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

NTP Technical Report on the Toxicology and Carcinogenesis Studies of

Urethane, Ethanol, and Urethane/Ethanol (Urethane, CAS No. 51-79-6; Ethanol, CAS No. 64-17-5) in B6C3F$_1$ Mice (Drinking Water Studies)

NTP TR 510

August 2004

NTP TECHNICAL REPORT

ON THE

TOXICOLOGY AND CARCINOGENESIS

STUDIES OF URETHANE, ETHANOL, AND URETHANE/ETHANOL

(URETHANE, CAS NO. 51-79-6; ETHANOL, CAS NO. 64-17-5)

IN B6C3F$_1$ MICE

(DRINKING WATER STUDIES)

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

August 2004

NTP TR 510

NIH Publication No. 04-4444

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

FOREWORD

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

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

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

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

Details about ongoing and completed NTP studies are available at the NTP's World Wide Web site: http://ntp-server.niehs.nih.gov. Abstracts of all NTP Technical Reports and full versions of the most recent reports and other publications are available from the NIEHS' Environmental Health Perspectives (EHP) http://ehp.niehs.nih.gov (866-541-3841 or 919-653-2590). In addition, printed copies of these reports are available from EHP as supplies last. A listing of all the NTP Technical Reports printed since 1982 appears at the end of this Technical Report.

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The studies on urethane, ethanol, and urethane/ethanol were conducted at the FDA's National Center for Toxicological Research under an interagency agreement between the FDA and the NIEHS. The studies were designed and monitored by a Toxicology Study Selection and Review Committee, composed of representatives from the NCTR and other FDA product centers, NIEHS, and other *ad hoc* members from other government agencies and academia. The interagency agreement was designed to use the staff and facilities of the NCTR in testing of FDA priority chemicals and to provide FDA scientists and regulatory policymakers information for hazard identification and risk assessment.

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CONTENTS

SUMMARY

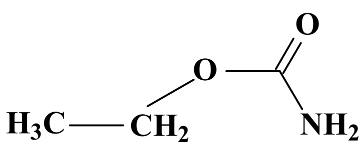
Background Urethane occurs naturally as a by-product of fermentation. The main exposure of humans to urethane is from drinking alcoholic beverages. The International Agency for Research on Cancer has determined that consumption of alcoholic beverages is clearly linked to certain cancers in humans. We studied mixtures of urethane and ethanol (alcohol) to determine if urethane, alone or in combination with ethanol, caused cancer in mice.

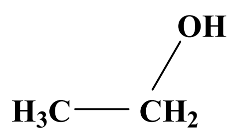
Methods We gave groups of 48 male and female mice drinking water containing combinations of urethane (0, 10, 30, or 90 parts per million) and ethanol (0%, 2.5%, or 5%) for two years. Tissues from more than 40 sites were examined for every animal.

Results There were more deaths and lower body weights in groups of animals exposed to higher concentrations of urethane. Higher concentrations of urethane increased the rates of cancer of the liver, lung, harderian gland, and of hemangiosarcomas in both male and female mice. Urethane also increased the rates of cancer of the skin and forestomach in male mice and of the mammary gland and ovary in female mice. There were also small increases in the occurrence of hemangiosarcoma in the spleen in male mice and in the uterus and skin of female mice.

Conclusion We conclude that urethane caused cancer at several sites in male and female mice. It was not possible to determine from this study whether ethanol alone caused cancer in mice, and there was weak evidence that ethanol may have affected the carcinogenicity of urethane, slightly lowering the incidence of lung and harderian gland tumors in male mice and increasing the incidence of heart and lung tumors in female mice.

ABSTRACT





URETHANE

CAS No. 51-79-6

Chemical Formula: $C_3H_7NO_2$ Molecular Weight: 89.09

Synonyms: Carbamic acid ethyl ester; ethyl carbamate; ethylurethan; ethyl urethan; ethyl urethane; leucothane; pracarbamin; urethan

ETHANOL

CAS No. 64-17-5

Chemical Formula: C_2H_6O Molecular Weight: 46.07

Synonyms: Ethyl alcohol; ethyl hydrate; ethyl hydroxide; absolute alcohol; anhydrous alcohol; dehydrated alcohol; grain alcohol

Urethane (ethyl carbamate) is produced commercially for use in the preparation and modification of amino resins and as a cosolvent during the manufacture of pesticides, fumigants, and cosmetics. It has also been used as a chemical intermediate in the textile industry to impart wash and wear properties to fabrics, as a cosolvent with drugs, and, for a brief period, as an antineoplastic agent for the treatment of chronic leukemia and multiple myeloma. The major source of human exposure to urethane is from fermented foods and beverages. Urethane in combination with ethanol was nominated by the U.S. Food and Drug Administration for in-depth toxicological evaluation by the NTP because of the widespread exposure to urethane in alcoholic beverages and a lack of adequate dose-response carcinogenicity data to conduct meaningful risk assessments. Male and female B6C3F$_1$ mice were exposed to urethane (99% pure) and/or ethanol (92.6% ethanol, 7.4% water) in drinking water for 4 weeks or 2 years.

4-Week Mechanistic Study

Groups of four male and four female mice were exposed to 0, 10, 30, or 90 ppm urethane in the presence of 0%, 2.5%, or 5% ethanol in drinking water *ad libitum* for 4 weeks. Concentrations of 10, 30, and 90 ppm urethane resulted in average daily consumption of approximately 35, 110, and 315 µg urethane for males and 30, 80, and 245 µg for females. Concentrations of 2.5% and 5% ethanol resulted in average daily consumption of approximately 85 and 170 mg ethanol for males and 70 and 130 mg for females. Liver and lung samples were collected for cell proliferation and apoptosis analyses. Additional groups of four male and four female mice were sacrificed after 4 weeks of exposure; liver and lung samples were collected for induction of glutathione, cytochromes P450 and P450 2E1, and DNA adduct formation, and blood was collected for measurement of urethane and ethanol serum concentrations.

Terminal group mean body weights were not affected by either urethane or ethanol. Increasing the urethane concentration had no effect on water consumption by mice. Increasing the ethanol concentration caused a significant decrease in water consumption by males. Increasing the ethanol concentration caused a significant exposure-related decrease in feed consumption by males.

Urethane was detected in the serum of mice exposed to 30 or 90 ppm urethane and 5% ethanol; ethanol was not detected in any of the samples. The percentage of hepatocytes in the G_0 phase was decreased and the percentage

in the G_1 phase was increased in females exposed to 30 or 90 ppm urethane; this effect was independent of the ethanol concentration. The percentage of PCNA-labeling was decreased in the lung of mice exposed to 30 or 90 ppm urethane, and the effect was independent of the ethanol concentration. Increasing the concentration of ethanol caused an exposure-related increase in cytochrome P450 2E1 activity and an exposure-related decrease in glutathione content in the liver of females; these parameters in females exposed to 2.5% or 5% ethanol were significantly greater or less than those in the controls; the changes were independent of the urethane concentration. Etheno-dA adduct concentrations in hepatic DNA were significantly increased by exposure to urethane and decreased by exposure to ethanol.

2-Year Study

Groups of 48 male and 48 female mice were exposed to 0, 10, 30, or 90 ppm urethane in the presence of 0%, 2.5%, or 5% ethanol in drinking water *ad libitum* for 2 years. Concentrations of 10, 30, and 90 ppm urethane resulted in average daily consumption of approximately 40, 115, and 360 µg urethane for males and 35, 105, and 325 µg for females. Concentrations of 2.5% and 5% ethanol resulted in average daily consumption of approximately 100 and 180 mg ethanol for males and 80 and 155 mg for females.

Survival, Body Weights, and Water Consumption

Urethane caused an exposure-related decrease in survival of mice. Ethanol caused a marginal exposure-related increase in survival of males, but had no effect on survival of females. Mean body weights of mice exposed to increasing concentrations of urethane and 0%, 2.5%, or 5% ethanol showed evidence of urethane-induced reductions in body weights, especially in female mice. Mean body weights of mice exposed to 90 ppm urethane and 0%, 2.5%, or 5% ethanol were generally decreased during the last 24 weeks of the study; in addition, females exposed to 10 or 30 ppm urethane and 2.5% ethanol or 0, 10, or 30 ppm urethane and 5% ethanol had generally reduced body weights during this time period. Water consumption by mice exposed to increasing concentrations of urethane and 0%, 2.5%, or 5% ethanol was unchanged throughout the study; water consumption by mice exposed to increasing concentrations of ethanol and 0, 10, 30, or 90 ppm urethane was generally decreased throughout the studies. This ethanol-induced reduction in water consumption was more marked in males than in females.

Pathology Findings

Exposure to increasing concentrations of ethanol and 0, 10, 30, or 90 ppm urethane caused an exposure-related decrease in liver weights of males. The incidences of hemangiosarcoma of the liver in mice exposed to 90 ppm urethane and 0%, 2.5%, or 5% ethanol were significantly increased. The incidences of hepatocellular neoplasms were significantly increased in males exposed to 30 or 90 ppm urethane and 0% ethanol or 90 ppm urethane and 2.5% ethanol. In female mice, an increase in the concentration of urethane in the presence of 0%, 2.5%, or 5% ethanol caused an exposure-related increase in the incidences of hepatocellular neoplasms. The incidences of hepatocellular neoplasms were higher in males exposed to greater concentrations of ethanol and 0 ppm urethane (hepatocellular adenoma: 0% ethanol, 7/46; 2.5% ethanol, 12/47; 5% ethanol, 19/48; hepatocellular adenoma or carcinoma: 12/46, 16/47, 25/48). Nonneoplastic liver lesions related to urethane exposure occurred in male and female mice.

Incidences of alveolar/bronchiolar neoplasms were higher in mice exposed to greater concentrations of urethane and 0%, 2.5%, or 5% ethanol. The incidences of alveolar/bronchiolar adenoma or carcinoma (combined) increased in females exposed to increasing concentrations of ethanol and 10 ppm urethane, and the incidence was significantly increased in females exposed to 5% ethanol. Incidences of alveolar/bronchiolar adenoma decreased in males exposed to ethanol and 10 or 30 ppm urethane.

Incidences of harderian gland neoplasms were higher in mice exposed to greater concentrations of urethane and 0%, 2.5%, or 5% ethanol. The incidences of harderian gland adenoma or carcinoma (combined) were significantly increased in all urethane-exposed groups except in females exposed to 10 ppm urethane and 2.5% ethanol. The incidences of harderian gland neoplasms were decreased in males exposed to ethanol and 30 ppm urethane.

Incidences of adenoacanthoma, adenocarcinoma, and adenoacanthoma or adenocarcinoma (combined) of the mammary gland were higher in females exposed to greater concentrations of urethane and 0%, 2.5%, or 5% ethanol. The incidences of adenocarcinoma were significantly increased at 90 ppm urethane and 0%, 2.5%, or 5% ethanol, and at 30 ppm urethane and 2.5% ethanol; the incidences of adenoacanthoma were significantly increased at 90 ppm urethane and 0% or 5% ethanol.

