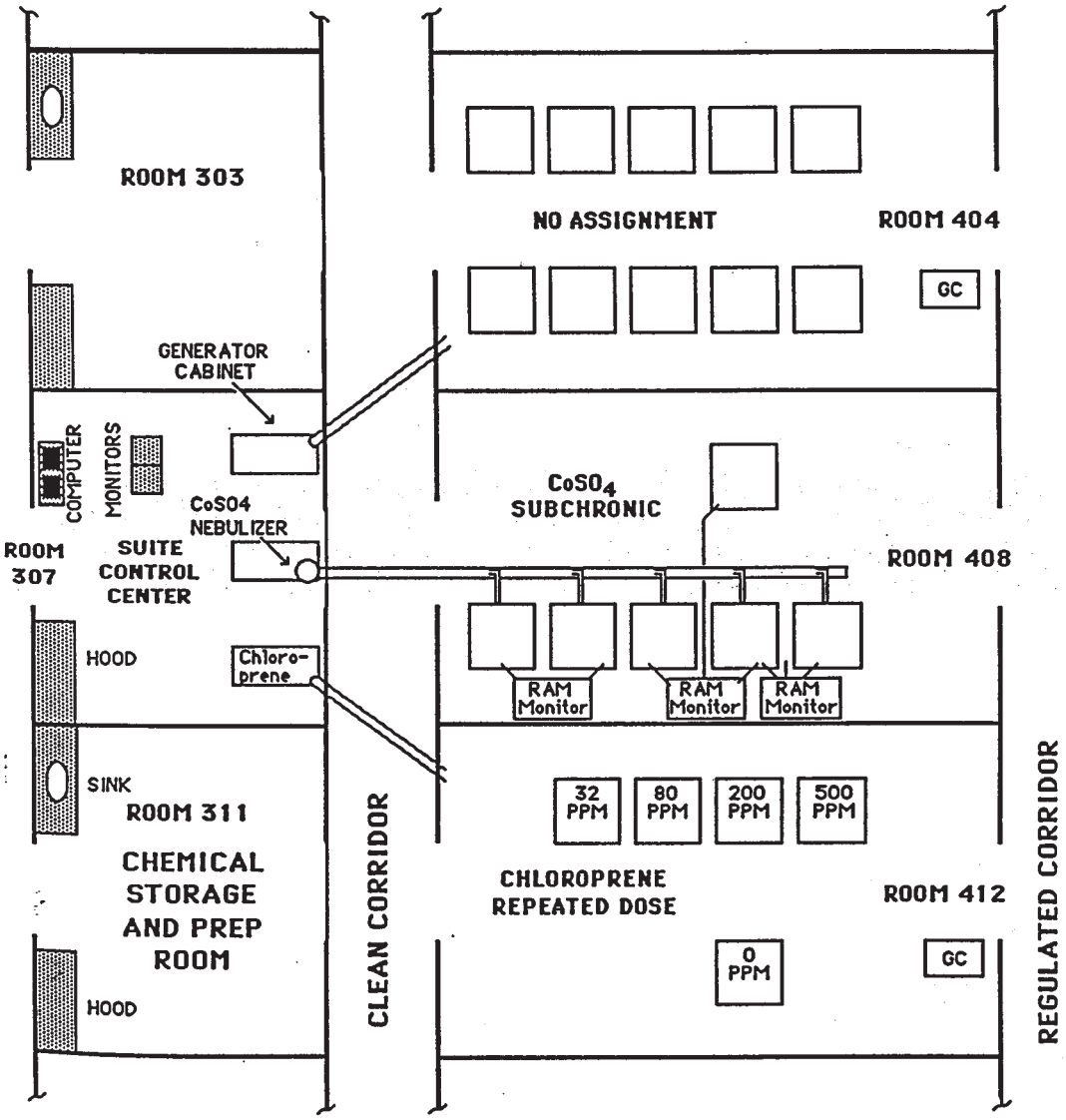


FIGURE K6
Inhalation Suite for the 16-Day Studies

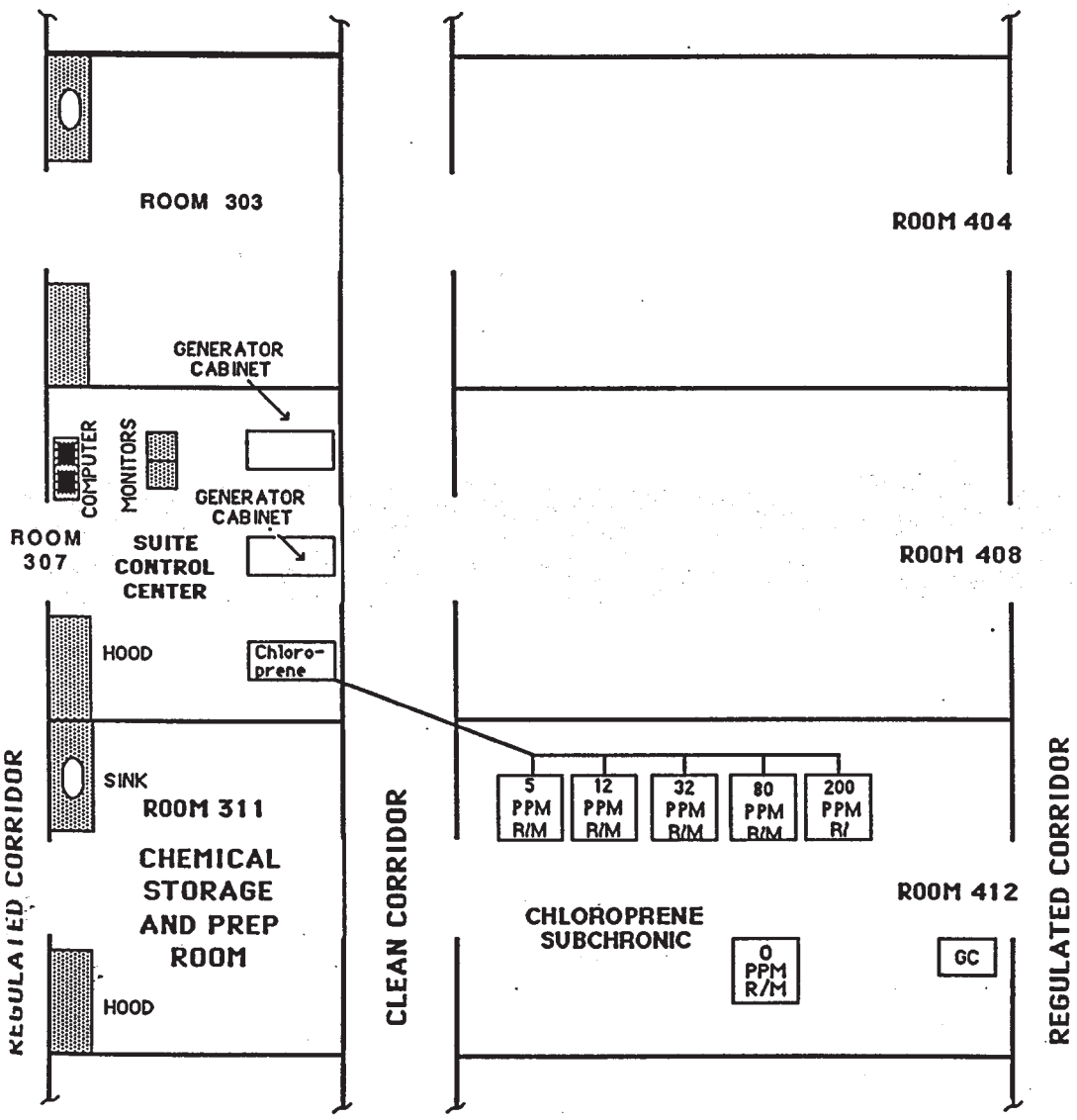


FIGURE K7
Inhalation Suite for the 13-Week Studies

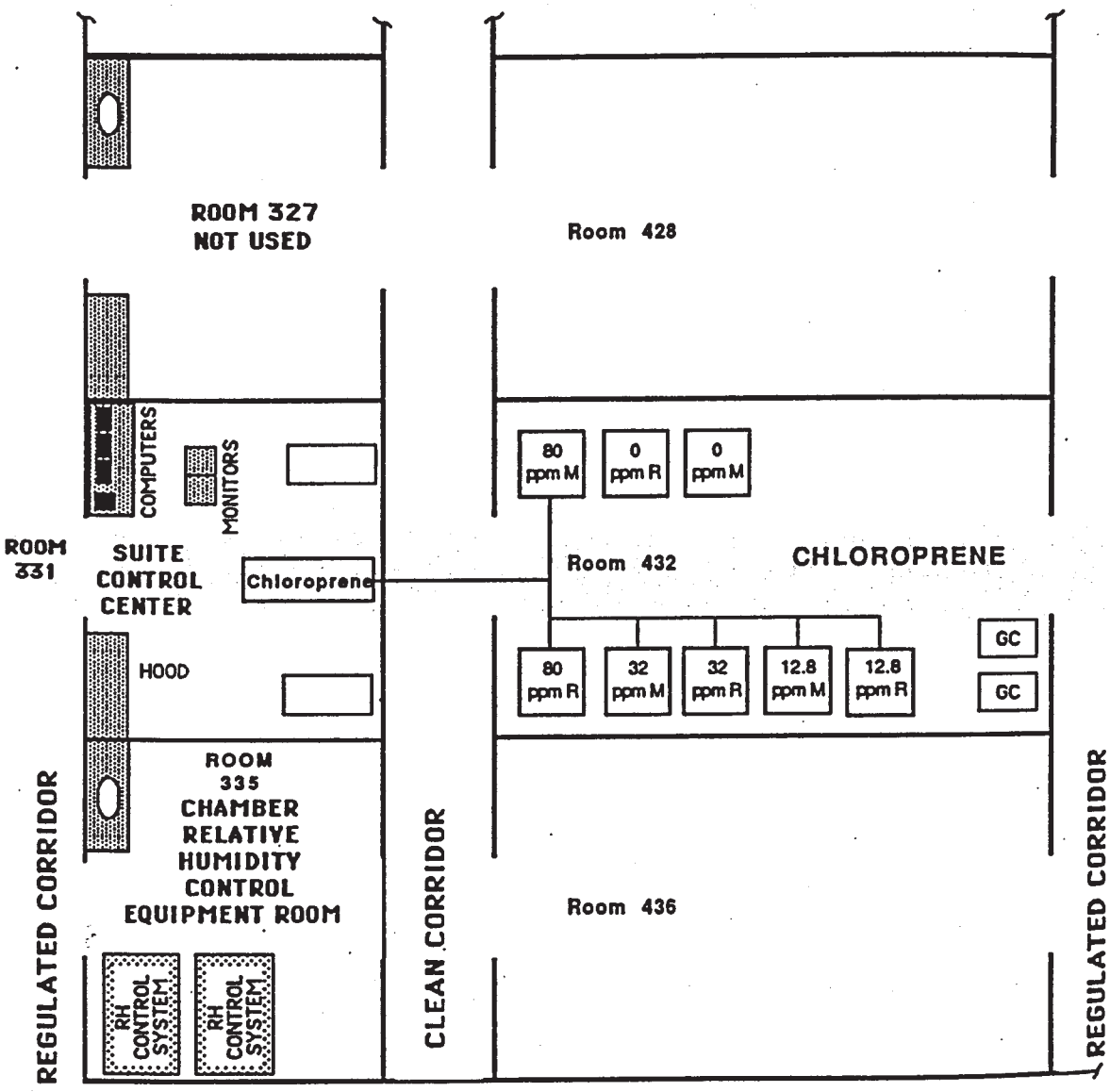


FIGURE K8
Inhalation Suite for the 2-Year Studies

TABLE K1
Summary of Chamber Concentrations in the 16-Day Inhalation Studies of Chloroprene

Target Concentration (ppm)	Total Number of Readings	Average Concentration[a] (ppm)
Rat Chambers		
32	145	31.1 ± 1.9
80	149	80.7 ± 5.0
200	140	198 ± 10
500	143	503 ± 24
Mouse Chambers		
12	142	11.9 ± 0.8
32	146	31.1 ± 2.0
80	153	80.8 ± 5.2
200	32[b]	201 ± 12

[a] Mean ± standard deviation
[b] All mice exposed to 200 ppm died by the third day of exposure; therefore, no readings from the 200 ppm chamber were made after this time.

TABLE K2
Summary of Chamber Concentrations in the 13-Week Inhalation Studies of Chloroprene

Target Concentration (ppm)	Total Number of Readings	Average Concentration[a] (ppm)
Rat Chambers		
5	761	5.03 ± 0.18
12	761	12.1 ± 0.4
32	787	31.9 ± 1.0
80	787	80.2 ± 1.7
200	785	200 ± 5.0
Mouse Chambers		
5	761	5.02 ± 0.2
12	761	12.1 ± 0.3
32	788	31.9 ± 0.9
80	788	80.2 ± 1.6

[a] Mean ± standard deviation

TABLE K3
Summary of Chamber Concentrations in the 2-Year Inhalation Studies of Chloroprene

Target Concentration (ppm)	Total Number of Readings	Average Concentration[a] (ppm)
Rat Chambers		
12.8	6,220	12.8 ± 0.4
32	6,084	31.7 ± 1.1
80	5,777	79.6 ± 1.6
Mouse Chambers		
12.8	6,049	12.7 ± 0.4
32	5,775	31.9 ± 0.9
80	5,755	79.7 ± 1.7

[a] Mean ± standard deviation

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

TABLE L1
Ingredients of NIH-07 Rat and Mouse Ration[a]

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

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

TABLE L2
Vitamins and Minerals in NIH-07 Rat and Mouse Ration[a]

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

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

TABLE L3
Nutrient Composition of NIH-07 Rat and Mouse Ration

Nutrient	Mean ± Standard Deviation	Range	Number of Samples
Protein (% by weight)	23.39 ± 0.57	22.2 — 24.3	24
Crude fat (% by weight)	5.32 ± 0.19	5.00 — 5.90	24
Crude fiber (% by weight)	3.36 ± 0.34	2.60 — 4.30	24
Ash (% by weight)	6.44 ± 0.19	6.12 — 6.81	24
Amino Acids (% total diet)			
Arginine	1.280 ± 0.083	1.110 — 1.390	11
Cystine	0.308 ± 0.071	0.181 — 0.400	11
Glycine	1.158 ± 0.048	1.060 — 1.220	11
Histidine	0.584 ± 0.027	0.531 — 0.630	11
Isoleucine	0.917 ± 0.033	0.867 — 0.965	11
Leucine	1.975 ± 0.051	1.850 — 2.040	11
Lysine	1.274 ± 0.049	1.200 — 1.370	11
Methionine	0.437 ± 0.109	0.306 — 0.699	11
Phenylalanine	0.999 ± 0.120	0.665 — 1.110	11
Threonine	0.904 ± 0.058	0.824 — 0.985	11
Tryptophan	0.218 ± 0.153	0.107 — 0.671	11
Tyrosine	0.685 ± 0.094	0.564 — 0.794	11
Valine	1.086 ± 0.055	0.962 — 1.170	11
Essential Fatty Acids (% of total diet)			
Linoleic	2.407 ± 0.227	1.830 — 2.570	10
Linolenic	0.259 ± 0.065	0.100 — 0.320	10
Vitamins			
Vitamin A (IU/kg)	6,768 ± 1,337	5,730 — 11,450	24
Vitamin D (IU/kg)	4,450 ± 1,382	3,000 — 6,300	4
α-Tocopherol (ppm)	35.43 ± 8.98	22.5 — 48.9	11
Thiamine (ppm)	17.50 ± 2.15	14.0 — 22.0	24
Riboflavin (ppm)	7.83 ± 0.923	6.10 — 9.00	11
Niacin (ppm)	99.22 ± 24.27	65.0 — 150.0	11
Pantothenic acid (ppm)	30.55 ± 3.52	23.0 — 34.6	11
Pyridoxine (ppm)	9.11 ± 2.53	5.60 — 14.0	11
Folic acid (ppm)	2.46 ± 0.63	1.80 — 3.70	11
Biotin (ppm)	0.268 ± 0.047	0.190 — 0.354	11
Vitamin B_{12} (ppb)	40.5 ± 19.1	10.6 — 65.0	11
Choline (ppm)	2,991 ± 382	2,300 — 3,430	10
Minerals			
Calcium (%)	1.17 ± 0.10	1.00 — 1.49	24
Phosphorus (%)	0.92 ± 0.05	0.760 — 1.00	24
Potassium (%)	0.886 ± 0.063	0.772 — 0.971	9
Chloride (%)	0.529 ± 0.087	0.380 — 0.635	9
Sodium (%)	0.316 ± 0.033	0.258 — 0.371	11
Magnesium (%)	0.166 ± 0.010	0.148 — 0.181	11
Sulfur (%)	0.272 ± 0.059	0.208 — 0.420	10
Iron (ppm)	350.5 ± 87.3	255.0 — 523.0	11
Manganese (ppm)	92.48 ± 5.14	81.7 — 99.4	11
Zinc (ppm)	59.33 ± 10.2	46.1 — 81.6	11
Copper (ppm)	11.81 ± 2.50	8.09 — 15.4	11
Iodine (ppm)	3.54 ± 1.19	1.52 — 5.83	10
Chromium (ppm)	1.66 ± 0.46	0.85 — 2.09	11
Cobalt (ppm)	0.76 ± 0.23	0.49 — 1.15	7

TABLE L4
Contaminant Levels in NIH-07 Rat and Mouse Ration[a]

	Mean ± Standard Deviation[b]	Range	Number of Samples
Contaminants			
Arsenic (ppm)	0.43 ± 0.19	0.10 — 0.70	24
Cadmium (ppm)	0.13 ± 0.07	0.04 — 0.20	24
Lead (ppm)	0.35 ± 0.25	0.10 — 1.00	24
Mercury (ppm)[c]	0.02	0.02 — 0.03	24
Selenium (ppm)	0.32 ± 0.11	0.05 — 0.40	24
Aflatoxins (ppm)	< 5.0		24
Nitrate nitrogen (ppm)[d]	8.65 ± 4.26	2.90 — 17.0	24
Nitrite nitrogen (ppm)[d]	0.14 ± 0.06	0.10 — 0.30	24
BHA (ppm)[e]	1.83 ± 1.97	1.00 — 10.0	24
BHT (ppm)[e]	1.58 ± 1.61	1.0 — 8.00	24
Aerobic plate count (CFU/g)	99,500 ± 165,049	4,100 — 710,000	24
Coliform (MPN/g)	3 ± 0.3	3 — 4	24
Escherichia coli (MPN/g)	< 3		24
Salmonella (MPN/g)	Negative		24
Total nitrosoamines (ppb)[f]	7.38 ± 1.78	4.70 — 11.40	24
N-Nitrosodimethylamine (ppb)[f]	5.40 ± 1.20	2.09 — 8.20	24
N-Nitrosopyrrolidine (ppb)[f]	1.98 ± 1.07	1.00 — 4.30	24
Pesticides (ppb)			
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 parathion	< 0.02		24
Ethyl parathion	< 0.02		24
Malathion	0.24 ± 0.23	0.05 — 0.97	24
Endosulfan I	< 0.01		24
Endosulfan II	< 0.01		24
Endosulfane sulfate	< 0.03		24

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

APPENDIX M
SENTINEL ANIMAL PROGRAM

SENTINEL ANIMAL PROGRAM

METHODS

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

Serum samples were collected from randomly selected rats and mice during the 13-week and 2-year studies of chloroprene. 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. (Bethesda, MD), for determination of antibody titers. The laboratory serology methods and viral agents for which testing was performed are tabulated below; the times at which blood was collected during the studies are also listed.

Method and Test	Time of Analysis
RATS	
13-Week Study	
ELISA	
PVM (Pneumonia virus of mice)	Study termination
RCV/SDA	
(Rat coronavirus/sialodacryoadenitis virus)	Study termination
Sendai	Study termination
Hemagglutination Inhibition	
H-1 (Toolan's H-1 virus)	Study termination
KRV (Kilham rat virus)	Study termination
2-Year Study	
ELISA	
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	
RCV/SDA	12 months
Sendai	18 months
Hemagglutination Inhibition	
H-1	6, 12, and 18 months, study termination
KRV	6, 12, and 18 months, study termination

MICE

13-Week Study

ELISA	
Ectromelia virus	Study termination
GDVII (Mouse encephalomyelitis virus)	Study termination
LCM (Lymphocytic choriomeningitis virus)	Study termination
MVM (Minute virus of mice)	Study termination
Mouse adenomavirus	Study termination
MHV (Mouse hepatitis virus)	Study termination
PVM	Study termination
Reovirus 3	Study termination
Sendai	Study termination
Immunofluorescence Assay	
EDIM (epizootic diarrhea of infant mice)	Study termination
Hemagglutination Inhibition	
Papovavirus (K)	Study termination
Polyoma virus	Study termination

2-Year Study

ELISA	
Ectromelia virus	6, 12, and 18 months, study termination
EDIM	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	6 and 18 months, study termination
LCM	6 months
Mouse adenoma virus-FL	6 and 18 months
PVM	12 months
Hemagglutination Inhibition	
K	6, 12, and 18 months, study termination
MVM	6, 12, and 18 months, study termination
Polyoma virus	6, 12, and 18 months, study termination

RESULTS

All test results were negative.

APPENDIX N
K-*RAS* MUTATION FREQUENCY AND SPECTRA IN LUNG AND HARDERIAN GLAND NEOPLASMS FROM B6C3F$_1$ MICE EXPOSED TO CHLOROPRENE FOR 2 YEARS

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K-*RAS* MUTATION FREQUENCY AND SPECTRA IN LUNG AND HARDERIAN GLAND NEOPLASMS FROM B6C3F$_1$ MICE EXPOSED TO CHLOROPRENE FOR 2 YEARS

INTRODUCTION

Lung neoplasms occur in B6C3F$_1$ mice with a typical incidence of 20% in control males and 10% in control females by 2 years of age, whereas harderian gland neoplasms occur with a typical incidence of 6% in control males and 4% in control females by 2 years of age. Molecular analysis of lung or harderian gland neoplasms for genetic alterations in cancer genes such as the *ras* proto-oncogene provides mechanistic information to help distinguish spontaneous neoplasms from chemical-induced neoplasms. For example, chemical-induced lung (Sills *et al.*, 1995) or harderian gland (Goodrow *et al.*, 1994) neoplasms in mice may have a higher frequency of proto-oncogene activation, particularly by point mutations in codon 12, 13, or 61 of K- or H-*ras* genes. The frequency of *ras* activation in these neoplasms is often greater than that detected in neoplasms occurring in control animals (Devereux *et al.*, 1991), and there is evidence for chemical specificity in the pattern of mutations. The specific types of oncogene-activating mutations induced by a chemical carcinogen often agree with what is expected based on the DNA adducts formed by the agent (Devereux *et al.*, 1993a). Even for "nongenotoxic carcinogens," patterns of *ras* gene mutations in neoplasms can give clues about the mechanism of tumorigenesis (Devereux *et al.*, 1993b).

MATERIALS AND METHODS

Lung and Harderian Gland Neoplasms: Male and female B6C3F$_1$ mice were exposed to 0, 12.8, 32, or 80 ppm chloroprene by inhalation for 6 hours per day, 5 days per week for 2 years. At necropsy, neoplasms were fixed in 10% neutral buffered formalin, routinely processed, embedded in paraffin, sectioned to a thickness of 5 µm, and stained with hematoxylin and eosin. Subsequently, five unstained serial sections (10 µm thick) were prepared from paraffin blocks containing alveolar/bronchiolar adenomas or carcinomas or harderian gland adenomas or carcinomas for isolation of DNA for polymerase chain reaction (PCR)-based assays. In order to isolate adequate amounts of DNA, neoplasms greater than 1 mm in diameter were identified for analysis. This included 46 paraffin-embedded lung neoplasms or 27 harderian gland neoplasms from chloroprene-exposed mice and six lung neoplasms or two harderian gland neoplasms from control mice.

DNA Isolation: The DNA isolation procedure is described in Marmur (1961) and Sills *et al*. (1995). The paraffin-embedded tissue was deparaffinized and rehydrated before digesting with proteinase K (Wright and Manos, 1990). DNA was extracted with phenol and chloroform and precipitated with ethanol.

DNA Amplification: DNA was amplified by PCR (Saiki *et al.*, 1988; Sills *et al.*, 1995); details of the use of nested primers are described in Devereux *et al*. (1991, 1993b).

Restriction Fragment Length Polymorphism Identification: For identification of H-*ras* mutations at codon 61, restriction fragment length polymorphism (RFLP) was used, and most of exon 2 surrounding codon 61 was amplified (Sukumuar and Barbacid, 1990). The sense primer used for amplification of exon 2 was 5′-GACATCTTAGACACAGCAGTT-3′. A restriction site for MSEI, XbaI, or TaqI enzyme (New England Biolaboratory, Beverly, MA) is created by the presence of a C to A, A to T, or A to G mutation in the first or second base of codon 61. By using this technique, codon 61 AAA, CTA, and CGA mutations were detected by MSEI, XbaI, and TaqI digestion, respectively; the normal sequence (CAA) of codon 61 is not cut by these enzymes. The mixture containing the H-*ras* exon 2 PCR products and the restriction enzyme was

incubated at 37° C (MSEI and XbaI) or 60° C (TaqI) for 2 hours. Fifteen µL of the mixture with bromophenol blue dye was loaded onto a 6% acrylamide tris-borate-EDTA (TBE) gel (8 cm × 8 cm × 1 mm; 15 wells) (Novex, San Diego, CA). The gel was run at 100 volts for 1 hour on a Novex gel electrophoresis unit. Gels were stained with a 5 µg/mL solution of ethidium bromide for 20 minutes and then destained in distilled water. Ethidium bromide-stained bands were visualized using a 312 nm ultraviolet (UV) viewing box and photographed.