The incidences of hemangiosarcoma of the heart were significantly higher in males exposed to 90 ppm urethane and 0%, 2.5%, or 5% ethanol and in females exposed to 90 ppm urethane and 5% ethanol; the incidence of this neoplasm in females exposed to 90 ppm urethane and 2.5% ethanol was also increased. Increasing the ethanol concentration in the 90 ppm female group caused an exposure-related increase in the incidence of this neoplasm. Incidences of endothelial hyperplasia and angiectasis of the heart increased in mice exposed to increasing concentrations of urethane and 0%, 2.5%, or 5% ethanol.

The incidences of granulosa cell tumor (benign or malignant) of the ovary were significantly higher in females exposed to 90 ppm urethane and 0% ethanol, and the incidences of benign and benign or malignant (combined) granulosa cell tumor were significantly increased in females exposed to 30 ppm urethane and 5% ethanol. The incidences of angiectasis and thrombosis of the uterus in females exposed to 30 or 90 ppm urethane and 0% or 2.5% ethanol were significantly increased.

The incidences of squamous cell papilloma or carcinoma (combined) of the forestomach were higher in males exposed to greater concentrations of urethane and 0% ethanol, and the incidence in the 90 ppm group was significantly increased.

The incidences of squamous cell papilloma or carcinoma (combined) of the skin were higher in males exposed to greater concentrations of urethane and 0%, 2.5%, or 5% ethanol. The incidence was significantly increased in the 30 and 90 ppm groups in the presence of 0% and 2.5% ethanol and in the 90 ppm group in the presence of 5% ethanol.

Incidences of hemangiosarcoma of the spleen was higher in males exposed to greater concentrations of urethane and 2.5% ethanol and in females exposed to increasing concentrations of urethane and 0% or 2.5% ethanol. The incidence of this neoplasm in females exposed to 90 ppm urethane and 0% ethanol was significantly increased. Urethane also caused slight increases in the incidences of hemangiosarcoma of the uterus and skin in females.

Conclusions

Under the conditions of this 2-year drinking water study, there was *clear evidence of carcinogenic activity** of urethane in male B6C3F$_1$ mice based on increased incidences of liver, lung, harderian gland, skin, and forestomach neoplasms and of hemangiosarcoma, primarily of the liver and heart. There was *clear evidence of carcinogenic activity* of urethane in female B6C3F$_1$ mice based on increased incidences of liver, lung, harderian gland, mammary gland, and ovarian neoplasms and of hemangiosarcoma, primarily of the liver and spleen. The occurrences of hemangiosarcoma of the spleen in males and of the uterus and skin in females may have been exposure related.

Exposure to urethane resulted in increased incidences of nonneoplastic lesions of the liver and heart in males and females and of the uterus in females.

The design of this 2-year drinking water study was inadequate to determine the carcinogenic activity of ethanol in male and female B6C3F$_1$ mice.

Overall, there was weak evidence of an interaction of ethanol in the carcinogenicity of urethane in B6C3F$_1$ mice. In males, increasing the ethanol concentration may have decreased the alveolar/bronchiolar and harderian gland adenoma or carcinoma responses to urethane. In females, increasing the ethanol concentration may have increased the incidence of hemangiosarcoma of the heart and alveolar/bronchiolar adenoma or carcinoma responses to urethane.

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* Explanation of Levels of Evidence of Carcinogenic Activity is on page 13. A summary of the Technical Reports Review Subcommittee comments and public discussion on this Technical Report appears on page 15.

Summary of the 2-Year Carcinogenesis Study of Urethane and Urethane/Ethanol

	Male B6C3F$_1$ Mice		
	Urethane and 0% Ethanol	**Urethane and 2.5% Ethanol**	**Urethane and 5% Ethanol**
Urethane concentrations in drinking water	0, 10, 30, or 90 ppm	0, 10, 30, or 90 ppm	0, 10, 30, or 90 ppm
Survival rates	27/48, 26/48, 26/48, 8/48	32/48, 30/48, 25/48, 16/48	36/48, 29/48, 25/48, 12/48
Body weights	90 ppm group less than the control group	90 ppm group less than the control group	90 ppm group less than the control group
Nonneoplastic effects	Liver: eosinophilic focus (6/46, 7/47, 19/46, 28/44); angiectasis (0/46, 4/47, 6/46, 17/44) Heart: hyperplasia, endothelium (0/48, 0/48, 4/47, 9/48); angiectasis (0/48, 1/48, 2/47, 11/48)	Liver: eosinophilic focus (6/47, 3/48, 17/46, 22/48); angiectasis (0/47, 0/48, 7/46, 16/48); regeneration (0/47, 1/48, 1/46, 9/48) Heart: hyperplasia, endothelium (0/48, 1/48, 4/47, 9/48); angiectasis (0/48, 0/48, 7/47, 13/48)	Liver: eosinophilic focus (10/48, 9/46, 18/48, 25/48); angiectasis (1/48, 1/46, 8/48, 19/48); regeneration (0/48, 0/46, 3/48, 5/48) Heart: hyperplasia, endothelium (0/47, 0/48, 0/48, 2/48); angiectasis (0/47, 0/48, 1/48, 5/48)
Neoplastic effects	Liver: hemangiosarcoma (1/46, 2/47, 5/46, 13/44); hepatocellular adenoma (7/46, 13/47, 17/46, 17/44); hepatocellular adenoma or carcinoma (12/46, 18/47, 24/46, 23/44) Lung: alveolar/bronchiolar adenoma (4/48, 17/48, 22/47, 34/48); alveolar/bronchiolar carcinoma (1/48, 1/48, 9/47, 9/48); alveolar/bronchiolar adenoma or carcinoma (5/48, 18/48, 29/47, 37/48) Harderian gland: adenoma (3/47, 11/47, 25/47, 28/47); carcinoma (0/47, 1/47, 7/47, 16/47); adenoma or carcinoma (3/47, 12/47, 30/47, 38/47) Heart: hemangiosarcoma (0/48, 0/48, 1/47, 5/48) Forestomach: squamous cell papilloma or squamous cell carcinoma (0/46, 2/47, 3/44, 5/45) Skin: squamous cell papilloma or squamous cell carcinoma (0/47, 1/48, 5/47, 8/48)	Liver: hemangiosarcoma (3/47, 4/48, 3/46, 11/48); hepatocellular adenoma (12/47, 15/48, 16/46, 24/48); hepatocellular adenoma or carcinoma (16/47, 19/48, 17/46, 24/48) Lung: alveolar/bronchiolar adenoma (10/48, 16/48, 19/47, 35/48); alveolar/bronchiolar carcinoma (2/48, 3/48, 8/47, 24/48); alveolar/bronchiolar adenoma or carcinoma (11/48, 19/48, 24/47, 43/48) Harderian gland: adenoma (6/48, 14/48, 21/47, 27/48); carcinoma (0/48, 0/48, 1/47, 16/48); adenoma or carcinoma (6/48, 14/48, 21/47, 38/48) Heart: hemangiosarcoma (0/48, 0/48, 2/47, 4/48) Spleen: hemangiosarcoma (0/46, 0/46, 1/46, 3/46) Skin: squamous cell papilloma or squamous cell carcinoma (0/48, 1/48, 4/46, 7/47)	Liver: hemangiosarcoma (2/48, 2/46, 4/48, 13/48) Lung: alveolar/bronchiolar adenoma (6/48, 8/48, 9/48, 33/48); alveolar/bronchiolar carcinoma (5/48, 4/48, 5/48, 17/48); alveolar/bronchiolar adenoma or carcinoma (11/48, 11/48, 14/48, 40/48) Harderian gland: adenoma (5/47, 12/48, 15/48, 26/45); carcinoma (0/47, 2/48, 2/48, 10/45); adenoma or carcinoma (5/47, 14/48, 17/48, 35/45) Heart: hemangiosarcoma (0/47, 0/48, 1/48, 4/48) Skin: squamous cell papilloma or squamous cell carcinoma (0/48, 2/47, 0/48, 7/48)
Level of evidence of carcinogenic activity		Clear evidence for urethane	

Summary of the 2-Year Carcinogenesis Study of Urethane and Urethane/Ethanol

	Female B6C3F$_1$ Mice		
	Urethane and 0% Ethanol	**Urethane and 2.5% Ethanol**	**Urethane and 5% Ethanol**
Urethane concentrations in drinking water	0, 10, 30, or 90 ppm	0, 10, 30, or 90 ppm	0, 10, 30, or 90 ppm
Survival rates	38/48, 37/48, 27/48, 1/48	39/48, 33/48, 19/48, 8/48	31/48, 32/48, 27/48, 4/48
Body weights	90 ppm group less than the control group	10, 30, and 90 ppm groups less than the control group	0, 10, 30, and 90 ppm groups less than the control group
Nonneoplastic effects	Liver: eosinophilic focus (3/48, 14/47, 32/47, 20/47); angiectasis (0/48, 3/47, 10/47, 24/47); thrombosis (0/48, 1/47, 1/47, 11/47) Heart: hyperplasia, endothelium (1/48, 0/48, 3/48, 6/48) Uterus: angiectasis (0/48, 4/47, 6/48, 7/46); thrombosis (0/48, 1/47, 4/48, 4/46)	Liver: eosinophilic focus (2/47, 20/47, 21/47, 28/46); angiectasis (2/47, 5/47, 7/47, 20/46); thrombosis (1/47, 0/47, 4/47, 9/46); regeneration (0/47, 0/47, 0/47, 2/46) Heart: hyperplasia, endothelium (0/47, 0/47, 3/48, 8/48); angiectasis (0/47, 0/47, 1/48, 4/48) Uterus: angiectasis (1/47, 2/47, 7/48, 9/48); thrombosis (0/47, 0/47, 5/48, 6/48)	Liver: eosinophilic focus (2/48, 26/47, 25/48, 21/48); angiectasis (2/48, 1/47, 5/48, 22/48); thrombosis (0/48, 0/47, 1/48, 8/48); regeneration (0/48, 0/47, 0/48, 3/48) Heart: hyperplasia, endothelium (0/47, 1/48, 3/48, 14/47); angiectasis (0/47, 0/48, 3/48, 4/47)
Neoplastic effects	Liver: hemangiosarcoma (0/48, 0/47, 1/47, 7/47); hepatocellular adenoma (5/48, 10/47, 19/47, 18/47); hepatocellular adenoma or carcinoma (5/48, 11/47, 20/47, 19/47) Lung: alveolar/bronchiolar adenoma (4/48, 6/48, 17/48, 29/47); alveolar/bronchiolar carcinoma (2/48, 4/48, 13/48, 19/47); alveolar/bronchiolar adenoma or carcinoma (6/48, 8/48, 28/48, 39/47) Harderian gland: adenoma (3/48, 10/48, 8/48, 21/48); carcinoma (0/48, 1/48, 11/48, 11/48); adenoma or carcinoma (3/48, 11/48, 19/48, 30/48)	Liver: hemangiosarcoma (1/47, 2/47, 0/47, 7/46); hepatocellular adenoma (6/47, 5/47, 15/47, 23/46); hepatocellular adenoma or carcinoma (7/47, 5/47, 16/47, 23/46) Lung: alveolar/bronchiolar adenoma (5/47, 10/47, 16/48, 28/48); alveolar/bronchiolar carcinoma (0/47, 2/47, 6/48, 23/48); alveolar/bronchiolar adenoma or carcinoma (5/47, 11/47, 21/48, 38/48) Harderian gland: adenoma (2/47, 3/47, 9/46, 19/47); carcinoma (1/47, 3/47, 6/46, 16/47); adenoma or carcinoma (3/47, 5/47, 15/46, 35/47)	Liver: hemangiosarcoma (0/48, 0/47, 0/48, 6/48); hepatocellular adenoma (3/48, 6/47, 16/48, 16/48); hepatocellular adenoma or carcinoma (3/48, 7/47, 16/48, 17/48) Lung: alveolar/bronchiolar adenoma (5/48, 10/48, 18/48, 30/48); alveolar/bronchiolar carcinoma (1/48, 7/48, 9/48, 23/48); alveolar/bronchiolar adenoma or carcinoma (5/48, 17/48, 24/48, 37/48) Harderian gland: adenoma (4/48, 7/48, 6/46, 20/46); carcinoma (1/48, 11/48, 7/46, 10/46); adenoma or carcinoma (5/48, 18/48, 13/46, 29/46)