"Cold" Single-Strand Conformation Polymorphism Analysis (SSCP): A mixture consisting of 5 µL of PCR products (double-stranded DNA), 0.6 µL of 1M methylmercury hydroxide, 1 µL of 15% W/V Ficoll (molecular weight 400,000) loading buffer containing 0.25% bromophenol blue and 0.25% xylene cyanol, and 13.4 µL of 1X TBE buffer (Novex, San Diego, CA) was prepared to yield a total volume of 20 µL (Hongyo *et al.*, 1993). This nonradioactive mixture was heated to 85° C for 5 minutes and then plunged into ice prior to loading the entire 20 µL onto the gel. A 20% polyacrylamide TBE gel was used for K-*ras* mutation analysis in the gel electrophoresis unit (Novex, San Diego, CA). The buffer chamber was filled with 1.5X TBE buffer. The gel was run at 300 volts in a 5° C cold room until a light blue marker reached the bottom of the gel. A positive control for K-*ras* mutations and one undenatured DNA control (without methylmercury hydroxide and no heat) were run with the unknown samples. Gels were stained with a 0.5 µg/mL solution of ethidium bromide for 20 minutes and destained in distilled water for 5 minutes. The stained bands were visualized under UV viewing box and photographed. For identification of K-*ras* mutations at codon 61, RFLP was used with XbaI enzyme digestion and "cold" SSCP analysis was performed on the same 20% polyacrylamide TBE gel.

Direct Sequencing: Direct sequencing of the amplified first and second exon of the K-*ras* gene was performed as described by Tindall and Stankowski (1989) using previously described sequencing primers (Devereux *et al.*, 1991).

RESULTS

Lung Neoplasms: A higher frequency (80%) of K-*ras* mutations was detected in chloroprene-induced lung neoplasms than in spontaneous lung neoplasms of control B6C3F$_1$ mice (30%) (Table N1). The predominant mutation in chloroprene-induced neoplasms consisted of an A to T transversion (CAA to CTA) in K-*ras* codon 61 (22/46). This pattern was similar to that in isoprene-induced lung neoplasms in which lung neoplasms (10/11) had this same K-*ras* mutation. In contrast, A to T transversions (CAA to CTA) in K-*ras* codon 61 were not apparent in butadiene-induced lung neoplasms nor in spontaneous lung neoplasms (Table N1). The majority (8/10, 12.8 ppm; 10/13, 32 ppm) of the K-*ras* CTA codon 61 mutations were from the 12.8 and 32 ppm groups, whereas 4/14 were from the 80 ppm exposure group (Table N2). We also investigated whether specific mutations were associated with a specific morphologic pattern of lung neoplasms or type of neoplasm, but no correlation was observed (Table N3).

Harderian Gland Neoplasms: A higher frequency (100%) of *ras* mutations was detected in chloroprene-induced harderian gland neoplasms than in harderian gland neoplasms from control B6C3F$_1$ mice (56%) or in butadiene-induced harderian gland neoplasms (69%) (Table N4; Goodrow *et al.*, 1994). The pattern of K-*ras* and H-*ras* mutations was generally similar to that of isoprene in which 100% of *ras* mutations were detected in the harderian gland (Table N4). The predominant mutation in chloroprene-induced neoplasms consisted of A to T transversions (CAA to CTA) at K-*ras* codon 61 (25/27). A similar response was detected in isoprene-induced harderian gland neoplasms in which the predominant mutation consisted of A to T transversions (CAA to CTA) at K-*ras* codon 61 (15/30). One difference between the mutation spectra of chloroprene and isoprene was the higher number of C to A (CAA to AAA) transversions at H-*ras* codon 61 (8/30) in isoprene-induced harderian gland neoplasms. This specific pattern of K-*ras* mutation was not apparent in butadiene-induced harderian gland neoplasms nor in spontaneous harderian gland neoplasms (Table N4). Only 3 (10%) of harderian gland neoplasms induced by butadiene had an A to T transversion in

the second base of K-*ras* codon 61, which is similar to the 7% frequency of K-*ras* mutations in spontaneous harderian gland neoplasms at this locus (Table N4). In harderian gland neoplasms, similar incidences for K-*ras* codon 61 CTA mutations of 100%, 80%, and 100% were detected in the 12.8, 32, or 80 ppm exposure groups, respectively (Table N5). The frequency and pattern of mutations in the K-*ras* genes were also examined to determine if a specific mutation was associated with the morphologic pattern of harderian gland neoplasms or type of neoplasms. No consistent morphologic pattern or type of harderian gland neoplasm was associated with specific K-*ras* mutations (Table N6).

DISCUSSION

The high frequency and unique pattern of *ras* mutations detected in lung and harderian gland neoplasms from chloroprene-, isoprene-, and butadiene-exposed B6C3F_1 mice compared to *ras* mutations in spontaneous lung and harderian gland neoplasms reflect the importance of *ras* activation in the carcinogenesis process of these structurally similar chemicals. Sixty percent of the chloroprene-induced lung neoplasms and 93% of chloroprene-induced harderian gland neoplasms exhibited K-*ras* codon 61 CTA mutations, an uncommon mutation in spontaneous lung or harderian gland neoplasms. The high frequency of specific *ras* mutations is consistent with the genotoxicity of the chemically related chemicals chloroprene, isoprene, and butadiene.

Similar to the high frequency of A to T transversions in chloroprene- and isoprene-induced lung and harderian gland neoplasms, an increased frequency of A to T transversions was detected in *lacI* mutant bone marrow cells of male B6C3F_1 *lacI* transgenic mice following 1,3-butadiene exposure (Sisk *et al.*, 1994). Increased A to T transversions were also detected in *hprt* mutant T-lymphocytes isolated from B6C3F_1 mice exposed to 1,3-butadiene (Cochrane and Skopek, 1994). Interestingly, in harderian gland neoplasms where chloroprene, isoprene, and butadiene targeted adenine bases, chloroprene and isoprene had selectivity for K-*ras* codon 61, whereas butadiene targeted H-*ras* codon 61, as indicated by the higher frequency of A to G transitions. Both guanine (Citti *et al.*, 1984) and adenine (Leuratti *et al.*, 1994) DNA adducts have been associated with epoxide intermediates of butadiene. In the lung, butadiene, unlike chloroprene and isoprene, targeted the first guanine base at codon 13, as indicated by the higher frequency of G to C base changes.

Leuratti *et al*. (1994) identified an adenine adduct(s) at the N^6 position and proposed that the adduct is involved in the mutagenesis of the diepoxide metabolite of butadiene. The mutagenic and alkylating activity of butadiene and isoprene are similar (Gervasi *et al*., 1985; Gervasi and Longo, 1990). We hypothesize that interactions of chloroprene, isoprene, and butadiene epoxides with DNA to form guanine or adenine adducts leads to point mutations in K-*ras* or H-*ras* proto-oncogenes that may represent a critical step in the carcinogenesis process of these structurally related chemicals.

REFERENCES

Citti, L., Gervasi, P.G., Turchi, G., Bellucci, F., and Bianchini, R. (1984). The reaction of 3,4-expoxy-1-butene with deoxyguanosine and DNA in vitro: Synthesis and characterization of the main adducts. *Carcinogenesis* **5**, 47-52.

Cochrane, J.E., and Skopek, T.R. (1994). Mutagenicity of butadiene and its epoxide metabolites: II. Mutational spectra of butadiene, 1,2-epoxybutene and diepoxybutane at the hprt locus in splenic T cells from exposed B6C3F1 mice. *Carcinogenesis* **15**, 719-723.

Devereux, T.R., Anderson, M.W., and Belinsky, S.A. (1991). Role of *ras* protooncogene activation in the formation of spontaneous and nitrosamine-induced lung tumors in the resistant C3H mouse. *Carcinogenesis* **12**, 299-303.

Devereux, T.R., Belinsky, S.A., Maronpot, R.R., White, C., Hegi, M., Patel, A.C., Foley, J.F., Greenwell, A., and Anderson, M.W. (1993a). Comparison of pulmonary O6-methylguanine DNA adduct levels and K-*ras* activation in lung tumors from resistant and susceptible mouse strains. *Mol. Carcinog.* **8**, 177-185.

Devereux, T.R., Foley, J.F., Maronpot, R.R., Kari, F., and Anderson, M.W. (1993b). *Ras* proto-oncogene activation in liver and lung tumors from $B6C3F_1$ mice exposed chronically to methylene chloride. *Carcinogenesis* **14**, 795-801.

Gervasi, P.G., and Longo, V. (1990). Metabolism and mutagenicity of isoprene. *Environ. Health Perspect.* **86**, 85-87.

Gervasi, P.G., Citti, L., Del Monte, M., Longo, V., and Benetti, D. (1985). Mutagenicity and chemical reactivity of epoxidic intermediates of the isoprene metabolism and other structurally related compounds. *Mutat. Res.* **156**, 77-82.

Goodrow, T.L., Nichols, W.W., Storer, R.D., Anderson, M.W., and Maronpot, R.R. (1994). Activation of H-*ras* is prevalent in 1,3-butadiene-induced and spontaneously occurring murine harderian gland tumors. *Carcinogenesis* **15**, 2665-2667.

Hongyo, T., Buzard, G.S., Calvert, R.J., and Weghorst, C.M. (1993). "Cold SSCP": A simple, rapid and non-radioactive method for optimized single-strand conformation polymorphism analyses. *Nucleic Acids Res.* **21**, 3637-3642.

Leuratti, C., Jones, N.J., Marafante, E., Kostiainen, R., Peltonen, K., and Waters, R. (1994). DNA damage induced by environmental carcinogen butadiene: Identification of a diepoxybutane-adenine adduct and its detection by 32P-postlabelling. *Carcinogenesis* **15**, 1903-1910.

Marmur, J. (1961). A procedure for the isolation of deoxyribonucleic acid from micro-organisms. *J. Mol. Biol.* **3**, 208-218.

Saiki, R.K., Gelfand, D.H., Stoffel, S., Scharf, S.J., Higuchi, R., Horn, G.T., Mullis, K.B., and Erlich, H.A. (1988). Primer-directed enzymatic amplification of DNA with a thermostable DNA polymerase. *Science* **239**, 487-491.

Sills, R.C., Hong, H.L., Greenwell, A., Herbert, R.A., Boorman, G.A., and Devereux, T.R. (1995). Increased frequency of K-*ras* mutations in lung neoplasms from female B6C3F1 mice exposed to ozone for 24 or 30 months. *Carcinogenesis* **16**, 1623-1628.

Sisk, S.S., Pluta, L.J., Bond, J.A., and Recio, L. (1994). Molecular analysis of lacI mutants from bone marrow of B6C3F1 transgenic mice following inhalation exposure to 1,3-butadiene. *Carcinogenesis* **15**, 471-477.

Sukumuar, S., and Barbacid, M. (1990). Specific patterns of oncogene activation in transplacentally induced tumors. *Proc. Natl. Acad. Sci. USA* **87**, 718-722.

Tindall, K.R., and Stankowski, L.F., Jr. (1989). Molecular analysis of spontaneous mutations at the *gpt* locus in Chinese hamster ovary (AS52) cells. *Mutat. Res.* **220**, 241-253.

Wright, D.K., and Manos, M.M. (1990). Sample preparation from paraffin-embedded tissues. In *PCR Protocols: A Guide to Methods and Applications* (M.A. Innis, D.H. Gelfand, J.J. Sninsky, and T.J. White, Eds.), pp. 153-158. Academic Press, Inc., San Diego.

TABLE N1
Pattern of K-*ras* Mutations in Lung Neoplasms from B6C3F$_1$ Mice Exposed to Chloroprene

Treatment	Activated K-*ras* (%)	Codon 12 Normal = GGT GTT	GAT	TGT	CGT	CTT	ATT	Codon 13 Normal = GGC CGC	Codon 61 Normal = CAA CTA	CAT	CAC	CGA
Historical Control[a]	25/81 (31%)	1	9	5				3		4	1	2
Chloroprene[b]	37/46 (80%)	2	5		1	1	1	2	22			3
Isoprene[c]	11/11 (100%)							1	10			
1,3-Butadiene[d]	6/9 (67%)							6				

[a] Spontaneous lung neoplasms of control B6C3F$_1$ mice
[b] Female B6C3F$_1$ mice were exposed to 12.8, 32, or 80 ppm chloroprene by inhalation 6 hours/day, 5 days/week, for 2 years.
[c] Male B6C3F$_1$ mice were exposed to 2,200 or 7,000 ppm isoprene by inhalation 6 hours/day, 5 days/week for a 26-week period followed by a 26-week recovery period.
[d] Male and female B6C3F$_1$ mice were exposed to 6.25 to 625 ppm 1,3-butadiene by inhalation 6 hours/day, 5 days/week, for 1 to 2 years (Goodrow *et al.*, 1994).