Summary of the 2-Year Carcinogenesis Study of Urethane and Urethane/Ethanol

	Female B6C3F$_1$ Mice		
	Urethane and 0% Ethanol	**Urethane and 2.5% Ethanol**	**Urethane and 5% Ethanol**
Neoplastic effects (continued)	Mammary gland: adenoacanthoma (0/47, 1/46, 1/46, 11/48); adenocarcinoma (4/47, 3/46, 3/46, 11/48); adenoacanthoma or adenocarcinoma (4/47, 4/46, 4/46, 22/48) Ovary: benign granulosa cell tumor (0/48, 0/46, 2/46, 3/39); malignant granulosa cell tumor (0/48, 0/46, 0/46, 3/39); benign or malignant granulosa cell tumor (0/48, 0/46, 2/46, 5/39) Spleen: hemangiosarcoma (0/48, 0/45, 1/47, 4/46) Uterus: hemangiosarcoma (0/48, 0/47, 0/48, 2/46) Skin: hemangiosarcoma (0/48, 0/48, 0/46, 2/48)	Mammary gland: adenoacanthoma (0/47, 0/45, 2/48, 3/47); adenocarcinoma (4/47, 3/45, 11/48, 14/47); adenoacanthoma or adenocarcinoma (4/47, 3/45, 12/48, 16/47) Heart: hemangiosarcoma (0/47, 0/47, 0/48, 3/48) Spleen: hemangiosarcoma (0/47, 0/46, 0/46, 3/46) Skin: hemangiosarcoma (0/47, 0/47, 0/48, 2/47)	Mammary gland: adenoacanthoma (0/47, 0/48, 1/48, 9/45); adenocarcinoma (3/47, 4/48, 6/48, 15/45); adenoacanthoma or adenocarcinoma (3/47, 4/48, 7/48, 23/45) Heart: hemangiosarcoma (0/47, 0/48, 0/48, 6/47) Ovary: benign granulosa cell tumor (0/46, 0/47, 5/46, 3/45); benign or malignant granulosa cell tumor (0/46, 0/47, 6/46, 3/45)
Level of evidence of carcinogenic activity		Clear evidence for urethane	

Summary of the 2-Year Carcinogenesis Study of Ethanol

	Male B6C3F$_1$ Mice		
	0% Ethanol	**2.5% Ethanol**	**5% Ethanol**
Neoplastic effects	Liver: hepatocellular adenoma (7/46); hepatocellular adenoma or carcinoma (12/46)	Liver: hepatocellular adenoma (12/47); hepatocellular adenoma or carcinoma (16/47)	Liver: hepatocellular adenoma (19/48); hepatocellular adenoma or carcinoma (25/48)
Level of evidence of carcinogenic activity		Inadequate study to determine carcinogenic activity	

EXPLANATION OF LEVELS OF EVIDENCE OF CARCINOGENIC ACTIVITY

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

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

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

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

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

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

NATIONAL TOXICOLOGY PROGRAM BOARD OF SCIENTIFIC COUNSELORS
TECHNICAL REPORTS REVIEW SUBCOMMITTEE

The members of the Technical Reports Review Subcommittee who evaluated the draft NTP Technical Report on urethane, ethanol, and urethane/ethanol on September 5, 2002, are listed below. Subcommittee members serve as independent scientists, not as representatives of any institution, company, or governmental agency. In this capacity, subcommittee members have five major responsibilities in reviewing the NTP studies:

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

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SUMMARY OF TECHNICAL REPORTS REVIEW SUBCOMMITTEE COMMENTS

On September 5, 2002, the draft Technical Report on the toxicology and carcinogenesis studies of urethane, ethanol, and urethane plus ethanol 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 Sciences, Research Triangle Park, NC.

Dr. F.A. Beland, NCTR, introduced the toxicology and carcinogenesis studies of urethane, ethanol, and urethane/ethanol by discussing the uses of the chemicals and the rationale for study, describing the experimental design, reporting on survival and body weight effects, and commenting on compound-related neoplastic and nonneoplastic lesions in mice. In addition, Dr. Beland described two competing hypotheses for possible metabolic interactions between urethane and ethanol, one which could increase the carcinogenic response, the other which could deminish it, and he described the drinking water studies that incorporated combinations of the two chemicals. The proposed conclusions for the 2-year study were *clear evidence of carcinogenic activity* of urethane in male and female B6C3F$_1$ mice, *equivocal evidence of carcinogenic activity* of ethanol in male B6C3F$_1$ mice, and *no evidence of carcinogenic activity* of ethanol in female B6C3F$_1$ mice.

Dr. Piegorsch, the first principal reviewer, questioned whether it would be appropriate to draw conclusions on the potential carcinogenicity of ethanol from this study. Dr. Roberts, the second principal reviewer, shared those concerns but he felt that additional conclusions about the interaction of urethane and ethanol were reasonable.

Dr. Elwell, the third principal reviewer, questioned the inclusion of certain sites such as the spleen, skin, and uterus in the list of hemangiocarcomas considered related to urethane administration. He noted the similarity in carcinogenic effects of urethane, butadiene, and isoprene. Regarding the conclusions, Dr. Elwell suggested that squamous cell neoplasms be added as an effect in male mice in that hemangiosarcomas in the spleen of males and the uterus and skin of females be considered "may have been related" to chemical exposure. He agreed with the conclusion that the data were insufficient to establish an effect of ethanol on the carcinogenicity of urethane.

Dr. Drinkwater observed that underlying several of the reviewers' comments was the question of whether the conclusions should be framed in the same format as standard NTP studies. Dr. Beland replied that the primary intent of these studies was to provide data for risk assessment rather than to serve as a traditional carcinogenicity screen, and thus other forms of conclusion statements could be considered. Dr. C.J. Portier, NIEHS, added that the single-chemical groups of this study might be consistent with the standard carcinogenicity bioassay, and the panel could determine the adequacy of the study design.

Dr. Beland agreed that the incidences of hemangiosarcomas in the spleen, skin, and uterus were not significant, unlike those in the heart and liver. Dr. P.W. Mellick, Pathology Associates, Inc., observed that the overall incidences of hemangiosarcomas for all sites combined were markedly increased in the high dose urethane groups. Dr. Elwell said that the usual approach has been to treat vascular tumors as site specific.

After group discussion on the phrasing for hemangiosarcomas, Dr. Piegorsch proposed that the first portion of the conclusion statement be *clear evidence of carcinogenic activity* in male mice based on increased incidences of liver, lung, harderian gland, skin, and forestomach neoplasms and hemangiosarcomas primarily of the liver and heart. For female mice he proposed *clear evidence of carcinogenic activity* based on increased incidences of liver, lung, harderian gland, mammary gland, and ovarian neoplasms and hemangiosarcomas primarily of the liver and spleen. Hemangiosarcomas of the spleen in males and of the uterus and skin in females may have been exposure related.

For the second portion of the conclusion, Dr. Piegorsch proposed that the design of the 2-year drinking water study was inadequate to determine the carcinogenic potential of ethanol.

For the third portion of the conclusion, the panel had an extensive discussion on whether the term "marginal" best described the changes caused by ethanol in the urethane-induced tumor incidences. Dr. Piegorsch then proposed using the language "the coadministration of urethane and ethanol resulted in alterations in the incidences of some neoplasms that were attributed to urethane alone. In males, increases in ethanol concentration may have decreased the alveolar/bronchiolar and harderian gland adenoma or carcinoma responses to urethane. In females, increasing the ethanol concentration may have increased the incidences of hemangiosarcoma of the heart and alveolar/bronchiolar adenoma or carcinoma response to urethane. Overall, the findings were insufficient to establish a definitive effect of ethanol on the carcinogenicity of urethane in B6C3F$_1$ mice."

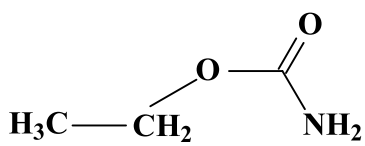
Dr. Boekelheide queried the implications of the word "definitive" in the final sentence of the proposed language for the coadministration study. Dr. Piegorsch suggested replacing it with "interactive." Dr. Piegorsch then moved that the three-part conclusion be adopted. Dr. Boekelheide felt there was an inconsistency between the first and last sentences of the third portion of the conclusion. Dr. Piegorsch suggested changing "resulted in" to "may have affected" in the first sentence. Dr. Klaunig asked if the final sentence could be deleted, and Dr. Roberts argued that without it there would be no conclusion. Dr. Storer proposed adding the word "consistent" before "interactive."

At this point, there was no second to the proposed wording of the third portion of the conclusion, so the panel acted on the first two portions separately. Dr. Klaunig seconded Dr. Piegorsch's motion to adopt the first two portions of the conclusion pertaining to the urethane alone study and the inadequacy of the ethanol alone study. After further discussion, the motion was approved unanimously with 10 votes.

Returning to the third portion of the conclusion pertaining to the coadministration study, Dr. Roberts suggested saying that mice cotreated with urethane and ethanol had altered incidences of some neoplasms. Dr. Boekelheide asked how the language in this report might set precedents for future studies of chemical interactions. Dr. Storer felt using the same levels of evidence categories as for carcinogenicity would be too complex.

For the final sentence, Dr. Ho proposed "Overall there was some evidence of interactive effects of ethanol on the carcinogenicity of urethane in B6C3F$_1$ mice." Dr. Drinkwater suggested the word "equivocal" could replace "some." Dr. Portier stated that the NTP would prefer not to use the same terms as occur in the levels of evidence of carcinogenic activity categories and suggested instead "strong" and "weak" as two levels of interaction. Dr. Piegorsch moved "weak evidence of an interaction" as the conclusion statement. Drs. Storer and Ho thought the teminology was an improvement, and Dr. Klaunig seconded the motion. Dr. Roberts proposed an amendment that the sentence be the first in the paragraph and Dr. Klaunig concurred. The motion was approved unanimously with 10 votes.