TABLE N2
K-*ras* Mutation Profile in Lung Neoplasms from B6C3F$_1$ Mice Exposed to Chloroprene

Treatment Concentration (ppm)	Activated K-*ras* (%)	Codon 12 Normal = GGT GTT	GAT	TGT	CGT	CTT	ATT	Codon 13 Normal = GGC CGC	Codon 61 Normal = CAA CTA	CAT	CAC	CGA
Chamber Control[a]												
	25/81 (31%)	1 (1%)	9 (11%)	5 (6%)				3 (4%)		4 (5%)	1 (1%)	2 (2%)
Chloroprene[b]												
12.8	10/10 (100%)	1 (10%)	1 (10%)						8 (80%)			
32	13/14 (93%)		2 (14%)		1 (7%)				10 (71%)			
80	14/22 (64%)	1 (5%)	2 (9%)			1 (5%)	1 (5%)	2 (9%)	4 (18%)			3 (14%)

[a] Study controls combined with historical spontaneous lung neoplasms of control B6C3F$_1$ mice
[b] Female B6C3F$_1$ mice were exposed to 12.8, 32, or 80 ppm chloroprene by inhalation 6 hours/day, 5 days/week, for 2 years.

TABLE N3
K-*ras* Mutations Detected in Alveolar/bronchiolar Adenomas and Carcinomas from B6C3F$_1$ Mice

Treatment	Activated K-*ras* (%)	Codon 12 Normal = GGT: GTT	GAT	TGT	CGT	CTT	ATT	Codon 13 Normal = GGC: CGC	Codon 61 Normal = CAA: CTA	CAT	CAC	CGA
Chamber Control[a]												
Adenoma	3/18 (17%)		1	2								
Carcinoma	22/63 (35%)	1	8	3				3		4	1	2
Chloroprene[b]												
Adenoma	23/29 (79%)	1	3		1	1			14			3
Papillary	5/8 (63%)		1						3			1
Solid	8/11 (73%)	1	1						6			
Mixed	10/10 (100%)		1		1	1			5			2
Carcinoma	14/17 (82%)	1	2				1	2	8			
Papillary	9/10 (90%)	1	1				1	2	4			
Solid	4/4 (100%)		1						3			
Mixed	1/3 (33%)								1			

[a] Study controls combined with historical spontaneous lung neoplasms of control B6C3F$_1$ mice
[b] Female B6C3F$_1$ mice were exposed to 12.8, 32, or 80 ppm chloroprene by inhalation 6 hours/day, 5 days/week, for 2 years.

TABLE N4
Pattern of *ras* Mutations in Harderian Gland Neoplasms from B6C3F$_1$ Mice

Treatment	Activated *ras* (%)	K-*ras* Codon 12 GAT	K-*ras* Codon 12 TGT	K-*ras* Codon 13 CGC	K-*ras* Codon 61 CTA	H-*ras* Codons 12 and 13	H-*ras* Codon 61 AAA	H-*ras* Codon 61 CTA	H-*ras* Codon 61 TAA	H-*ras* Codon 61 CGA
Historical Control[a]	15/27 (56%)				2 (7%)		4 (15%)	4 (15%)		5 (19%)
Chloroprene[b]	27/27 (100%)				25[e] (93%)	ND	1 (4%)	2[e] (7%)		2[e] (7%)
Isoprene[c]	30/30 (100%)	2 (7%)	1 (3%)		15 (50%)		8 (27%)	3 (10%)	1 (3%)	
1,3-Butadiene[d]	20/29 (69%)			1 (3%)	3 (10%)[f]		2 (7%)	2 (7%)		12 (41%)

[a] Study controls combined with historical spontaneous lung neoplasms of control B6C3F$_1$ mice
[b] Male B6C3F$_1$ mice were exposed to 12.8, 32, or 80 ppm chloroprene by inhalation 6 hours/day, 5 days/week, for 2 years.
[c] Male B6C3F$_1$ mice were exposed to 2,200 or 7,000 ppm isoprene by inhalation 6 hours/day, 5 days/week for a 26-week period followed by a 26-week recovery period.
[d] Male and female B6C3F$_1$ mice were exposed to 6.25 to 625 ppm 1,3-butadiene by inhalation for 1 to 2 years (Goodrow *et al*., 1994).
[e] Same neoplasm had CTA mutation in both K- and H-*ras* at codon 61 from two mice; another one neoplasm had CTA mutation at codon 61 of K-*ras* and CGA mutation of H-*ras*.
[f] K-*ras* codon 61 mutations were evaluated in 12 harderian gland neoplasms without other mutations tested from butadiene study.

TABLE N5
K-*ras* Codon 61 Mutations in Harderian Gland Neoplasms from B6C3F$_1$ Mice Exposed to Chloroprene

Treatment Concentration (ppm)	Activated K-*ras* (%)	Codon 61 Normal = CAA CTA
Chamber Control[a]	2/27 (7%)	2
Chloroprene[b]		
12.8	5/5 (100%)	5
32	8/10 (80%)	8
80	12/12 (100%)	12

[a] Spontaneous lung neoplasms of control B6C3F$_1$ mice
[b] Male B6C3F$_1$ mice were exposed to 12.8, 32, or 80 ppm chloroprene by inhalation 6 hours/day, 5 days/week, for 2 years.

TABLE N6
K-*ras* Codon 61 Mutations Detected in Harderian Gland Adenomas and Carcinomas in B6C3F$_1$ Mice Exposed to Chloroprene[a]

Tumor Type/ Morphology Pattern	Activated K-*ras* (%)	Codon 61 Normal = CAA CTA
Adenoma	22/23 (96%)	
Papillary	15/16 (94%)	15
Acinar	5/5 (100%)	5
Solid	1/1 (100%)	1
Mixed	1/1 (100%)	1
Carcinoma	3/4 (75%)	
Papillary	1/1 (100%)	1
Solid	1/1 (100%)	1
Mixed	1/1 (100%)	1

[a] Male B6C3F$_1$ mice were exposed to 12.8, 32, or 80 ppm chloroprene by inhalation 6 hours/day, 5 days/week, for 2 years.

APPENDIX O
IMPACT OF *HELICOBACTER HEPATICUS* INFECTION IN B6C3F$_1$ MICE FROM 12 NTP 2-YEAR CARCINOGENESIS STUDIES

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IMPACT OF *HELICOBACTER HEPATICUS* INFECTION IN B6C3F$_1$ MICE FROM 12 NTP 2-YEAR CARCINOGENESIS STUDIES

ABSTRACT

Male and female B6C3F$_1$ mice from 12 NTP 2-year carcinogenesis studies were found to be infected with *Helicobacter hepaticus*. Many of the male mice from nine of these studies ("affected" studies) had an associated hepatitis. The current evaluations were performed in an attempt to determine if the data from the *H. hepaticus*-affected NTP B6C3F$_1$ mouse studies were compromised and unsuitable for cancer hazard identification. The incidences of neoplasms of the liver (both hepatocellular neoplasms and hemangiosarcoma), but not of other organs in control male B6C3F$_1$ mice, were found to be increased in affected studies compared to control males from unaffected studies. The increased incidence of hepatocellular neoplasms was observed in those males exhibiting *H. hepaticus*-associated hepatitis. Other observations further differentiated control male mice from affected and unaffected studies. H-*ras* codon 61 CAA-to-AAA mutations were less common in liver neoplasms in males from affected studies compared to historical and unaffected study controls. In addition, increases in cell proliferation rates and apoptosis were observed in the livers of male mice with *H. hepaticus*-associated hepatitis. These data support the hypothesis that the increased incidence of liver neoplasms is associated with *H. hepaticus* and that hepatitis may be important in the pathogenesis. Therefore, interpretation of carcinogenic effects in the liver of B6C3F$_1$ mice may be confounded if there is *H. hepaticus*-associated hepatitis.

INTRODUCTION

Helicobacter-Induced Diseases

Since the bacterium *H. pylori* was isolated from humans in 1983, numerous *Helicobacter* species have been identified in several laboratory and domestic animal species. Their pathogenicity varies, with some species inducing significant disease while others appear merely to colonize the gastrointestinal tract. *H. pylori* is known to cause chronic gastritis and peptic ulcers in humans (Marshall and Warren, 1984; Graham, 1989; Lee *et al.*, 1993) and, more recently, has been linked to adenocarcinoma and mucosa-associated lymphoma of the stomach (Fox *et al.*, 1989; Nomura *et al.*, 1991; Parsonnet *et al.*, 1991; Wotherspoon *et al.*, 1993). Based on epidemiological and pathology findings, the International Agency for Research on Cancer (1994) has classified *H. pylori* as a group 1 carcinogen in humans. *H. hepaticus* is associated with an increase in liver neoplasm incidences in A/JCr mice (Ward *et al.*, 1994a; Fox *et al.*, 1996).

H. hepaticus commonly colonizes the gastrointestinal tract of many strains of mice from many sources (Fox *et al.*, 1994; Ward *et al.*, 1994b; Shames *et al.*, 1995). It has been shown to be pathogenic, with hepatitis highly prevalent in some strains of mice (A/JCr, BALB/cAnNCr, C3H/HeNCr, SJL/NCr, and SCID/NCr) (Ward *et al.*, 1994b). Intestinal colonization does not necessarily result in subsequent hepatitis, and the conditions that lead to migration of the organism from the intestine to the liver have not been determined. *H. hepaticus* appears to reside primarily within the bile canaliculi. Male mice were reported to have a greater incidence and severity of hepatitis than female mice, and this finding occurred in NTP studies as well. The recently identified *H. bilis*, like *H. hepaticus*, colonizes the biliary tract, liver, and intestine of mice. While *H. bilis* has been identified in animals with chronic hepatitis, whether it caused the hepatitis is not known (Fox *et al.*, 1995).

The pathogenesis of *H. hepaticus*-induced disease has not been fully characterized. In susceptible strains of mice, *H. hepaticus* can cause acute, focal, nonsuppurative, necrotizing hepatitis, which progresses to chronic, active hepatitis characterized by minimal necrosis, hepatocytomegaly, oval cell hyperplasia, and

cholangitis. *H. hepaticus* has been found to possess high levels of urease (Fox *et al.*, 1994). *H. hepaticus* is often isolated from the cecum and colon but is not necessarily isolated from the liver of A/JCr mice, even though these animals develop severe hepatitis. Culture supernatants from several strains of *H. hepaticus* and several other *Helicobacter* species were shown to cause cytopathic effects in a rodent hepatocyte cell line (Taylor *et al.*, 1995). Ward *et al.* (1996) suggested that autoimmunity may play a role in the progressive hepatitis and carcinogenesis in livers infected with *H. hepaticus*.

NTP Infectious Disease Surveillance

In 1993, during the histological evaluation of an NTP 2-year study, pathologists identified a constellation of liver lesions (hepatitis) in control and treated male mice that was consistent with what would later be described in mice infected with *H. hepaticus* (Ward *et al.*, 1993, 1994a; Fox *et al.*, 1994). Subsequently, pathology results from all mouse studies begun since 1984 (67 two-year studies) were reviewed for diagnoses of the characteristic hepatitis; the lesions were identified in nine studies (NTP, 1998a,b,c,d,e,f). Silver stains revealed helical bacteria consistent with *Helicobacter* present in the liver of male mice in the nine studies.

Every reasonable measure is taken to prevent the occurrence of infectious diseases during NTP 2-year carcinogenicity studies. When infections occasionally occur, care is taken to identify the causal agent and its source, measures are taken to ensure that animals in later studies will not be infected, and the potential impact on biological parameters (primarily neoplastic endpoints) important in interpretation of the study is determined. To date, animals (control and treated) from a few studies have had a mild pulmonary inflammatory response presumed to be caused by an infectious agent. In other studies, there have been utero-ovarian infections with *Klebsiella* sp. (Rao *et al.*, 1987) and fungal infections of the nasal cavity. For scientifically valid reasons, interpretation of chemical-related effects was not considered significantly compromised in any of these studies. Unlike the previous infections, *H. hepaticus* involves the liver, the major metabolic organ, and has been associated with an increase in incidences of liver neoplasms in the A/JCr mouse (Ward *et al.*, 1994a). Therefore, when the contemporary epizootic of *H. hepaticus* infection in the United States affected several NTP studies, use of the data for hazard identification was questioned. The first step was to determine the extent of the infection within NTP studies and then evaluate the impact the infection had on biological parameters important in interpretation of the carcinogenic potential of test chemicals.

MATERIALS AND METHODS

Histologic Examination

Studies in which mice were potentially infected with *H. hepaticus* were identified by reviewing the summary pathology tables for characteristic diagnoses: oval and/or biliary epithelial hyperplasia, hepatocyte enlargement (often diagnosed as karyomegaly), chronic inflammation, and regenerative hyperplasia. All 13-week and 2-year studies begun by the NTP since 1984 and for which complete pathology data were available (67 two-year studies) were examined. Eight contemporary studies in which the characteristic lesions were not identified from pathology tables were randomly selected for histologic reevaluation. Slides containing sections of hematoxylin- and eosin-stained livers from 20 to 25 control and 20 to 25 high-dose male mice from each of seven 2-year studies and one 13-week study (10 animals from each group) were reexamined microscopically for the presence of hepatitis potentially related to *H. hepaticus* infection. Hepatitis consistent with that observed with *H. hepaticus* infection was not observed in any of these studies.

Liver sections from five or more animals from each of nine 2-year studies in which hepatitis was observed were prepared using the Warthin-Starry silver stain or Steiner's modification to identify silver-positive helical bacteria.

PCR-RFLP Detection of *Helicobacter* DNA

Assays based on polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) were conducted at the NIEHS (Malarkey *et al.*, 1997) and the University of Missouri Research Animal Diagnostic and Investigative Laboratory (MU-RADIL) (Riley *et al.*, 1996) on liver tissue from approximately 20 animals from each of 32 NTP 2-year studies (including the nine affected studies) and three NTP 13-week studies. The majority of these studies were selected because they were begun at approximately the same time (1988-1990) as the nine affected studies. Also, two earlier studies (1984-1985; mouse life-span and *p*-nitroaniline studies) and one later study (1993; methyleugenol) were selected. The mouse life-span study was designed to evaluate the incidences of spontaneous changes associated with age; therefore, there is no NTP Technical Report. Pathology peer review is not complete for the methyleugenol study, and the NTP Technical Report (NTP, 1998g) has not been completed. Frozen tissue was available from 22 of these studies, while only formalin-fixed tissue was available for the remaining ten 2-year studies and the three 13-week studies. Most of the assays were conducted by MU-RADIL, which used *Helicobacter* genus-specific primers; MU-RADIL used restriction endonucleases on a subset of positives to determine if the species was *H. hepaticus*. DNA was isolated from frozen liver samples with a QIAamp Tissue Kit (Qiagen Inc., Chatsworth, CA) according to the manufacturer's recommendations or routine phenol/chloroform extraction (Malarkey *et al.*, 1997). DNA content and purity were determined spectrophotometrically by measuring the A_{260}/A_{280} optical density ratio. To isolate DNA from paraffin-embedded samples, five 10-µm sections were washed twice with 1 mL xylene and twice with 500 µL ethanol. Tissues were then dried within a vacuum centrifuge prior to DNA isolation as described above. Routine measures were taken to avoid contamination at every step from tissue collection to PCR amplification, and concurrently run controls without DNA were consistently negative.

Statistical Analyses

Multiple regression procedures were used to compare control neoplasm rates in the nine affected studies with the 26 unaffected contemporary studies which had no histologic evidence of *H. hepaticus*-associated liver disease. While frozen liver tissue was unavailable from 13 of these 26 studies, none showed the hepatitis indicative of *H. hepaticus* and thus were assumed to be unaffected. Potential confounding factors such as body weight, date study was begun, route of administration, and animal supplier were included as covariables in the statistical analysis.

Analysis for H-*ras* Codon 61 CAA-to-AAA Mutations

For analyses of formalin-fixed tissue, three to five unstained serial sections (10 µm thick) were cut from paraffin blocks containing hepatocellular adenomas or carcinomas. Paraffin-embedded tissues were deparaffinized and rehydrated prior to being digested with proteinase k overnight at 55° C to isolate DNA. Frozen tissues were digested with 10 mg/mL pronase in 1% sodium dodecyl sulfate in TNE buffer (10 mM TRIS, 150 mM NaCl, and 2 mM EDTA; pH 7.5) overnight at 37° C; DNA was isolated by phenol chloroform extraction and precipitated with ethanol (Marmur, 1961; Sills *et al.*, 1995).

Nested primers were used for amplification of exon 2 of H-*ras* by PCR. The outer primers were 5'-CCA CTA AGC CTG TTG TGT TTT GCA G-3' (forward primer) and 5'-CTG TAC TGA TGG ATG TCC TCG AAG GA-3' (reverse primer). The inner primers (second round of amplification) were 5'-GAC ATC TTA GAC ACA GCA GTT-3' (forward primer) and 5'-GGT GTT GTT GAT GGC AAA TAC-3' (reverse primer). Although the normal sequence of codon 60 is GCT, the forward PCR primer is made with a T at the penultimate 3' base to create the restriction site for Mse1.

A nonradioactive RFLP method was employed to identify CAA-to-AAA mutations in the H-*ras* gene at codon 61 in liver neoplasms (Lee and Drinkwater, 1995). This was based on Mse1 enzyme restriction cutting only the sequence 5'-TTAA-3'. Thus, Mse1 will detect C→A conversion mutation at the first position of codon 61.

Analysis of PCNA and Apoptosis

Detailed methods are included in a report by Nyska *et al*. (1997). Cell proliferation was assessed in nonneoplastic areas of the liver, kidney, and lung by determining a PCNA S-phase labeling index (the percentage of cells in S phase). The identification of apoptotic cells was based on morphologic criteria (Garewal *et al.*, 1996; Goldsworthy *et al.*, 1996) and confirmed immunohistochemically by the terminal deoxynucleotidyl transferase-mediated dUTP-biotin nick end labeling (TUNEL) procedure (Gavrieli *et al.*, 1992).

RESULTS AND DISCUSSION

Identification of *H. hepaticus* Infection in NTP Studies

Determining the extent of *H. hepaticus* infection involved a three-pronged approach of histologic evaluation, silver stains, and PCR-RFLP based assays; all were necessary because of the limitations identified for each. In NTP studies, and as reported in other studies (Ward *et al.*, 1994b), there were no obvious clinical signs of infection, and the only significant histologic lesion (hepatitis) was observed in the liver, primarily in males. Therefore, summary pathology tables were reviewed to identify studies that may have been affected by *H. hepaticus*-associated hepatitis. Male mice from nine studies were identified (Table O1) as having the hepatitis. Eight of the nine studies were begun during a time span of about 6 months (July 1990 to January 1991), while the other study was begun much earlier (October 1988). The hepatitis was not observed in any 13-week studies. Use of histologic evaluation for identification of infected animals has limitations, however. It is somewhat insensitive, as *H. hepaticus* has been cultured and identified by PCR-RFLP methods within livers of animals with no histological evidence of infection (Fox *et al.*, 1998). This may be explained in part by the limited sampling (two liver sections) and the sometimes focal nature of *H. hepaticus*-associated hepatitis. Also, while in the more severely affected animals the hepatitis appears somewhat characteristic, component lesions of the hepatitis are not pathognomonic, and, when the hepatitis is subtle in 2-year old animals, it is more difficult to recognize or attribute to *H. hepaticus*.

Within affected studies, the incidences of the hepatitis in male mice varied from 16% to 78% (Table O1). While generally mild to moderate, the hepatitis varied in severity from barely detectable in some animals to extensive liver involvement and regeneration in others. Only a few females were identified as having the characteristic hepatitis (Table O1). In general, the incidences and severities of *H. hepaticus*-associated hepatitis were similar between control and treated groups. This constellation of nonneoplastic liver lesions, while not pathognomonic, was certainly suggestive of an *H. hepaticus* infection, particularly when observed in control animals. Characteristic lesions included proliferation of oval and/or biliary epithelial cells, hepatocyte enlargement (diagnosed as karyomegaly), and chronic inflammation. In many instances, areas of regenerative hyperplasia were identified within diseased liver.

Helicobacter spp. are not usually observed on routine histologic examination of hematoxylin and eosin-stained sections of liver. The methods for confirmation of infection with *Helicobacter* include Warthin-Starry silver stain or Steiner's modification (Garvey *et al.*, 1985) of this stain for direct microscopic observation of the organisms in tissue; however, this can be a relatively insensitive technique when few organisms are present. In most instances, histologic differentiation between *Helicobacter* species is not possible. Speciation can usually be accomplished with electron microscopy, but this technique is both time consuming and labor intensive. Microbiologic culture of feces, cecal smears, and fresh or frozen liver is also possible. Currently, assays involving amplification of the DNA of the organism using PCR are the most rapid and perhaps the most sensitive methods of detection, and the use of restriction endonucleases has allowed a determination of the species present. PCR-based methods also can be used on feces, cecal contents, or liver homogenates and are most sensitive when using fresh or frozen tissue (Riley *et al.*, 1996; Malarkey *et al.*, 1997).

Using Warthin-Starry silver stains or Steiner's modification on the livers of five or more animals per study, helical bacteria (*Helicobacter*) were identified in animals from the nine affected studies. In some animals, helical bacteria were numerous, suggesting a heavy bacterial burden in these infected animals. However, even in these animals with abundant organisms, few to none were observed in proliferative hepatic lesions such as foci and neoplasms. Helical bacteria were not identified in approximately 25% of males with moderate hepatitis and were rarely identified in males without hepatitis or in females. The absence of identification of helical organisms by silver stains does not preclude infection, nor does the presence of organisms confirm *H. hepaticus*. Based upon current knowledge, however, the characteristic liver lesions in $B6C3F_1$ mice, coupled with the presence of silver-positive helical organisms, are highly suggestive of *H. hepaticus* infection.

As the NTP evaluation evolved, PCR-based assays were developed that appeared more sensitive than histologic evaluation and silver stains for identification and speciation of *Helicobacter*. Therefore, PCR-RFLP-based assays were used to confirm the presence of pathogenic *Helicobacter* (primarily *H. hepaticus*) within the nine affected studies and to determine whether there was *H. hepaticus* infection in other NTP studies. Unfortunately, none of the PCR-based assays had been specifically developed for, or proven reliable for use with, formalin-fixed tissue. Frozen tissue was available from a limited number of animals from a limited number of NTP studies, including only three of the nine affected studies. Furthermore, available frozen liver was almost always limited to tissue from a neoplasm, and, based upon results obtained with silver stains, organisms are generally not readily observed within proliferative hepatic lesions, even when organisms are abundant in adjacent liver tissue. Because the availability of frozen tissue was limited, a PCR-RFLP-based assay was developed and evaluated (Malarkey *et al.*, 1997) for use with frozen or formalin-fixed tissue.

The NIEHS and MU-RADIL laboratories conducted PCR-RFLP-based assays on 32 NTP 2-year studies and three NTP 13-week studies (data not shown); frozen tissues from 22 of the 2-year studies were available. All three bioassays in which hepatitis was identified and for which frozen tissue was available were positive for *H. hepaticus* by the PCR-RFLP-based assays (Table O2). At a third laboratory, *H. hepaticus* was also cultured from the liver tissue of animals in one of these studies (Fox *et al.*, 1998). Formalin-fixed tissues from two of the three studies were evaluated and were also positive; these tissues had been fixed in formalin for less than 48 hours. In the other six affected studies, for which only formalin-fixed tissue was available, *H. hepaticus* was identified in only 1 of 120 animals (Table O2). This decreased sensitivity was considered to be related to the prolonged formalin fixation (Malarkey *et al.*, 1997) rather than proof of an absence of *H. hepaticus*. The presence or absence of *H. hepaticus* apparently cannot be confirmed with current PCR-RFLP-based assays in liver that has been fixed in formalin for long periods (weeks or months). In the three 13-week studies with formalin-fixed tissue, only 1 of 30 animals was positive for *H. hepaticus*.

Within the three affected, PCR-RFLP-positive 2-year studies, *H. hepaticus* was often identified by PCR in frozen livers of mice that had no overt hepatitis. In fact, based upon the combined data from two studies (including PCR results from three laboratories), of 57 animals without characteristic liver lesions, 13 of 24 male mice (54%) and 17 of 33 female mice (52%) were positive for *H. hepaticus*. Furthermore, *H. hepaticus* was identified by PCR in frozen liver of several animals from three "unaffected" studies in which hepatitis typical of that associated with *H. hepaticus* was not observed (Table O2). Apparent variability occurs between various strains of mice and between individual mice from affected studies in developing hepatitis in response to *H. hepaticus* infection. One would assume that, within affected studies, most or all animals have been exposed to the organism, and even animals resistant to developing hepatitis may have organisms within the liver. This assumption is supported by the fact that animals without hepatitis are often positive with PCR-RFLP-based assays. Therefore, although alternative explanations are possible, the three PCR-RFLP-positive studies in which liver lesions are absent are assumed to be true positives. In fact, helical organisms were identified with a silver stain in one animal from one of these studies (Malarkey *et al.*, 1997). Therefore, in addition to assessing the affect of *H. hepaticus* in the nine affected 2-year

studies, the significance of a positive PCR-RFLP assay for *H. hepaticus* in the absence of liver lesions is also an important question.

Inconsistent Results with PCR-Based Methods

As with any technique, the PCR-RFLP-based assays have limitations even when used to assay fresh and frozen tissue. One assessment of the variability in results of PCR and serologic analyses for *Helicobacter* among three commercial laboratories revealed significant inconsistencies (Dew *et al.*, 1997). Others (J.M. Ward and J. Thigpen, personal communications) have obtained similarly inconsistent results when sending replicate samples to different laboratories. Though the number of samples evaluated by both the NIEHS and MU-RADIL laboratories was limited, there was good, but not complete, correlation of PCR-RFLP results. Also, within the affected studies, the PCR assays were not positive in some animals with liver disease. This result may be explained, in part, by the fact that the only frozen tissues available were neoplasms; as described above, neoplasms are expected to have fewer organisms.