INTRODUCTION

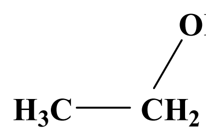


URETHANE

CAS No. 51-79-6

Chemical Formula: $C_3H_7NO_2$ Molecular Weight: 89.09

Synonyms: Carbamic acid ethyl ester; ethyl carbamate; ethylurethan; ethyl urethan; ethyl urethane; leucothane; pracarbamin; urethan



ETHANOL

CAS No. 64-17-5

Chemical Formula: C_2H_6O Molecular Weight: 46.07

Synonyms: Ethyl alcohol; ethyl hydrate; ethyl hydroxide; absolute alcohol; anhydrous alcohol; dehydrated alcohol; grain alcohol

Chemical and Physical Properties of Urethane, and Production, Use, and Human Exposure

Urethane (ethyl carbamate), the ethyl ester of carbamic acid, is an odorless, white crystalline powder that is produced commercially for use in the preparation and modification of amino resins and as a cosolvent during the manufacture of pesticides, fumigants, and cosmetics (IARC, 1974). It has also been used as a chemical intermediate in the textile industry to impart wash and wear properties to fabrics (IARC, 1974), as a cosolvent with drugs (Nomura, 1975), and, for a brief period, as an antineoplastic agent for the treatment of chronic leukemia and multiple myeloma (IARC, 1974). Urethane has also been identified in the food supply as an inadvertent by-product of fermentation (IARC, 1974).

The major source of human exposure to urethane is from fermented foods and beverages, and it is estimated that the average daily intake for adults is 10 to 20 ng urethane/kg body weight, assuming the major source of urethane is from bread (Schlatter and Lutz, 1990; Zimmerli and Schlatter, 1991). Smoking twenty cigarettes per day can double this amount, while the consumption of 30 mL of some stone-fruit brandies can increase daily intake 60-fold. Surveys of urethane concentrations in various food products have been presented by Clegg *et al.* (1988), Canas *et al.* (1989), Dennis *et al.* (1989), Battaglia *et al.* (1990), Dunn *et al.* (1991), Vahl (1993), and Haddon *et al.* (1994).

Pharmacodynamics of Urethane

In early pharmacodynamic studies of urethane, rats and mice were typically treated intravenously, intraperitoneally, or dermally instead of orally, the usual route of human exposure. Regardless of the route of administration, urethane underwent a rapid systemic distribution, including to the fetuses of pregnant mice (Boyland and Nery, 1965; IARC, 1974). In mice, an estimated 90% of the administered dose of [carboxy-^{14}C]-urethane and [methylene-^{14}C]-urethane was excreted as exhaled $^{14}CO_2$ within 24 hours. During the same time period, approximately 6% of the total ^{14}C remained in the body, and a similar amount was excreted in the urine (Mirvish, 1968; IARC, 1974); less than 1% was eliminated in the feces (Mirvish, 1968).

In subsequent studies, Fossa *et al.* (1985) compared the distribution and binding of [ethyl-1-^{14}C]-urethane in male SENCAR and BALB/c mice. Mice were fasted

24 hours and treated with 100 mg/kg urethane either orally in water or dermally in acetone. Total tissue radioactivity in the skin, liver, lung, and stomach was measured at selected times. Peak absorption occurred at the first sampling (1 hour) regardless of strain or route of administration. One hour after oral dosing, SENCAR mice absorbed two to three times more [^{14}C]-urethane than did BALB/c mice; however, this difference was not evident at the later time periods (6, 12, 24, and 48 hours). When [^{14}C]-urethane was applied dermally, there was a consistently greater binding of urethane to protein, RNA, and DNA in the skin of BALB/c mice than in the skin of SENCAR mice. Because SENCAR mice are more susceptible to urethane-initiated skin papillomas than BALB/c mice, this suggests that factors in addition to macromolecular binding contribute to the carcinogenic response.

Nomeir *et al.* (1989) determined the absorption, distribution, and excretion of urethane in male F344 rats and male B6C3F$_1$ mice that received 475 µg/kg to 475 mg/kg [carbonyl-^{14}C]-urethane orally by gavage or by intravenous injection. Tissues, including blood, lung, liver, skin, fat, muscle, and kidneys were assayed for radioactivity 15 minutes to 72 hours after treatment. In rats dosed intravenously with 47.5 mg/kg [carbonyl-^{14}C]-urethane, the highest levels of radioactivity were found in the kidneys, the lowest in fat, and radioactivity in all other tissues was similar. The maximum levels of radioactivity in fat and skin occurred 2 hours after dosing; in all other tissues, the peak levels were observed 15 minutes after treatment. At 475 mg/kg, maximum levels of radioactivity in all tissues occurred 2 hours after dosing; again, the kidneys had the greatest amount of radioactivity and fat the least. At both 47.5 and 475 mg/kg, radioactivity rapidly decreased in all the tissues. Mice treated intravenously with 47.5 mg/kg [carbonyl-^{14}C]-urethane had lower peak levels of radioactivity than did rats, and the radioactivity was eliminated at a faster rate in mice. The initial radioactivity levels in the tissues of mice administered 475 mg/kg [carbonyl-^{14}C]-urethane intravenously were similar to the levels in rats; but as with the 47.5 mg/kg dose, the radioactivity was eliminated at a faster rate by mice. The faster elimination of urethane by mice was also observed by Mirvish (1968), who reported elimination rates of 50, 60, 25, and 4 µg/mL per hour for rats, adult Swiss mice, rabbits, and humans, respectively, based on the disappearance of urethane from the blood. Twenty-four hours after treatment, rats administered 47.5 mg/kg [carbonyl-^{14}C]-urethane intravenously had similar tissue levels of radioactivity as those treated orally (Nomeir *et al.*, 1989). At 475 mg/kg, higher levels occurred in rats treated orally, which presumably reflects impaired absorption. Regardless of the route of administration, species, or dose, a minimum of 90% of the ^{14}C derived from urethane was exhaled as $^{14}CO_2$, 2% to 8% was excreted in the urine, 0.3% to 2% was exhaled as volatiles other than carbon dioxide, and 0.3% to 1% was eliminated in the feces. Other than CO_2 and urethane, no metabolite was identified. Saturation of metabolism and elimination occurred after intravenous doses greater than 4.75 mg/kg in rats and 47.5 mg/kg in mice. Urethane elimination was saturated in male outbred Swiss mice at 400 to 1,800 mg/kg (O'Flaherty and Sichak, 1983), and in female NMRI mice at 37.5 mg/kg (Kristiansen *et al.*, 1994). Based on these data, it appears that early investigations of the carcinogenicity of urethane using high-dose, single-treatment protocols probably used doses of urethane that saturated metabolism and clearance.

Neonatal and weanling mice eliminate urethane at a much slower rate than adult mice (Cividalli *et al.*, 1965); the rate of elimination in neonates increases slowly for the first 10 days, then more rapidly from days 15 to 20. The longer retention times in very young mouse liver have been attributed to the lack of an esterase capable of metabolizing urethane to CO_2; this enzyme is active in adult mouse liver (Kaye, 1960; IARC, 1974). Urethane is a far more potent carcinogen to very young mice than to adult mice (Mirvish, 1968), which suggests that the esterase-catalyzed metabolism of urethane is a detoxification pathway.

Metabolism of Urethane

Ninety to ninety-five percent of urethane is metabolized by an esterase to ethanol, CO_2, and NH_3 before it is eliminated (IARC, 1974; Nomeir *et al.*, 1989), while 3% to 4% is excreted in the urine as the parent compound or as *N*-hydroxyurethane, *N*-acetyl-*N*-hydroxyurethane, *N*-acetyl-*S*-ethylcysteine, and *N*-acetyl-*S*-carbethoxycysteine (Boyland and Nery, 1965). Because Cramer *et al.* (1960) demonstrated that metabolic activation of carcinogenic aromatic amines and amides was mediated via an *N*-hydroxylation pathway, finding *N*-hydroxyl urethane metabolites in the urine (Boyland and Nery,

1965) suggested that urethane might be metabolically activated by the same pathway. However, carcinogenicity studies conducted by Kaye and Trainin (1966) showed that *N*-hydroxyurethane had only half the carcinogenic potency of urethane in weanling mice and less than half the potency in neonatal mice. In addition, Mirvish (1968) estimated that 70% of the administered dose of *N*-hydroxyurethane was metabolized by reduction to the parent compound, urethane. Because the majority of *N*-hydroxyurethane is converted to urethane, and because the carcinogenicity of urethane is approximately twice that of its *N*-hydroxy metabolite, it is unlikely that the *N*-hydroxylation pathway plays a major role in the carcinogenicity of urethane.

Studies of structure-activity relationships of urethane and congeners indicated that small structural changes produced large changes in carcinogenicity (Mirvish, 1968). For example, structurally similar alkyl carbamates such as methyl, *n*-propyl, *iso*-propyl, and *n*-butyl carbamate were either not carcinogenic or only weakly carcinogenic. Furthermore, Lawson and Pound (1973) showed that only the ethyl carbons of ethyl carbamate became covalently bound to mouse DNA *in vivo*, and that significant amounts of methyl, *n*-propyl, and *n*-butyl carbamate did not bind to liver DNA. These data, plus observations on the carcinogenicity of vinyl chloride, led Dahl *et al.* (1978) to postulate that urethane was metabolically activated via a C-oxidation pathway, with vinyl carbamate being the proximate carcinogenic metabolite (Figure 1). They further postulated that if vinyl carbamate was formed, it would be further oxidized to the ultimate carcinogen, vinyl carbamate epoxide. In accord with this hypothesis, these investigators reported that vinyl carbamate was 10 to 50 times more carcinogenic than urethane in the skin and lungs of female CD-1 mice. Similar results were subsequently obtained in F344 rats and B6C3F$_1$ mice (Dahl *et al.*, 1980).

Using an approach analogous to that for identifying the presence of the epoxide derivative of vinyl chloride, Ribovich *et al.* (1982) injected B6C3F$_1$ and A/Jax mice with either [ethyl-1,2-^{3}H]-urethane or [ethyl-1-^{14}C]-urethane and demonstrated the presence of 1,*N*^{6}-ethenoadenosine and 3,*N*^{4}-ethenocytidine in hepatic RNA (Figure 1). They further noted that these adducts were derived from metabolic activation of urethane and not the hydrolysis product ethanol, and thus concluded that vinyl carbamate and its epoxide were the carcinogenic metabolites of urethane. This interpretation was supported by the fact that the target tissue levels of RNA adducts derived from vinyl carbamate were greater than those obtained from urethane (Miller and Miller, 1983). In addition, Scherer *et al.* (1986) showed that 7-(2-oxoethyl)deoxyguanosine, isolated from the liver of rats or mice, was formed to a 100-fold greater extent from vinyl carbamate than from urethane.

The synthesis of vinyl carbamate epoxide was first reported by Park *et al.* (1990), who demonstrated its reactivity with adenosine to form 1,*N*^{6}-ethenoadenosine. When injected intraperitoneally into 12-day-old male B6C3F$_1$ mice, vinyl carbamate epoxide resulted in more of this etheno nucleoside in hepatic RNA than in mice treated similarly with vinyl carbamate. Vinyl carbamate epoxide was also a direct mutagen in *Salmonella typhimurium* TA1535, whereas vinyl carbamate required a metabolic system (Leithauser *et al.*, 1990; Park *et al.*, 1990). In subsequent studies, vinyl carbamate epoxide reacted with DNA *in vitro* and *in vivo* to form 7-(2-oxoethyl)-deoxyguanosine, 3,*N*^{2}-ethenodeoxyguanosine, and 1,*N*^{6}-ethenodeoxyadenosine (Park *et al.*, 1993) (Figure 1). It was also a stronger tumor initiator than urethane or vinyl carbamate on the skin of CD-1 mice and in the liver of B6C3F$_1$ mice. More recently, Fernando *et al.* (1996) used immunoaffinity chromatography and ^{32}P-postlabeling analyses to demonstrate the presence of 3,*N*^{4}-ethenodeoxycytidine and 1,*N*^{6}-ethenodeoxyadenosine (Figure 1) in DNA from the lungs and liver of neonatal and adult mice treated with urethane, vinyl carbamate, and vinyl carbamate epoxide. The binding of urethane and vinyl carbamate to hepatic DNA was greater in neonatal mice than in adults, which was consistent with the greater susceptibility of neonatal mice to the carcinogenicity of urethane.