Analysis of *H. hepaticus*-Affected and Unaffected Studies for Incidence of Common Neoplasms

To determine whether the incidences of various neoplasms were different between control groups from affected and unaffected studies, the nine affected studies were compared to 26 unaffected studies begun at relatively similar times (Table O3). There were no statistically significant differences in body weight or survival among the affected and unaffected studies. The neoplasms evaluated represent those that occurred at high enough incidences in various organs for statistically significant differences to be detected. Using multiple regression procedures, male mice in the nine affected studies were demonstrated to have a significantly ($P < 0.05$) increased incidence of only two neoplasm types, both of which were in the liver (hepatocellular neoplasms and hemangiosarcoma), when compared to the unaffected studies. Because of these differences, there was also a corresponding significant difference in the overall incidence of malignant neoplasms (all sites) as well as in the overall proportion of neoplasm-bearing animals. No other tissue site showed a significant difference in the incidence of neoplasms. For female mice, the slightly increased incidence of hepatocellular neoplasms observed in the affected studies was not statistically significant.

This seemingly simple analysis is complicated by several potential confounding variables. There have been coordinate, time-related increases in body weight and in the incidence of liver neoplasms in mice in NTP studies (Haseman, 1992). Table O4 presents the liver neoplasm incidences in relation to the dates the studies began and clearly shows the increases in liver neoplasm incidences and body weights (Seilkop, 1995). In assessing differences in neoplasm incidences between *H. hepaticus*-affected and unaffected studies, the most relevant comparison would be between studies begun at approximately the same time. The starts of 20 of the 26 unaffected studies were clustered near the early part of the time frame (April 1988 to June 1990), while the starts of the affected studies were clustered toward the later end, with eight of the nine studies begun between July 1990 and January 1991; incidences of liver neoplasms in these later studies are expected to be higher based on trends in body weight alone. While the slightly increased incidences of liver neoplasms observed in female control mice in the nine affected studies is likely due to clustering in time, clearly, this alone cannot account for the increased liver neoplasm incidences observed in control male mice in the affected studies (Table O3).

Ideally, unaffected studies used in the above comparison should not only be free of histologic evidence of infection with *H. hepaticus* but should be confirmed as negative by PCR assays. Thirteen of these 26 studies could not be confirmed as negative by PCR because frozen tissue was not available; however, *H. hepaticus*-associated hepatitis was not present in any of the 26 studies. Because these and other data reported to date suggest that hepatitis is associated with neoplasm development in the liver, it seems reasonable to include those 13 studies, unconfirmed by PCR, in this analysis. The majority of the 13 studies confirmed as negative by PCR were begun much earlier than the clearly affected studies, and, therefore, comparing them alone to the nine affected studies is not reasonable. Although not presented here, a number

of comparisons were made with various groupings of studies based on the degree of confidence in their infection status. Although the outcomes of the various comparisons varied somewhat, incidences of hepatocellular neoplasms and hemangiosarcomas of the liver were consistently increased in control male mice from affected studies compared to control males from unaffected studies. Significantly increased liver neoplasm incidences generally were not observed in females. Importantly, the following data corroborate the findings and association with *H. hepaticus* identified in these analyses.

Analysis of Hepatitis-Positive and Hepatitis-Negative Mice for Liver Neoplasm Incidence

Several infectious agents known to be associated with increased incidences of neoplasms cause chronic inflammation in the target tissue or organ. It is commonly hypothesized that this inflammatory process may cause or contribute to the development of neoplasms. One approach to address this was to stratify the mice from the affected studies according to the severity of hepatitis and examine liver neoplasm incidences in relation to these groupings. Thus, animals within the nine affected studies were placed into three groups: 1) animals with mild to moderate hepatitis considered related to *H. hepaticus* infection (+), 2) animals with minimal to mild hepatitis that may have been associated with *H. hepaticus* (±), and 3) animals with no hepatitis that was considered to be associated with *H. hepaticus* (–). Within these groupings, the incidence of liver neoplasms was significantly increased ($P < 0.05$) in males with mild to moderate *H. hepaticus*-associated hepatitis (+) when compared to animals without such hepatitis (Table O5). The neoplasm incidence in animals with minimal lesions (±) was also increased. The liver neoplasm incidence in males without hepatitis (58%) was similar to the incidence (54.8%) in males from the 26 unaffected studies (Table O3). This analysis clearly suggests an association of *H. hepaticus*-associated hepatitis with increased liver neoplasm incidences. Females showed a similar trend, albeit not significant; however, these comparisons are weak because of the low numbers of females with hepatitis.

Analysis of H-*ras* Oncogene Mutations in Liver Neoplasms in Mice from Affected and Unaffected Studies

Liver neoplasms commonly occur in control $B6C3F_1$ mice in 2-year studies. In the historical database of 333 male and female mice with liver neoplasms, 106 (32%) had H-*ras* codon 61 CAA-to-AAA mutations (Maronpot *et al.*, 1995). This historical control database is composed primarily of male data; however, adequate numbers of females have been assayed, and there was no significant difference in the incidences of CAA-to-AAA mutations between males and females.

In an attempt to examine further whether *H. hepaticus* infection had an effect on the development of hepatocellular neoplasms, neoplasms from control male mice from selected affected (NTP, 1998a,b,c) and unaffected (NTP, 1993, 1998h) studies were evaluated for H-*ras* codon 61 CAA-to-AAA mutations (Table O6). Only 6% (2/33) of the hepatocellular neoplasms from control males with hepatitis from three affected studies had this mutation. This percentage is significantly ($P < 0.01$) less than the 32% (11/34) observed in males from the two unaffected studies and less than the 32% (106/333) that occurred in historical control animals. In addition, neoplasms from males without hepatitis from the affected, PCR-positive triethanolamine study (NTP, 1998a) and the unaffected, PCR-positive methyleugenol study (NTP, 1998g) were evaluated; the incidences of mutations in those groups were 3/14 (21%) and 2/17 (12%), respectively.

Neoplasms from control female mice (none had hepatitis) from affected and unaffected studies were evaluated for the CAA-to-AAA mutation (Table O6). The mutation rate was low in both the affected studies (1/25; 4%) and the unaffected study (1/11; 9%) when compared to the 32% observed in the historical control groups.

The finding of a different H-*ras* mutation profile in neoplasms of male mice from affected studies tends to support the association of increased neoplasm incidences with *H. hepaticus*, although there is no mechanistic

understanding behind this observation. In a study of *H. hepaticus*-infected A/JCr mice, *ras* mutations were not detected in the 25 hepatocellular neoplasms analyzed using a PCR/single-strand conformation polymorphism assay (Sipowicz *et al.*, 1997). Because of the low spontaneous rate of liver neoplasms in the A/JCr mouse, there are few or no conclusive data on *ras* mutations in uninfected animals, however. Point mutations at codons 12, 13, and 61 of the Ki-, Ha- and N-*ras* genes were not identified in 45 early gastric carcinomas in humans, whether or not *H. pylori* was present (Craanen *et al.*, 1995). If the increased incidence of hepatocellular neoplasms is associated with hepatitis, as many suspect, then one would expect the neoplasms from animals without hepatitis to have a similar mutational profile as that of the historical controls. The data do not provide a clear answer, because the hepatitis-free males from the affected triethanolamine study (NTP, 1998a) and the males from the methyleugenol study (NTP, 1998g), which were positive by PCR but lacked hepatitis, had mutation frequencies between those of the unaffected controls and the hepatitis-positive mice. Furthermore, mutations in neoplasms from females, none of which had hepatitis, from two affected and one unaffected study were very low compared to the historical controls. These findings were unexpected, and their significance is not understood.

H. hepaticus-Associated Alterations in Cell Kinetics

Studies evaluating cell kinetics were completed to explore further the link between hepatitis and the increased incidence of liver neoplasms (Table O7; Nyska *et al.*, 1997). One of the major objectives was to determine whether there were differences between PCNA labeling indices in the livers of animals with hepatitis from three affected studies, cobalt sulfate heptahydrate, chloroprene, and triethanolamine (NTP, 1998a,b,c), compared to animals without hepatitis, whether from the same three affected studies or from an unaffected study, 1-trans-delta^9-tetrahydrocannabinol (NTP, 1996). Male mice with hepatitis from the three affected studies had a significantly increased ($P < 0.001$) labeling index, with a 24-fold increase over males from the unaffected study and a sixfold increase over males without hepatitis from the same three affected studies (Table O7). The labeling index increase in these mice was substantial and was considered biologically significant. Male mice without hepatitis from the three affected studies had a significantly greater labeling index (increased fourfold) than male mice from the unaffected study (Table O7). The significance of this finding is uncertain, as differences of a similar magnitude were observed in other comparisons. For example, the labeling index of females from the unaffected 1-trans-delta^9-tetrahydrocannabinol study (Table O7; NTP, 1996) was increased fivefold over females from the PCR-positive, hepatitis-negative scopolamine hydrobromide trihydrate study (NTP, 1997). Such differences may be within the limits of normal variability for 2-year-old animals.

A second objective of the cell proliferation studies of the liver was to determine if labeling indices were increased in animals from the PCR-positive, hepatitis-negative methyleugenol (NTP, 1998g), scopolamine hydrobromide trihydrate (NTP, 1997), and mouse life-span studies compared to an unaffected PCR-negative and hepatitis-negative 1-trans-delta^9-tetrahydrocannabinol study (NTP, 1996). The scopolamine hydrobromide trihydrate study was evaluated and included in the study by Nyska *et al.* (1997), while the methyleugenol and mouse life-span studies were completed later and are included in Table O7. The labeling indices of males from two of these three studies were almost identical to those of males from the unaffected study. However, the labeling index of males from the mouse life-span study is increased approximately fivefold over that of males from the unaffected study as well as fivefold over the labeling indices of males from the two like studies of scopolamine hydrobromide trihydrate and methyleugenol. This finding suggests that the increase observed in the mouse life-span study is not attributable to the presence of *H. hepaticus*, as two other studies also positive for *H. hepaticus* did not show a similar increase.

The cell proliferation data for the liver from NTP studies are consistent with data from a study by Fox *et al.* (1996) in which cell proliferation indices were evaluated at 8, 10, and 13 months in the A/JCr mouse, which is generally believed to be more susceptible to *H. hepaticus*-associated hepatitis than the B6C3F$_1$ mouse. In the study by Fox *et al.* (1996), cell proliferation rates were significantly increased at all time points in males. Some increases were observed in females in that study but did not reach statistical significance. An increased

incidence of hepatocellular neoplasms was observed only in the males. Though liver lesions were observed in females in that study, they were less severe than those in males.

In addition to the liver, cell proliferation indices (PCNA) were evaluated in the kidneys and lungs of male and female mice in affected studies versus those in unaffected studies (Nyska *et al.*, 1997). No apparent effect of *H. hepaticus* infection or the presence of hepatitis on PCNA indices was observed for the kidneys or lungs.

Apoptosis (programmed cell death) is another important parameter in evaluations of cell kinetics. The apoptotic index in the liver of male mice with hepatitis from an affected study, cobalt sulfate heptahydrate (NTP, 1998b), was significantly ($P < 0.01$) greater than that observed in males from the unaffected 1-trans-delta^9-tetrahydrocannabinol study and the PCR-positive, hepatitis-negative scopolamine hydrobromide trihydrate study (Nyska *et al.*, 1997). For females, there were no significant differences among the three studies.

Two 13-week studies which were begun during the same time as the nine affected studies were randomly selected for evaluation of PCNA indices. *H. hepaticus* was not identified in either of the studies by PCR-RFLP; however, as with all NTP 13-week studies, only tissue fixed in formalin for an unspecified period was available. Because of this, no true negative control group was available; therefore, the labeling index of these 19- to 20-week-old animals was compared to values cited in the literature (Eldridge and Goldsworthy, 1996) for 20-week-old B6C3F$_1$ mice. The labeling index in the NTP studies clearly was not increased (data not shown).

The Impact of *H. hepaticus* on the Interpretation of 2-Year Carcinogenesis Studies

Increases in the incidences of neoplasms are associated with a number of infectious agents. The chronic inflammation caused by these agents has been hypothesized to be important in the pathogenesis of the increased neoplasm incidences (e.g., gastric cancer associated with *H. pylori*). The increased incidences of liver neoplasms in male mice from the nine affected NTP studies were observed in the animals with *H. hepaticus*-associated hepatitis. Neoplasms from males with hepatitis tended to have an H-*ras* mutation profile different from that of animals from unaffected studies. Further, cell replication rates at 2 years were significantly higher in males with hepatitis compared to those in males without hepatitis. The data suggest that *H. hepaticus*-associated hepatitis is associated with the increased incidences of liver neoplasms in the male B6C3F$_1$ mouse. Therefore, the most important consideration in evaluating the impact of *H. hepaticus* infection on the interpretation of study results appears to be the presence or absence of significant hepatitis.

For any carcinogenicity study, data within and specific to the individual study provide the greatest basis for an accurate interpretation. However, it is prudent to consider and evaluate all data or information which may affect the interpretation. Based upon the data presented in this and other reports, general guidelines emerge that may be useful in interpreting potential chemical-associated carcinogenic effects in *H. hepaticus*-infected B6C3F$_1$ mice. In a study with sufficient evidence of *H. hepaticus*-associated hepatitis (> 10% of the animals having the characteristic hepatitis may be a reasonable guideline), interpretation of increased incidences of liver neoplasms (hepatocellular neoplasms and hemangiosarcoma) of male mice is considered to be potentially confounded.