By using competitive substrates, Guengerich and Kim (1991) demonstrated that human liver cytochrome P450 2E1 was a major isoform responsible for the oxidation of urethane and vinyl carbamate. They further showed that the microsomal oxidation of both urethane and vinyl carbamate in the presence of adenosine would lead to the formation of 1,*N*^{6}-ethenoadenosine, and that the rate of conversion was 500 times faster for vinyl carbamate than for urethane. The difference in rate appeared to be the reason for the failure to detect vinyl carbamate as a metabolite of urethane in earlier metabolic studies.

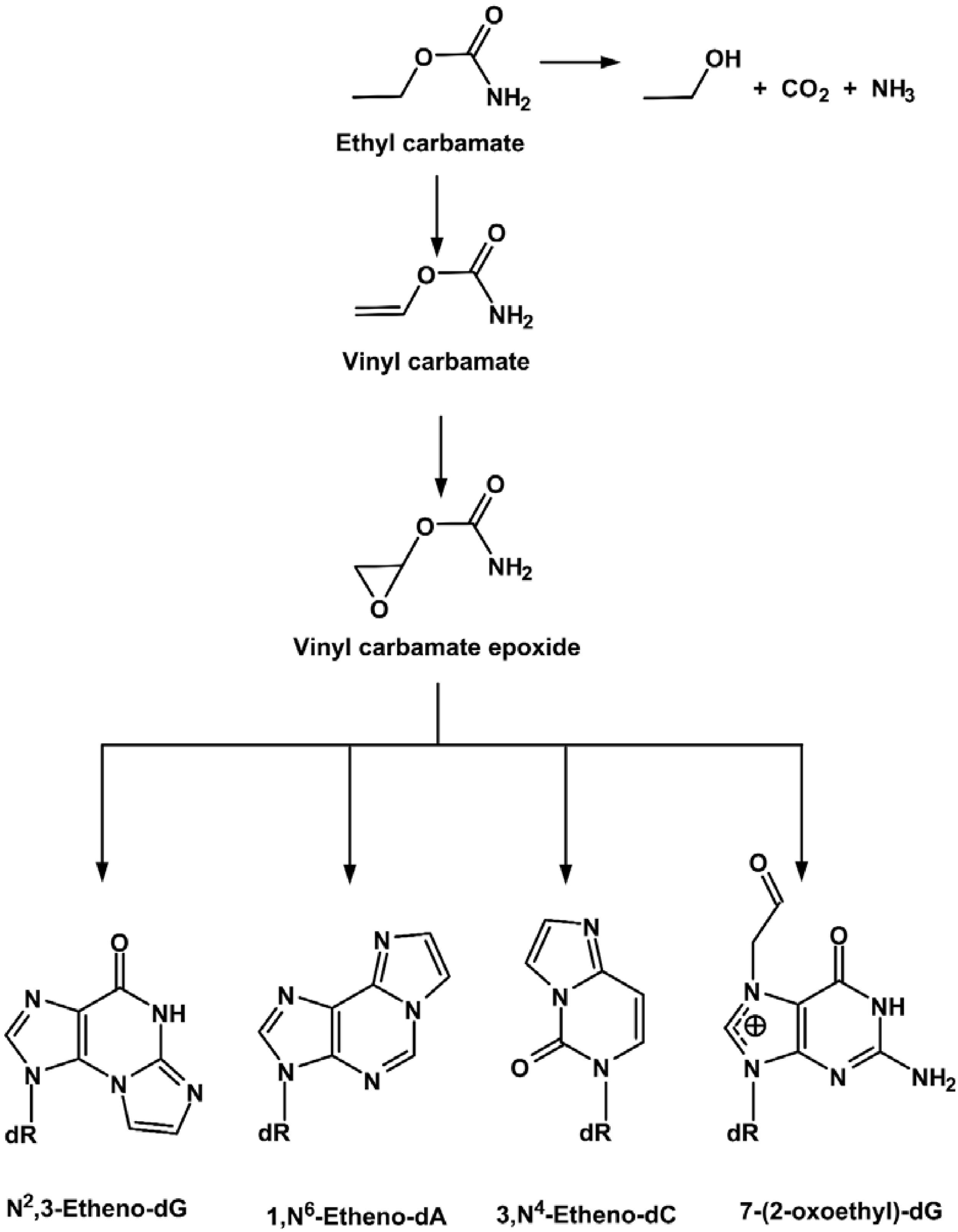


FIGURE 1
Metabolism of Urethane

Carcinogenicity and Metabolism of Ethanol

The carcinogenicity of ethanol was evaluated in rats (Gibel, 1967; Schmähl, 1976; Mendenhall and Chedid, 1980; Radike *et al.*, 1981; Griciute *et al.*, 1986; Takahashi *et al.*, 1986), mice (Horie *et al.*, 1965; Schrauzer *et al.*, 1979; Griciute *et al.*, 1981; Schmidt *et al.*, 1987), and hamsters (McCoy *et al.*, 1981, 1986; Pour *et al.*, 1983). The International Agency for Research on Cancer (IARC, 1988) reviewed these data and concluded that the results were inadequate for the classification of ethanol as a carcinogen in experimental animals. The IARC did feel, however, that there was clear evidence that the consumption of alcoholic beverages by humans was causally related to the occurrence of malignant tumors of the oral cavity, pharynx, larynx, esophagus, and liver. Accordingly, alcoholic beverages were classified as carcinogenic to humans (Group 1). More recently, Holmberg and Ekström (1995) assessed the carcinogenicity of ethanol in Sprague-Dawley rats exposed to 1% or 3% ethanol in the diet and compared them to rats exposed to an isocaloric amount of glucose in a semisynthetic liquid diet. Although there was an increase in mammary tumors in the 1% females, there was no exposure-related increase in tumorigenicity in either sex or in any organ.

The absorption and metabolism of ethanol have been reviewed (IARC, 1988). It is absorbed by simple diffusion and then sequential oxidation to acetaldehyde and acetic acid (Figure 2). The metabolism of ethanol occurs primarily in the liver, where the oxidation to acetaldehyde is catalyzed primarily by alcohol dehydrogenase, and to a lesser extent, by cytochrome P450 and catalase. The carcinogenicity of acetaldehyde has been assessed in rats exposed by inhalation (Woutersen *et al.*, 1986) and in hamsters exposed by inhalation (Feron *et al.*, 1982) and intratracheal instillation (Feron, 1979). Exposure by inhalation resulted in respiratory tract tumors in both species; tumors were not induced after intratracheal administration in hamsters. After considering these results and reviewing epidemiological data, the IARC concluded that acetaldehyde is a carcinogen in experimental animals and possibly carcinogenic in humans (Group 2B) (IARC, 1985, 1987).

Acetaldehyde reacts with the N^2 position of deoxyguanosine to form a Schiff's base that can be detected following reduction to N^2-ethyldeoxyguanosine (Figure 2). N^2-Ethyldeoxyguanosine was found in liver DNA of mice administered ethanol (Fang and Vaca, 1995), in granulocyte and lymphocyte DNA of alcoholic and control human patients (Fang and Vaca, 1997), and in the urine of individuals who had abstained from alcohol consumption (Matsuda *et al.*, 1999). When incorporated into DNA, N^2-ethyldeoxyguanosine led to the misincorporation of deoxyguanosine opposite the lesion (Terashima *et al.*, 2001). This suggests that tumors that arise from acetaldehyde and, by extension ethanol, could result from G to C transversion mutations. More recently, additional DNA adducts of acetaldehyde were characterized (Wang *et al.*, 2000); however, it is not known if these are formed *in vivo*.

Metabolic Interactions of Urethane and Ethanol

The oxidation of urethane to vinyl carbamate and vinyl carbamate epoxide (Figure 1) is catalyzed by cytochrome P450 2E1 (Guengerich and Kim, 1991; Guengerich *et al.*, 1991), an isoform that is induced 5- to 20-fold by ethanol in rats, mice, and humans (Lieber, 1988, 1990; Kurata *et al.*, 1991a; Ingelman-Sundberg *et al.*, 1993). This suggests that chronic ethanol treatment could increase the oxidation of urethane to its epoxide derivative.

Waddell *et al.* (1987) treated fasted adult A/Jax male mice orally with [ethyl-1-^{14}C]-urethane and demonstrated with whole-body autoradiography that concurrent ethanol administration inhibited the localization of urethane 1 hour after treatment. Because more than 90% of the urethane dose in mice was eliminated by metabolism, they postulated that ethanol was interfering with urethane metabolism. The interpretation of these experiments is complicated to some extent by the use of fasted mice because fasting induces cytochrome P450 2E1 (Imaoka *et al.*, 1990), the principal isoform responsible for the metabolism of urethane (Guengerich and Kim, 1991). In a later study, fasted adult male A/Jax mice were dosed orally with [ethyl-1-^{14}C]-urethane dissolved in water or 10% ethanol (Yamamoto *et al.*, 1988). In this study, ethanol inhibited the initial metabolism of urethane and delayed covalent binding of the reactive metabolites for 8 hours, after which urethane metabolism proceeded normally. In addition, blood ethanol concentrations of 15 mg/mL produced complete inhibition of urethane metabolism *in vivo*. This contrasted with *in vitro* experiments in which liver homogenates were only inhibited 50% by 35 mg/mL ethanol, and

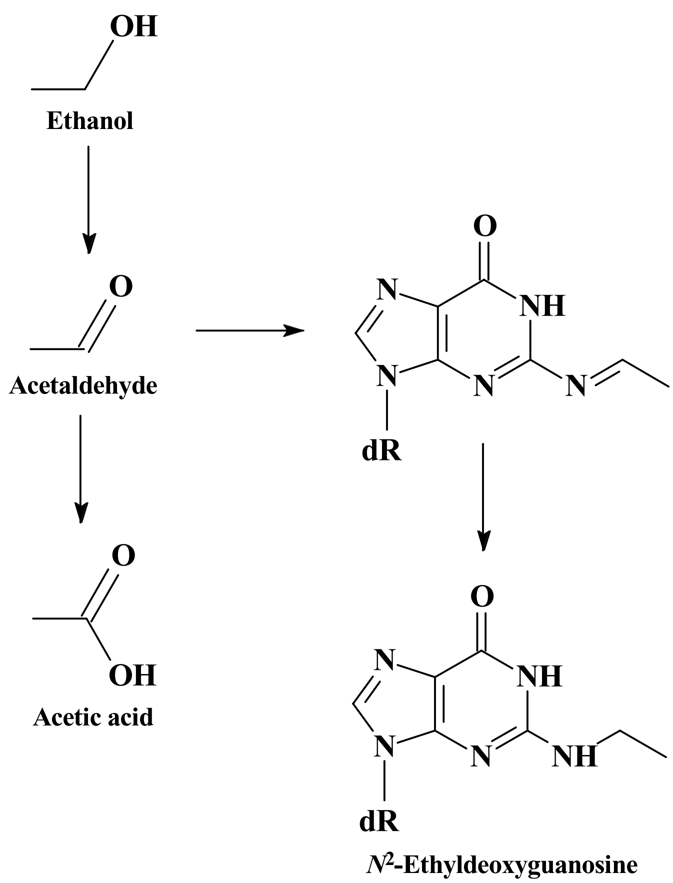


FIGURE 2
Metabolism of Ethanol

suggested that extrahepatic urethane metabolism may occur *in vivo*. The inhibition of urethane metabolism by ethanol was released when the ethanol concentration in blood decreased to approximately 10 mg/mL, at which the metabolism proceeded at apparently normal rates (Kurata *et al.*, 1991b).

To characterize the enzyme systems responsible for the metabolism of urethane, Kurata *et al.* (1990) focused on acetaldehyde as a possible inhibitor of urethane metabolism. Adult male A/Jax mice were treated orally with urethane and immediately given an intraperitoneal injection of acetaldehyde, paraldehyde, or sodium acetate. Additional mice were injected with disulfiram prior to receiving the urethane or with D-penicillamine before and after the urethane treatment. Acetaldehyde and ethanol inhibited urethane metabolism approximately equally for the first 2 hours, and then the effect of acetaldehyde rapidly diminished. The diminution in inhibition by acetaldehyde (compared to ethanol) was attributed to its rapid metabolism (i.e., 3 µmol/g liver per minute). This interpretation was supported by the fact that sodium acetate (the second oxidation product of ethanol metabolism) did not inhibit urethane metabolism, while paraldehyde, which is hydrolyzed to acetaldehyde, produced a more prolonged inhibition than acetaldehyde itself. In addition, D-penicillamine, a compound that sequesters acetaldehyde, abolished the inhibitory effects of acetaldehyde, as did a combination of ethanol and D-penicillamine. Finally, disulfiram, a nonspecific inhibitor of aldehyde dehydrogenase, produced prolonged and stable concentrations of urethane in blood, indicating that urethane may be metabolized by this enzyme. Disulfiram is also an inhibitor of cytochrome P450 2E1 (Parkinson, 1996), which suggests that the oxidation of urethane would also be inhibited.

The temporal relationship between ethanol and urethane administration can result in marked differences in urethane metabolism. For example, when ethanol was given concurrently with urethane, urethane metabolism was inhibited (Waddell *et al.*, 1987); however, when a single dose of urethane was given to adult male A/Jax mice 48 hours after they received 10% ethanol in the drinking water continuously for 36 hours and followed by water without ethanol for the next 12 hours, the metabolism of urethane was enhanced by 50% (Kurata *et al.*, 1991b). In contrast, when 5% ethanol was given for 7 consecutive days and then water without ethanol for 24 hours prior to oral treatment with urethane, the metabolism of urethane was not altered; the same was true when 5 g/kg ethanol was given by gavage 24 and 48 hours prior to an oral dose of urethane. In another study (Carlson, 1994), one group of male adult Sprague-Dawley rats was dosed with ethanol by gavage 1 hour prior to an intraperitoneal dose of urethane. A second group received 10% ethanol in the drinking water for 3 weeks, water without ethanol for the next day, and then an intraperitoneal injection of urethane. The group that received a bolus dose of ethanol 1 hour prior to the urethane dose had greatly diminished urethane metabolism, while the 3-week administration of ethanol had no effect on urethane metabolism measured as exhaled $^{14}CO_2$.

Plasma levels of urethane have been determined in male and female B6C3F$_1$ mice administered 110, 330, or 1,100 ppm urethane in drinking water in the presence or absence of 5% ethanol (NTP, 1996). The average half-life for urethane elimination in male mice was 0.77 hours (range, 0.6 to 0.9 hours) and was not affected by the presence of ethanol. Kinetic values could not be calculated for female mice. In nearly all the plasma samples, the ethanol concentration was below the limit of detection.

Effects of Ethanol on Urethane Carcinogenicity

The effect of ethanol on the tumorigenicity of urethane has been evaluated in three studies. Kristiansen *et al.* (1990) exposed adult female A/Ph mice to 0, 200, 500, or 1,000 ppm urethane in 5%, 10%, or 20% ethanol for 12 weeks. All mice treated with urethane developed lung adenomas, and the multiplicity of these increased in a dose-dependent manner. The coadministration of ethanol decreased the tumor multiplicity in a dose-related manner, and the differences were significant in the 10% and 20% ethanol groups.

Altmann *et al.* (1991) treated groups of adult female NMRI mice daily for 8 weeks by gavage with urethane in water or 20% ethanol. The treatment was discontinued and, after an additional 8 weeks, the mice were killed to assess the extent of lung tumor induction. As with the Kristiansen *et al.* (1990) study, urethane treatment increased the incidence of lung tumors in mice as well as the tumor multiplicity; however, as opposed to the results of Kristiansen *et al.* (1990), the coadministration of ethanol did not decrease the tumor incidence or tumor multiplicity. The failure of Altmann *et al.* (1991)

to detect an ethanol effect may have been due to the fact that the animals were treated by gavage with very small amounts of ethanol compared to studies in which ethanol was given in the drinking water.

In a drinking water study, Stoewsand *et al.* (1991) exposed weanling male C3H/Hej mice to 0, 10, or 20 mg urethane/kg body weight in either water or 12% ethanol for 41 weeks. Urethane caused increases in the incidences of hepatocellular adenoma or carcinoma (combined), hemangioendothelioma, and hemangiosarcoma in the liver, and Clara cell and alveolar adenoma in the lungs. The coadministration of urethane with 12% ethanol significantly decreased the incidence of hepatocellular adenoma in the 10 mg/kg urethane group, but increased (although not significantly) the incidences in the 0 and 20 mg/kg groups. Ethanol also decreased the incidences of hepatocelluar carcinoma in the 10 and 20 mg/kg groups, although the decrease was not significant. Ethanol treatment did not affect the incidence of hemangioendothelioma but did decrease the incidence of hemangiosarcoma, although the difference was not statistically significant except for the 20 mg/kg group. In the lung, ethanol coadministation decreased tumor incidence, and the incidence of Clara cell adenoma was significantly decreased in the 10 mg/kg group.

Urethane was evaluated in a 13-week toxicity study (NTP, 1996). Male and female F344/N rats and B6C3F$_1$ mice were exposed to 0, 110, 330, 1,100, 3,300, or 10,000 ppm urethane in drinking water or in 5% ethanol. Thirty percent of the male rats and 60% of the female rats exposed to 10,000 ppm urethane survived the entire treatment period. All of the male rats and 90% of the female rats also survived the 3,300 ppm treatment. When 10,000 ppm urethane was coadministered with 5% ethanol, 80% of the male rats and none of the female rats survived. Urethane at concentrations of 1,100 ppm or greater caused lymphoid cell depletion, liver lesions, and increased severity of nephropathy and cardiomyopathy in male and/or female rats. None of the mice exposed to 10,000 ppm urethane or 10,000 ppm urethane in 5% ethanol survived. Ninety percent of the male mice and 60% of the female mice given 3,300 ppm urethane in 5% ethanol survived the entire treatment period, whereas none of the mice exposed to 3,300 ppm urethane in water survived. Although ethanol appeared to protect the mice from the toxicities of urethane, the difference in mortality may have been due to a decreased intake of urethane by mice coadministered ethanol. Urethane administered in drinking water to mice induced lung inflammation, alveolar and bronchiolar hyperplasia, nephropathy, cardiomyopathy, lymphoid and bone marrow cell depletion, seminiferous tubule degeneration, ovarian atrophy, and follicular degeneration. In female mice, exposure to 5% ethanol appeared to exacerbate ovarian atrophy. The incidences and severities of alveolar epithelial hyperplasia were slightly increased in mice exposed to urethane in 5% ethanol compared to mice exposed to urethane in drinking water. One 330 ppm male mouse exposed to urethane in drinking water had an alveolar/bronchiolar adenoma; males exposed to 110, 1,100, or 3,300 ppm urethane in 5% ethanol had alveolar/bronchiolar adenomas.

GENETIC TOXICITY

Urethane is a demonstrated mutagen. A review of the extensive published studies of urethane genotoxicity was presented by NTP (1996), along with results of NTP studies. Results from *in vivo* somatic cell assays with urethane were generally positive, with the strongest responses seen in mouse bone marrow micronucleus tests. The results of *in vitro* tests varied among assays; the infrequent positive responses appeared most often with high doses of urethane tested with exogenous metabolic activation in specific cell types under stringent conditions. No mammalian germ cell mutagenicity has been demonstrated for urethane in classical assays, including mouse specific locus and dominant lethal assays (Bateman, 1967; Tutikawa, 1969; Epstein *et al.*, 1972; Russell *et al.*, 1987; NTP, unpublished data). However, there was one report in which mice were exposed to urethane prior to mating, and significantly increased tumor incidences were observed in the F$_1$ offspring (Nomura, 1982). The heritability of these presumed parental germline tumor mutations was demonstrated by breeding the F$_1$ mice and then observing increased tumor incidences in the F$_2$ offspring.

Urethane was mutagenic in *Salmonella typhimurium* strain TA1535 with induced liver S9 enzymes (Zeiger *et al.*, 1992), and it induced sister chromatid exchanges, but not chromosomal aberrations, in Chinese hamster ovary cells with and without S9 enzymes (NTP, 1996). *In vivo*, urethane induced sex-linked recessive lethal mutations and reciprocal translocations in germ cells of male *Drosophila melanogaster* (Foureman *et al.*, 1994). Significantly increased frequencies of micronucleated erythrocytes were observed in peripheral blood obtained from male and female B6C3F$_1$ mice after 45 days of exposure and in bone marrow and peripheral blood obtained after 13 weeks of exposure to urethane in drinking water (Witt *et al.*, 2000).

In contrast to urethane, ethanol is generally considered to be nonmutagenic. It showed little, if any, indication of mutagenic activity in bacterial assays (Zeiger *et al.*, 1992). Chromosomal breakage and aneuploidy have occasionally been reported in eukaryotic cells exposed *in vitro* (Meisner *et al.*, 1970; Badr *et al.*, 1977; Alvarez *et al.*, 1980; de Raat *et al.*, 1983) or *in vivo* (Baraona *et al.*, 1981), particularly when experimental conditions permit generation of the genetically active metabolite acetaldehyde, but most tests for somatic cell chromosomal damage by ethanol were negative (Chaubey *et al.*, 1977; Korte *et al.*, 1979; Jansson, 1982; Banduhn and Obe, 1985). However, there are several reports of ethanol-induced dominant lethal mutations in germ cells of male rats (Klassen and Persaud, 1976; Mankes *et al.*, 1982) and mice (Badr and Badr, 1975; Anderson and Beyler, 1978; James and Smith, 1982; Berryman *et al.*, 1992). The mutagenicity data for ethanol (IARC, 1988; Phillips and Jenkinson, 2001) and for acetaldehyde (Obe and Anderson, 1987) have been reviewed.