Altered chemical uptake and metabolism, due to the intestinal load of *H. hepaticus* and to *H. hepaticus*-associated liver disease, respectively, are possible reasons for considering that the male mouse response to chemical administration at sites other than the liver should also be considered confounded. Data do not currently exist that definitively answer this question. In this group of nine studies, however, there is no evidence to suggest that affected mice responded to chemical treatment in organs other than the liver in a manner different from mice in nonaffected studies. Within each study, there was excellent concordance in chemical-associated neoplasms between the male mice and the females, which had little or no hepatitis

(Table O8). Furthermore, analyses indicate that *H. hepaticus* is not associated with neoplastic responses outside the liver; incidences of neoplasms at sites other than the liver were not different between control groups from affected and unaffected studies (Table O3). Cell replication rates in two major organs (lung and kidney) also were not increased in control groups from affected studies compared to those from unaffected studies.

One of the more difficult issues to address is whether interpretation of a treatment-related increase in liver neoplasm incidences in the female mouse is confounded when *H. hepaticus*-associated hepatitis is present within the male mice in the study. Most evidence to date links hepatitis with the increased liver neoplasm incidences observed in males, and female B6C3F$_1$ mice in affected studies do not have significant hepatitis at 2 years. The lack of hepatitis in females, however, is based on an analysis in which only late time points were evaluated histologically. Therefore, it is conceivable that hepatitis along with increased cell proliferation could have occurred earlier and resolved by 18 months to 2 years. Data collected to date, however, suggest that *H. hepaticus*-associated hepatitis is a late-developing and persistent disease in the B6C3F$_1$ mouse. *H. hepaticus*-associated hepatitis has never been observed in any NTP 13-week studies, including five begun during the same 6-month time span as eight of the nine affected 2-year studies. Also, within affected 2-year studies, more males (51%) that were 18 to 24 months of age had hepatitis than those (34%) that were 12 to 18 months of age. This is consistent with a report by Ward *et al*. (1994b) that *H. hepaticus*-associated liver lesions are not observed at early time points in the B6C3F$_1$ mouse.

Nonetheless, within affected studies, female control mice did have a slightly elevated incidence of liver neoplasms when compared to control mice from unaffected studies, and the data derived from the H-*ras* mutation frequency analysis were inconclusive. The possibility that *H. hepaticus*-infected female mice from affected studies may respond differently to a liver carcinogen than mice from unaffected studies cannot be eliminated at this time. However, because within an affected study hepatitis is observed only rarely in females, until definitive data suggest otherwise, it is concluded that the interpretation of an apparent chemical-induced neoplastic effect in the liver of female mice is not confounded. To censor the few females with *H. hepaticus*-associated hepatitis from any statistical analyses of hepatocellular neoplasms would be prudent. Studies in the ostensibly more sensitive A/JCr mouse (Fox *et al.*, 1996) also showed significant increases in neoplasm incidences and cell proliferation rates in the liver of *H. hepaticus*-infected males, but not females.

Another concern is how to interpret possible chemical-related effects in a study in which the status of *H. hepaticus* infection cannot be determined by PCR-RFLP because only tissues fixed in formalin for more than 48 hours are available. While histologic evaluation is inadequate to identify infection, it appears adequate for identifying hepatitis severe enough to alter the outcome of the study. Therefore, in the absence of significant histologic evidence of *H. hepaticus*-associated hepatitis, the outcome of a 2-year study should not be considered potentially compromised.

The causality between *H. hepaticus* infection and neoplasia has not been proven in the B6C3F$_1$ mouse in these studies, nor has the mechanism of this association been determined; further studies are needed. However, sufficient information exists to make reasonable scientific judgments relative to the interpretation of data from the nine 2-year carcinogenicity studies in the B6C3F$_1$ mouse. Refinements to the above interpretive positions may occur if warranted by future information.

REFERENCES

Craanen, M.E., Blok, P., Top, B., Boerrigter, L., Dekker, W., Offerhaus, G.J.A., Tytgat, G.N.J., and Rodenhuis, S. (1995). Absence of ras gene mutations in early gastric carcinomas. *Gut* **37**, 758-762.

Dew, J.A., Clifton, L.G., Sanders, B.L., and Reynolds, R.P. (1997). Comparison of results of *Helicobacter* tests performed by commercial laboratories. *Contemp. Top. (AALAS)* **36**, 60. (Abstr.)

Eldridge, S.R., and Goldsworthy, S.M. (1996). Cell proliferation rates in common cancer target tissues of B6C3F1 mice and F344 rats: Effects of age, gender, and choice of marker. *Fundam. Appl. Toxicol.* **32**, 159-167.

Fox, J.G., Correa, P., Taylor, N.S., Zavala, D., Fontham, E., Janney, F., Rodriquez, E., Hunter, F., and Diavolitsis, S. (1989). *Campylobacter pylori*-associated gastritis and immune response in a population at increased risk of gastric carcinoma. *Am. J. Gastroenterol.* **84**, 775-781.

Fox, J.G., Dewhirst, F.E., Tully, J.G., Paster, B.J., Yan, L., Taylor, N.S., Collins, M.J., Jr., Gorelick, P.L., and Ward, J.M. (1994). *Helicobacter hepaticus* sp. nov., a microaerophilic bacterium isolated from livers and intestinal mucosal scrapings from mice. *J. Clin. Microbiol.* **32**, 1238-1245.

Fox, J.G., Yan, L.L., Dewhirst, F.E., Paster, B.J., Shames, B., Murphy, J.C., Hayward, A., Belcher, J.C., and Mendes, E.N. (1995). *Helicobacter bilis* sp. nov., a novel *Helicobacter* species isolated from bile, livers, and intestines of aged, inbred mice. *J. Clin. Microbiol.* **33**, 445-454.

Fox, J.G., Li, X., Yan, L., Cahill, R.J., Hurley, R., Lewis, R., and Murphy, J.C. (1996). Chronic proliferative hepatitis in A/JCr mice associated with persistent *Helicobacter hepaticus* infection: A model of Helicobacter-induced carcinogenesis. *Infect. Immun.* **64**, 1548-1558.

Fox, J.G., MacGregor, J., Shen, Z., Li, X., Lewis, R., and Dangler, C.A. (1998). Role of *Helicobacter hepaticus* in confounding results of a triethanolamine carcinogenesis study in mice. *J. Clin. Microbiol.* (in press)

Garewal, H., Bernstein, H., Bernstein, C., Sampliner, R., and Payne, C. (1996). Reduced bile acid-induced apoptosis in "normal" colorectal mucosa: A potential biological marker for cancer risk. *Cancer Res.* **56**, 1480-1483.

Garvey, W., Fathi, A., and Bigelow, F. (1985). Modified Steiner for the demonstration of spirochetes. *J. Histotechnol.* **8**, 15-17.

Gavrieli, Y., Sherman, Y., and Ben-Sasson, S.A. (1992). Identification of programmed cell death in situ via specific labeling of nuclear DNA fragmentation. *J. Cell Biol.* **119**, 493-501.

Goldsworthy, T.L., Fransson-Steen, R., and Maronpot, R.R. (1996). Importance of and approaches to quantification of hepatocyte apoptosis. *Toxicol. Pathol.* **24**, 24-35.

Graham, D.Y. (1989). *Campylobacter pylori* and peptic ulcer disease. *Gastroenterology* **96**, 615-625.

Haseman, J.K. (1992). Value of historical controls in the interpretation of rodent tumor data. *Drug Inf. J.* **26**, 191-200.

International Agency for Research on Cancer (IARC) (1994). *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans: Schistosomes, Liver Flukes and Helicobacter pylori*, Vol. 61. IARC, Lyon, France.

Lee, A., Fox, J., and Hazell, S. (1993). Pathogenicity of *Helicobacter pylori:* A perspective. *Infect. Immun.* **61**, 1601-1610.

Lee, G.-H., and Drinkwater, N.R. (1995). Hepatocarcinogenesis in BXH recombinant inbred strains of mice: Analysis of diverse phenotypic effects of the hepatocarcinogen sensitivity loci. *Mol. Carcinog.* **14**, 190-197.

Malarkey, D.E., Ton, T.-V., Hailey, J.R., and Devereaux, T.R. (1997). A PCR-RFLP method for the detection of *Helicobacter hepaticus* in frozen or fixed liver from B6C3F$_1$ mice. *Toxicol. Pathol.* **25**, 606-612.

Marmur, J. (1961). A procedure for the isolation of deoxyribonucleic acid from micro-organisms. *J. Mol. Biol.* **3**, 208-218.

Maronpot, R.R., Fox, T., Malarkey, D.E., and Goldsworthy, T.L. (1995). Mutations in the *ras* proto-oncogene: Clues to etiology and molecular pathogenesis of mouse liver tumors. *Toxicology* **101**, 125-156.

Marshall, B.J., and Warren, J.R. (1984). Unidentified curved bacilli in the stomach of patients with gastritis and peptic ulceration. *Lancet* **1**, 1311-1314.

National Toxicology Program (NTP) (1993). Toxicology and Carcinogenesis Studies of Oxazepam (CAS No. 604-75-1) in Swiss Webster and B6C3F$_1$ Mice (Feed Studies). Technical Report Series No. 443. NIH Publication No. 93-3359. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, Research Triangle Park, NC.

National Toxicology Program (NTP) (1996). Toxicology and Carcinogenesis Studies of 1-Trans-delta^9-tetrahydrocannabinol (CAS No. 1972-08-3) in F344/N Rats and B6C3F$_1$ Mice (Gavage Studies). Technical Report Series No. 446. NIH Publication No. 97-3362. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, Research Triangle Park, NC.

National Toxicology Program (NTP) (1997). Toxicology and Carcinogenesis Studies of Scopolamine Hydrobromide Trihydrate (CAS No. 6533-68-2) in F344/N Rats and B6C3F$_1$ Mice (Gavage Studies). Technical Report Series No. 445. NIH Publication No. 97-3361. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, Research Triangle Park, NC.

National Toxicology Program (NTP) (1998a). Toxicology and Carcinogenesis Studies of Triethanolamine (CAS No. 102-71-6) in F344/N Rats and B6C3F$_1$ Mice (Dermal Studies). Technical Report Series No. 449. NIH Publication No. 98-3365. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, Research Triangle Park, NC. (in preparation)

National Toxicology Program (NTP) (1998b). Toxicology and Carcinogenesis Studies of Cobalt Sulfate Heptahydrate (CAS No. 10026-24-1) in F344/N Rats and B6C3F$_1$ Mice (Inhalation Studies). Technical Report Series No. 471. NIH Publication No. 98-3961. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, Research Triangle Park, NC. (in press)

National Toxicology Program (NTP) (1998c). Toxicology and Carcinogenesis Studies of Chloroprene (CAS No. 126-99-8) in F344/N Rats and B6C3F$_1$ Mice (Inhalation Studies). Technical Report Series No. 467. NIH Publication No. 98-3957. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, Research Triangle Park, NC. (in press)

National Toxicology Program (NTP) (1998d). Toxicology and Carcinogenesis Studies of Technical Grade Sodium Xylenesulfonate (CAS No. 1300-72-7) in F344/N Rats and B6C3F$_1$ Mice (Dermal Studies). Technical Report Series No. 464. NIH Publication No. 98-3380. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, Research Triangle Park, NC. (in press)

National Toxicology Program (NTP) (1998e). Toxicology and Carcinogenesis Studies of AZT (CAS No. 30516-87-1) and AZT/α-Interferon A/D in B6C3F$_1$ Mice (Gavage Studies). Technical Report Series No. 469. NIH Publication No. 98-3959. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, Research Triangle Park, NC. (in press)

National Toxicology Program (NTP) (1998f). Toxicology and Carcinogenesis Studies of Theophylline (CAS No. 58-55-9) in F344/N Rats and B6C3F$_1$ Mice (Feed and Gavage Studies). Technical Report Series No. 473. NIH Publication No. 98-3963. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, Research Triangle Park, NC. (in press)

National Toxicology Program (NTP) (1998g). Toxicology and Carcinogenesis Studies of Methyleugenol (CAS No. 93-15-2) in F344/N Rats and B6C3F$_1$ Mice (Gavage Studies). Technical Report Series No. 491. NIH Publication No. 98-3950. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, Research Triangle Park, NC. (in preparation)

National Toxicology Program (NTP) (1998h). Toxicology and Carcinogenesis Studies of Diethanolamine (CAS No. 111-42-2) in F344/N Rats and B6C3F$_1$ Mice (Dermal Studies). Technical Report Series No. 478. NIH Publication No. 98-3968. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, Research Triangle Park, NC. (in press)

Nomura, A., Stemmermann, G.N., Chyou, P., Kato, I., Perez-Perez, G.I., and Blaser, M.J. (1991). *Helicobacter pylori* infection and gastric carcinoma among Japanese Americans in Hawaii. *N. Engl. J. Med.* **325**, 1132-1136.

Nyska, A., Maronpot, R.R., Eldridge, S.R., Haseman, J.K., and Hailey, J.R. (1997). Alteration in cell kinetics in control B6C3F$_1$ mice infected with *Helicobacter hepaticus*. *Toxicol. Pathol.* **25**, 591-596.