Only two experiments investigating genotoxicity after coadministration of urethane and ethanol have been identified, and both were mouse micronucleus tests. Significant increases in micronucleated erythrocytes were observed in male and female mice treated with urethane in 5% ethanol for 13 weeks (NTP, 1996). Choy *et al.* (1996) reported that coadministration of ethanol produced a transient inhibition of micronucleus induction by urethane in mice, but they concluded that there was no reduction in the final magnitude of the urethane response. The NTP (1996) data are consistent with those of Choy *et al.* (1996) in that there appeared to be little difference in the magnitude of the response between mice administered urethane in drinking water and mice administered urethane in 5% ethanol. In both instances, the increases in micronucleus frequencies were highly significant.

Study Design and Dose Selection Rationale

Urethane is carcinogenic in a number of species including rats, mice, hamsters, and monkeys (Mirvish, 1968; Salmon *et al.*, 1991; Thorgeirsson *et al.*, 1994), which suggests a potential carcinogenic risk to humans. Based on experimental and epidemiological data, urethane is classified as a possible human carcinogen (Group 2B) by the IARC (1987). Because of the widespread exposure to urethane in fermented foods and alcoholic beverages and a lack of adequate dose-response carcinogenicity data to conduct meaningful risk assessments, urethane in combination with ethanol was nominated by the U.S. Food and Drug Administration for in-depth toxicological evaluation by the NTP.

The evaluation of urethane and ethanol consisted of a bioassay and ancillary studies to provide mechanistic information. Data in the literature suggested that mice were more sensitive than rats to the tumorigenic effects of urethane (Zeise *et al.*, 1991; NTP, 1996); thus, the studies were restricted to male and female B6C3F$_1$ mice.

The most comprehensive dose response study of urethane in mice has been conducted by Inai *et al*. (1991), who administered 0, 0.6, 3, 6, 60, and 600 ppm urethane in the drinking water to male B6C3F$_1$ mice for 70 weeks. Treatment-related tumors included lung alveolar/bronchiolar adenomas, which were significantly increased at the 60 ppm dose, and lunch carcinomas and liver hemangiomas and angiosarcomas, which were significantly increased at only the 600 ppm dose. Since ethanol has been suggested to increase (NTP, 1996), decrease (Kristiansen *et al*., 1990; Stoewsand *et al*., 1991), or not affect (Altmann *et al*., 1991) the tumorigenicity of urethane, it was considered necessary to have a range of doses that would give both high and low tumor incidencces. Doses of 10, 60, and 90 ppm urethane were felt to meet these criteria and allow a dose response for urethane to be described.

A dose of 5% ethanol was selected as a maximum dose of ethanol based upon concern for decreases in food and/or water consumption and because it is comparable to the concentration of ethanol in a typical drink consumed by humans. A lower dose of 2.5% ethanol was chosen for determining a dose response.

MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF URETHANE AND ETHANOL

Urethane was obtained from Aldrich Chemical Company (Milwaukee, WI) in one lot (09101PN), and ethanol was obtained from AAPER Alcohol (Shelbyville, KY) in one lot (961730BB). Identity, purity, and stability analyses were conducted by the study laboratory (Appendix I).

Lot 09101PN, a white crystalline solid, was identified as urethane by ^{1}H- and ^{13}C-nuclear magnetic resonance (NMR) spectroscopy and mass spectrometry (MS). Lot 961730BB, a clear liquid, was identified as ethanol by ^{1}H- and ^{13}C-NMR spectroscopy. The purity of lots 09101PN and 961730BB were determined by ^{1}H- and ^{13}C-NMR and gas chromatography (GC)/MS (lot 09101PN). The water content of urethane and ethanol was determined by Karl Fischer titration. For urethane, the results of ^{1}H- and ^{13}C-NMR spectroscopy indicated a purity of 99% or greater, and GC/MS indicated a purity of greater than 95% with no minor impurity peaks detected. For ethanol, no impurities other than water were detected; ^{1}H-NMR spectroscopy indicated 92.6% ethanol and 7.4% water. Karl Fischer titration indicated 0.1% water in urethane and 7.4% water in ethanol.

The bulk urethane was stored in sealed plastic bags in glass dessicators under phosphorus pentoxide at ambient temperature. The bulk ethanol was stored in glass containers at ambient temperature. Stability of urethane and ethanol in aqueous solutions was monitored for 56 (urethane) or 35 (ethanol) days using GC with a flame ionization detector. Concentrations of 10 ppm urethane and 0%, 2.5%, and 5% ethanol and 1% urethane were used to monitor the stability of urethane; concentrations of 2.5% ethanol and water and 2.5% ethanol and 90 ppm urethane were used to monitor the stability of ethanol. No degradation of the bulk chemical was detected.

PREPARATION AND ANALYSIS OF DOSE FORMULATIONS

The dose formulations were prepared once weekly during the 4-week study and approximately every 8 weeks during the 2-year study by mixing urethane with deionized water, ethanol with Millipore-filtered tap water, and then urethane with Millipore-filtered tap water or Millipore-filtered tap water containing ethanol (Table I1).

Periodic analyses of the dose formulations were conducted by the study laboratory using GC as described above. The dose formulations were analyzed once weekly during the 4-week study (Table I2) and approximately every 8 weeks during the 2-year study (Table I3). During the 2-year study, animal room samples of the dose formulations were analyzed approximately every 6 months. Of the urethane dose formulations used during the 4-week study, 90 of 90 were within the target concentrations (± 20% for the 10 ppm or ± 10% for the 30 and 90 ppm dose formulations); of the ethanol dose formulations, 80 of 80 were within the target concentrations (± 20% for the 2.5% or ± 10% for the 5% dose formulations). Of the urethane dose formulations used during the 2-year study, 223 of 228 were within the target concentrations; of the animal room samples analyzed, 35 of 36 were within the target concentrations. Of the ethanol dose formulations, 200 of 203 were within the target concentrations; of the animal room samples analyzed, 31 of 32 were within the target concentrations.

2-YEAR STUDY

Study Design

Groups of 48 male and 48 female mice received 0, 10, 30, or 90 ppm urethane in the presence of 0%, 2.5%, or 5% ethanol in drinking water *ad libitum* for 105 weeks. A 4-week study was conducted separately and consisted of additional groups of four male and four female mice designated for cell proliferation and apoptosis analyses;

additional groups of four male and four female mice were also designated for measurement of induction of liver microsomal cytochromes (P450 and P450 2E1) and glutathione, liver and lung DNA adduct formation, and serum concentrations of urethane and ethanol. Liver, lung, and body weights were measured in four mice per group, and feed and water consumption were measured for all 4-week study mice; the results were combined.

Source and Specification of Animals

In this study, male and female B6C3F$_1$/Nctr BR (C57BL/6N × C3H/HeN MTV$^-$) mice were obtained from the study laboratory's breeding colony. Mice were quarantined for 7 days before the beginning of the study and were approximately 5 weeks old on the first day of the study. The health of the mice was monitored during the studies according to the protocols of the study laboratory's Sentinel Animal Program (Appendix M).

Animal Maintenance

Mice were housed four per cage. Feed and water were available *ad libitum*. Feed and water consumption were measured once per week. Cages were changed once weekly, and racks were changed once monthly. Further details of animal maintenance are given in Table 1. Information on feed composition and contaminants is provided in Appendix L.

Cell Proliferation and Apoptosis Analyses: 4-Week Mechanistic Study

Liver and lung slices (approximately 5 mm thick) were fixed in 10% neutral buffered formalin for 24 hours, processed for 8 hours on a Shandon Pathcenter Tissue+ Processor (Shandon, Inc., Pittsburgh, PA), embedded in paraffin, sectioned to a thickness of 4 µm, and mounted on positive-charged slides. Cell proliferation indices were determined by immunohistochemical localization of proliferating cell nuclear antigen (PCNA), slightly modified from Foley *et al.* (1991). Tissue sections were deparaffinized in xylene and rehydrated with decreasing concentrations of ethanol into phosphate-buffered saline. Endogenous peroxidase was quenched with 3% hydrogen peroxide containing 0.1% sodium azide. The sections were placed in an antigen-retrieval solution consisting of 1% zinc sulfate in deionized water and heated for 7.5 minutes in a 700-watt microwave oven set to full power. A routine streptavidin procedure was performed, beginning with application of 0.5% casein to block nonspecific binding of subsequent antibody and sequential incubation of sections in a mouse monoclonal anti-PCNA antibody (clone PC10, Dako Corp., Carpinteria, CA), biotinylated goat anti-mouse IgG (Boehringer-Mannheim, Indianapolis, IN), and streptavidin-conjugated horseradish peroxidase (Jackson Immunoresearch Laboratories, West Grove, PA). The PCNA-positive cells were visualized by incubating the sections in 3,3′-diaminobenzidine hydrochloride chromogen followed by counterstaining with Mayer's hematoxylin. The stained slides were analyzed with the point counting feature of an image analysis system (Optimas Corporation, Bothell, WA). Approximately 2,000 cells per liver were analyzed to determine the percentage of cells in the G_0, G_1, G_2, S, and M phases of the cell cycle. A similar number of cells were analyzed from the terminal bronchioles in the lung, and the data were reported as percentage of PCNA-labeled cells.

Apoptotic cell indices were determined with an Apoptag detection system (Oncor, Gaithersburg, MD), which measures *in situ* end-labeling of 3′-hydroxy DNA strand breaks localized in apoptotic bodies (Gavrieli *et al.*, 1992). Permeabilized tissue sections were enzymatically labeled with digoxigenin-nucleotide via terminal deoxynucleotidyl transferase and subsequently exposed to horseradish peroxidase-conjugated anti-digoxigenin antibody. Staining was developed with 3,3′-diaminobenzidine, and sections were counterstained with methyl green. Approximately 2,000 cells per liver were analyzed.

Induction of Cytochromes P450 and P450 2E1: 4-Week Mechanistic Study

Liver samples were rinsed in ice-cold saline, blotted, weighed, and homogenized in five volumes of 100 mM Tris-hydrochloride (pH 7.2) buffer containing 50 mM potassium chloride. A 400 µL aliquot of the homogenate was removed, 20 µL of 20% sulfosalicyclic acid was added, and the mixture was vortexed and centrifuged at 2,000 × g for 20 minutes at 4° C. The clear supernatant was stored at –70° C for glutathione determinations. Microsomes were prepared from the homogenate by differential centrifugation described by Leakey *et al.* (1989). The washed microsomal pellets were suspended in 50 mM Tris-hydrochloride (pH 7.2) buffer, without the addition of glycerol, a known substrate for cytochrome P450 2E1, and stored at –80° C. Microsomal protein concentrations were determined using the method of Lowry *et al.* (1951), with bovine serum albumin as the standard. Differential spectrophotometric determinations of liver microsomal total cytochrome P450 were conducted according to Omura and Sato (1964). Liver microsomal cytochrome P450 2E1 activity was assessed by measuring the oxidation of *p*-nitrophenol to 4-nitrocatechol. Incubation conditions were essentially as described by Mishin *et al.* (1996), except that incubation volumes were reduced to 575 µL. Final concentrations in the reaction mixtures were magnesium chloride, 2.5 mM; NADPH, 1 mM; *p*-nitrophenol, 0.1 mM; and microsomal protein, 0.14 mg/mL. Reactions were stopped by addition of trifluoroacetic acid, the pH was raised by addition of 10 N sodium hydroxide as described by Reinke and Moyer (1985), and the reactions were read in duplicate on a Thermomax (Molecular Devices Corp., Sunnyvale, CA) plate reader at 340 nm. Under these conditions, the conversion of *p*-nitrophenol to 4-nitrocatechol was linear with regard to both incubation time and the concentration of microsomal protein. Glutathione was measured by a modification of the spectrophotometric method of Sedlak and Lindsay (1968), which is based on the reductive cleavage of 5,5′-dithiobis(2-nitrobenzoic acid) (DTNB). Aliquots (60 µL) were mixed with 682 µL 100 mM sodium phosphate buffer (pH 8), and 200 µL portions were assayed in triplicate on a Thermomax plate reader at 412 nm after the addition of 25 µL 1 mM DTNB.