Parsonnet, J., Friedman, G.D., Vandersteen, D.P., Chang, Y., Vogelman, J.H., Orentreich, N., and Sibley, R.K. (1991). *Helicobacter pylori* infection and the risk of gastric carcinoma. *N. Engl. J. Med.* **325**, 1127-1131.

Rao, G.N., Hickman, R.L., Seilkop, S.K., and Boorman, G.A. (1987). Utero-ovarian infection in aged B6C3F1 mice. *Lab. Animal Sci.* **37**, 153-158.

Riley, L.K., Franklin, C.L., Hook, R.R., Jr., and Besch-Williford, C. (1996). Identification of murine Helicobacters by PCR and restriction enzyme analyses. *J. Clin. Microbiol.* **34**, 942-946.

Seilkop, S.K. (1995). The effect of body weight on tumor incidence and carcinogenicity testing in B6C3F$_1$ mice and F344 rats. *Fundam. Appl. Toxicol.* **24**, 247-259.

Shames, B., Fox, J.G., Dewhirst, F., Yan, L., Shen, Z., and Taylor, N.S. (1995). Identification of widespread *Helicobacter hepaticus* infection in feces in commercial mouse colonies by culture and PCR assay. *J. Clin. Microbiol.* **33**, 2968-2972.

Sills, R.C., Hong, H.L., Greenwell, A., Herbert, R.A., Boorman, G.A., and Devereux, T.R. (1995). Increased frequency of K-*ras* mutations in lung neoplasms from female B6C3F1 mice exposed to ozone for 24 or 30 months. *Carcinogenesis* **16**, 1623-1628.

Sipowicz, M.A., Weghorst, C.M., Shio, Y.-H., Buzard, G.S., Calvert, R.J., Anver, M.R., Anderson, L.M., and Rice, J.M. (1997). Lack of *p*53 and *ras* mutations in *Helicobacter hepaticus*-induced liver tumors in A/JCr mice. *Carcinogenesis* **18**, 233-236.

Taylor, N.S., Fox, J.G., and Yan, L. (1995). In-vitro hepatotoxic factor in *Helicobacter hepaticus*, *H. pylori* and other *Helicobacter* species. *J. Med. Microbiol*. **42**, 48-52.

Ward, J.M., Anver, M.R., Haines, D.C., Tully, J.G., Jr., Collins, M.J., Jr., Gorelick, P.L., Anderson, L., Rice, J.M., and Russell, R.J. (1993). A unique hepatitis in mice associated with a helical bacterium. *Toxicol. Pathol*. **21**, 591. (Abstr.)

Ward, J.M., Fox, J.G., Anver, M.R., Haines, D.C., George, C.V., Collins, M.J., Jr., Gorelick, P.L., Nagashima, K., Gonda, M.A., Gilden, R.V., Tully, J.G., Russell, R.J., Benveniste, R.E., Paster, B.J., Dewhirst, F.E., Donovan, J.C., Anderson, L.M., and Rice, J.M. (1994a). Chronic active hepatitis and associated liver tumors in mice caused by a persistent bacterial infection with a novel *Helicobacter* species. *J. Natl. Cancer Inst*. **86**, 1222-1227.

Ward, J.M., Anver, M.R., Haines, D.C., and Benveniste, R.E. (1994b). Chronic active hepatitis in mice caused by *Helicobacter hepaticus*. *Am. J. Pathol*. **145**, 959-968.

Ward, J.M., Benveniste, R.E., Fox, C.H., Battles, J.K., Gonda, M.A., and Tully, J.G. (1996). Autoimmunity in chronic active *Helicobacter* hepatitis of mice. *Am. J. Pathol*. **148**, 509-517.

Wotherspoon, A.C., Doglioni, C., Diss, T.C., Pan, L., Moschini, A., de Boni, M., and Isaacson, P.G. (1993). Regression of primary low-grade B-cell gastric lymphoma of mucosa-associated lymphoid tissue type after eradication *of Helicobacter pylori*. *Lancet* **342**, 575-577.

TABLE O1
Incidence of *Helicobacter hepaticus*-Associated Hepatitis in Control B6C3F$_1$ Mice from Nine NTP 2-Year Studies[a]

Study	Incidence of Hepatitis (%)	
	Males	Females
Sodium xylenesulfonate	78	4
AZT/5,000 U α-interferon A/D	76	4
Cobalt sulfate heptahydrate	72	8
AZT/500 U α-interferon A/D	66	0
Chloroprene	54	0
Theophylline	32	0
α-Interferon A/D	22	4
Triethanolamine	20	0
AZT	16	2
Average	48	2

[a] Includes regeneration and mild to marked (excludes minimal) chronic inflammation, karyomegaly, oval cell hyperplasia, and bile duct hyperplasia. AZT = 3′-azido-3′-deoxythymidine

TABLE O2
Identification of *Helicobacter hepaticus* with PCR-RFLP-Based Assays in Control B6C3F$_1$ Mice from 32 NTP 2-Year Studies and Three NTP 13-Week Studies[a]

Type of Sample	Total Studies	*H. hepaticus*-Positive Studies[b]	
		Affected Studies	Unaffected Studies
13-Week Studies			
Formalin-fixed liver	3	—	1/3[c]
2-Year Studies			
Frozen liver	22	3/3	3/19
Formalin-fixed liver	10	1/6[c]	0/4

[a] PCR-RFLP = polymerase chain reaction-restriction fragment length polymorphism
[b] Number of *H. hepaticus*-positive studies/number of affected or unaffected studies. Affected studies are those in which hepatitis typical of that associated with *H. hepaticus* infection occurred in many male mice.
[c] Only one animal in the positive study was positive for *H. hepaticus*.

TABLE O3
Comparison of Neoplasm Incidences in Control B6C3F$_1$ Mice from *Helicobacter hepaticus*-Affected and Unaffected NTP 2-Year Studies

	Males		Females	
	Affected Studies[a]	Unaffected Studies	Affected Studies	Unaffected Studies
Number of studies	9	26	9	26
Survival (%)	64	71	68	68
12-Month body wt (g)	48.0	48.3	48.1	47.0
Neoplasm incidence (%)				
Liver	71.3*	54.8	50.3	40.5
Lung	26.6	23.2	7.6	10.3
Pituitary gland	0.4	0.8	14.7	14.3
Harderian gland	5.6	6.1	6.0	4.9
Lymphoma	6.9	6.3	16.2	15.5
Circulatory system	9.8	6.0	5.3	4.7
liver only	7.1*	2.5	—	—
All benign	61.8	57.2	59.1	54.6
All malignant	61.3*	40.9	50.0	44.2
All neoplasms	88.0*	77.4	82.7	75.4

* Significantly different ($P \leq 0.05$) from the unaffected studies
[a] Affected studies are those in which hepatitis typical of that associated with *H. hepaticus* infection occurred in many male mice.

TABLE O4
Liver Neoplasm Incidences and Body Weights of Control B6C3F$_1$ Mice in Relation to Study Start Dates of *Helicobacter hepaticus*-Affected and Unaffected NTP 2-Year Studies[a]

Study Start Date	Liver Neoplasm Incidence (%)		Mean Body Weight (g)	
	Affected Studies[a]	Unaffected Studies	Affected Studies	Unaffected Studies
Male				
April to September 1988	—	43.8 (8)[b]	—	46.2 (8)
October 1988	62.0 (1)	—	48.3 (1)	—
November 1988 to September 1989	—	52.6 (7)	—	48.7 (7)
October 1989 to June 1990	—	61.2 (5)	—	48.9 (5)
July 1990 to January 1991	72.5 (8)	66.2 (4)	48.0 (8)	49.0 (4)
February 1991 to April 1992	—	68.0 (2)	—	52.8 (2)
Average	71.3	54.8	48.0	48.3
Female				
April to September 1988	—	31.1 (8)	—	44.8 (8)
October 1988	46.0 (1)	—	46.4 (1)	—
November 1988 to September 1989	—	39.9 (7)	—	47.2 (7)
October 1989 to June 1990	—	38.6 (5)	—	45.9 (5)
July 1990 to January 1991	50.9 (8)	54.2 (4)	48.3 (8)	48.0 (4)
February 1991 to April 1992	—	58.0 (2)	—	55.6 (2)
Average	50.3	40.5	48.1	47.0

[a] Includes nine affected studies (those in which hepatitis typical of that associated with *H. hepaticus* infection occurred in many male mice) and 26 unaffected studies
[b] Number of studies is given in parentheses.

TABLE O5
Association of Liver Neoplasm Incidence and Severity of *Helicobacter hepaticus*-Associated Hepatitis in Control B6C3F$_1$ Mice from Nine Affected NTP 2-Year Studies[a]

Severity of Hepatitis	Liver Neoplasm Incidence	
	Males	Females
Absent	101/175 (58%)	196/396 (49%)
Minimal	44/57 (77%)	23/42 (55%)
Mild/moderate	176/218 (81%)	7/11 (64%)
Significance of association	P < 0.05	NS[b]

[a] Affected studies are those in which hepatitis typical of that associated with *H. hepaticus* infection occurred in many male mice.
[b] NS = not significant

TABLE O6
H-*ras* Codon 61 AAA Mutations in Spontaneous Liver Neoplasms in Control B6C3F$_1$ Mice from *Helicobacter hepaticus*-Affected and Unaffected NTP 2-Year Studies

Study	Affected[a]	H-*ras* AAA Mutations
Male		
Cobalt sulfate heptahydrate	+	0/10 (0%)
Chloroprene	+	1/13 (8%)
Triethanolamine	+	1/10 (10%)
Oxazepam	—	7/18 (39%)
Diethanolamine	—	4/16 (25%)
Historical control database		106/333 (32%)
Female		
Chloroprene	+	0/10 (0%)
Triethanolamine	+	1/15 (7%)
Diethanolamine	—	1/11 (9%)
Historical control database		106/333 (32%)

[a] + = affected; — = not affected. Affected studies are those in which hepatitis typical of that associated with *H. hepaticus* infection occurred in many male mice.

TABLE O7
Proliferating Cell Nuclear Antigen Labeling Indices in the Liver of Control B6C3F$_1$ Mice[a]

	Hepatitis	No. of Animals	PCNA Labeling Index[b]	Average PCNA Labeling Index[c]
Male				
Cobalt sulfate heptahydrate[d]	+	15	0.535 ± 0.129	
Chloroprene[d]	+	12	1.452 ± 0.386	
Triethanolamine[d]	+	9	1.215 ± 0.374	1.011
Cobalt sulfate heptahydrate	—	7	0.175 ± 0.117	
Chloroprene	—	10	0.296 ± 0.124	
Triethanolamine	—	12	0.100 ± 0.042	0.186
1-Trans-delta^9-tetrahydrocannabinol[e]	—	15	0.042 ± 0.011	
Scopolamine hydrobromide trihydrate[f]	—	14	0.043 ± 0.012	
Methyleugenol[f]	—	14	0.077 ± 0.020	
Mouse life-span study[f]	—	15	0.217 ± 0.880	
Female				
Cobalt sulfate heptahydrate	+	5	0.161 ± 0.062	
Cobalt sulfate heptahydrate	—	17	0.055 ± 0.015	
Chloroprene	—	12	0.154 ± 0.050	
Triethanolamine	—	12	0.138 ± 0.053	0.108
1-Trans-delta^9-tetrahydrocannabinol	—	13	0.156 ± 0.047	
Scopolamine hydrobromide trihydrate	—	15	0.032 ± 0.009	

[a] A portion of these data are presented in Nyska *et al*. (1997). + = hepatitis present; — = no hepatitis present
[b] Mean ± standard error; PCNA = proliferating cell nuclear antigen
[c] Average of the mean labeling indices for animals from all three studies
[d] Affected study (one in which hepatitis typical of that associated with *H. hepaticus* occurred in many male mice)
[e] Unaffected study (one in which the typical hepatitis did not occur in mice)
[f] Unaffected study with no typical hepatitis, but positive for *H. hepaticus* by polymerase chain reaction-restriction fragment length polymorphism-based assay

TABLE O8
Summary of Target Sites of Carcinogenicity in B6C3F$_1$ Mice from NTP 2-Year Studies with *Helicobacter hepaticus*-Associated Hepatitis

	Males	Females
Chloroprene	Lung Circulatory system[a] Harderian gland Forestomach Kidney	Lung Circulatory system Harderian gland Forestomach Liver Skin Mesentery Zymbal's gland Mammary gland
Cobalt sulfate heptahydrate[b]	Lung	Lung
Triethanolamine	Liver	Liver
AZT[c]	None	Vagina
Sodium xylenesulfonate	None	None
Theophylline	None	None

[a] Hemangioma and hemangiosarcoma of the liver were excluded from the analysis in males.
[b] An apparent treatment-related increase in the incidence of hemangiosarcoma of the liver was discounted in male mice because of the presence of *H. hepaticus*.
[c] AZT = 3′-azido-3′-deoxythymidine. Includes four studies: AZT; α-interferon A/D; AZT/500 U α-interferon A/D; and AZT/5,000 U α-interferon A/D