DNA Adduct Formation: 4-Week Mechanistic Study

Ethenodeoxyadenosine (etheno-dA) and $^{15}N_3$-etheno-dA were synthesized according to the procedure of Green and Hathway (1978) using 1 M sodium acetate (pH 4.5). After the reaction, the solvent was evaporated under reduced pressure, the residue was dissolved in water, and the adducts were purified by high-performance liquid chromatography (HPLC) and quantified by ultraviolet (UV) spectrometry (Barrio *et al.*, 1972). Ethenodeoxycytidine (etheno-dC) and $^{15}N_5$-etheno-dC were prepared in a similar manner using 200 mM ammonium acetate (pH 3.5). HPLC purifications were conducted by reversed-phase HPLC using a µBondapak C18 column (0.39 cm × 30 cm; Waters Associates, Milford, MA) with an HPLC system consisting of two Waters Model 510 pumps, a Rheodyne Model 7125 injector (Rheodyne, Cotati, CA), and a Waters Model 660 automated gradient controller. The peaks were monitored at 280 nm with a Hewlett-Packard 1050 diode array spectrophotometric detector (Hewlett-Packard, Wilmington, DE). Samples were eluted with a 30-minute linear gradient of 0% to 20% solvent B; solvent A was 10 mM ammonium acetate (pH 5.3), and solvent B was methanol. The flow rate was 2 mL per minute. Etheno-dA eluted at 25 minutes, and etheno-dC eluted at 22 minutes.

The *in vitro*- and *in vivo*-modified DNA samples (approximately 100 µg in 100 to 200 µL total volume) were spiked with the internal standards (10 to 20 pg). Initially, the DNA was hydrolyzed enzymatically to nucleosides with DNase I, followed by snake venom phosphodiesterase and alkaline phosphatase (Heflich *et al.*, 1986). Because unsatisfactory results were obtained, subsequent hydrolyses were conducted with micrococcal nuclease, spleen phosphodiesterase, and nuclease P1. Specifically, the samples were incubated with 2 U micrococcal nuclease (Sigma Chemical Co., St. Louis, MO) and 0.2 U spleen phosphodiesterase (Sigma) for 4 hours at 37° C in 20 mM sodium succinate buffer (pH 6) containing 10 mM calcium chloride. These enzymes were previously dialyzed against water (Randerath *et al.,* 1981). Nuclease P1 (5 µg, Sigma) was then added, and the hydrolysis was continued an additional 2 hours.

The deoxyadenosine present in each hydrolysate was converted to deoxyinosine by the action of adenosine deaminase; more than 99% of the deoxyadenosine was hydrolyzed after 30 minutes using 0.01 units per sample. Etheno-dA and etheno-dC were stable under these conditions. Complete hydrolysis of the DNA to nucleosides was verified using HPLC-UV spectrometry.

Liver and lung etheno DNA adducts were determined by liquid chromatography-electrospray mass spectrometry/mass spectrometry (LC-ES MS/MS) by direct injection of incubations into the LC system. The liquid handling system consisted of an autosampler (AS3500, Dionex, Sunnyvale, CA), two automated switching valves (TPMV, Rheodyne, Cotati, CA), and two HPLC pumps (a Dionex GP40 quaternary gradient pump and a Hewlett Packard 1050 pump, Palo Alto, CA). Valve 1 allowed the gradient pump eluent to either load a sample onto the trap column and then wash it or bypass the trap column and clean the analytical column (Doerge *et al.*, 1999). Valve 2 was used to divert the trap column effluent to either waste or to the analytical column. The gradient pump was used for sample injection, cleanup, and regeneration of the trap and analytical columns; the isocratic pump, containing water:acetonitrile (90:10), was used to backflush the trap column to the analytical column during the analysis and to keep a constant flow of mobile phase going into the mass spectrometer during sample loading and preparation periods. The sample was loaded and washed for 4.5 minutes at 1 mL per minute with 100% water onto a reverse phase trap column (Luna C18, 2 mm × 30 mm, 5 µm, Phenomenex, Torrance, CA), and then the trap column was washed with water:acetonitrile (95:5) for 1.5 minutes at 1 mL per minute to waste. After switching valve 2, the concentrated sample zone was backflushed from the trap column onto the analytical column (Luna C18, 2 mm × 150 mm, 3 µm, Phenomenex) at 200 µL per minute with water:acetonitrile (90:10), and sample components were eluted into the mass spectrometer. When the 12-minute run was finished, valve 2 was switched, and the trap column was cleaned with water:acetonitrile (5:95) for 2 minutes at 1 mL per minute to waste. Valve 1 was then switched, and the analytical column was cleaned with water:acetonitrile (5:95) for 2 minutes at 200 µL/minute. Both valves were switched to their initial positions to equilibrate the trap and analytical columns at the starting mobile phase compositions, and the process was repeated.

Analyses were conducted with a Quattro LC triple quadrupole mass spectrometer (Micromass, Manchester, England) equipped with an ES interface with a source block temperature of 150° C and desolvation temperature of 450° C. Nitrogen gas was used as the desolvation gas (750 L/hour) and nebulizing gas (90 L/hour). Argon was used as the collision gas at a collision cell pressure of 1.5×10^{-3} mBar. Positive ions were acquired in multiple reaction monitoring mode (dwell time = 0.3 seconds, span = 0.02 Da, and interchannel delay = 0.03 seconds) for the $(M+H)^+$ to BH_2^+ transitions for both etheno-dA (m/z 276/160) and etheno-dC (m/z 252/136) and the internal standards, $^{15}N_5$-etheno-dA (m/z 281/165) and $^{15}N_3$-etheno-dC (m/z 255/139). The cone voltage was 25 V for the etheno-dA transitions and 20 V for the etheno-dC transitions. The collision energy was 15 eV for all four transitions.

Urethane and Ethanol Serum Concentrations: 4-Week Mechanistic Study

Blood samples for urethane and ethanol measurements were obtained from between approximately 8:30 and 11:30 over six days. Sixteen animals (four cages) were assayed per day. Each day the ethanol level was constant and the urethane was varied in a random manner. Drinking water was available until the animal was sampled.

Serum urethane was quantified by isotope dilution gas chromatography (GC)/MS according to Hurst *et al.* (1990). Isotopically labeled (^{13}C,^{15}N) urethane was used as the internal standard. Serum ethanol was measured spectrophotometrically using Sigma Diagnostics Ethanol Procedure No. 332-UV and reagents (Sigma). This procedure measures the ethanol concentration by assessing the reduction of NAD to NADH during the alcohol dehydrogenase-catalyzed oxidation of ethanol to acetaldehyde (Poklis and Mackell, 1982). The serum ethanol assays were conducted in quartz 96-well microtiter plates (Molecular Devices Corp.) and NADH was quantified at 340 nm using a Thermomax microplate reader.

Clinical Examinations and Pathology

All animals were observed twice daily. Clinical findings were recorded weekly. Body weights were recorded weekly and at the end of the study.

Complete necropsies and microscopic examinations were performed on all mice. The liver and lung were weighed, and all organs and tissues were examined for grossly visible lesions. All major tissues were fixed and preserved in 10% neutral buffered formalin, processed and trimmed, embedded in Tissue-Prep II, sectioned to a thickness of 4 to 6 µm, and stained with hematoxylin and eosin for microscopic examination. 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 study laboratory's Micropath Data Collection System. The slides, paraffin blocks, and residual wet tissues were sent to the study laboratory's Block and Slide Laboratory for inventory, slide/block match, and wet tissue audit. The slides, individual animal data records, and pathology tables were evaluated by an independent quality assurance group. 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 study, a quality assessment pathologist evaluated slides from all tumors. In addition, slides from the heart, liver, lung, harderian gland, spleen, and thymus of males and females, the adrenal, coagulating, and preputial glands of males, and the ovary and uterus of females were examined.

Differences of opinion were reconciled between the study and quality assessment pathologists. The quality assessment pathologist served as the Pathology Working Group (PWG) chairperson and presented histopathology slides containing 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, the study 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, 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 2-Year Drinking Water Study of Urethane, Ethanol, and Urethane/Ethanol

Study Laboratory
National Center for Toxicological Research (NCTR) (Jefferson, AR)

Strain and Species
$B6C3F_1$/Nctr BR (C57BL/6N × C3H/HeN MTV^-) mice

Animal Source
NCTR breeding colony (Jefferson, AR)

Time Held Before Study
7 days

Average Age When Study Began
5 weeks

Date of First Exposure
March 10-June 9, 1997

Duration of Exposure
105 weeks

Date of Last Exposure
March 8-June 7, 1999

Necropsy Dates
March 9-June 8, 1999

Average Age at Necropsy
110 weeks

Size of Study Groups
48 males and 48 females

Method of Distribution
Animals were distributed randomly into groups of approximately equal initial mean body weights.

Animals per Cage
4

Method of Animal Identification
Ear clip and cage number

Diet
NIH-31 autoclaved pelleted diet (Purina Mills, Richmond, IN), available *ad libitum*

Water
Millipore-filtered water (Jefferson municipal supply) via water bottle, available *ad libitum*

TABLE 1
Experimental Design and Materials and Methods in the 2-Year Drinking Water Study of Urethane, Ethanol, and Urethane/Ethanol

Cages
Polycarbonate (Lab Products, Seaford, DE), changed once weekly

Bedding
Hardwood chips (Northeastern Products, Warrensburg, NY), changed once weekly

Racks
Stainless steel (Allentown Caging Equipment Co., Inc., Allentown, NJ), changed once monthly

Animal Room Environment
Temperature: 72° ± 3° F
Relative humidity: 50% ± 20%
Room fluorescent light: 12 hours/day
Room air changes: 10/hour

Exposure Concentrations
0, 10, 30, or 90 ppm urethane and 0%, 2.5%, or 5% ethanol in drinking water

Type and Frequency of Observation
Observed twice daily; clinical findings and food and water consumption were recorded weekly; mice were weighed once weekly and at the end of the study

Method of Sacrifice
Carbon dioxide asphyxiation

Necropsy
Necropsy was performed on all animals. The liver and lung were weighed.

Histopathology
Complete histopathology was performed on all 2-year study mice. In addition to gross lesions and tissue masses, the following tissues were examined: adrenal gland, bone with marrow, brain, clitoral gland, coagulating gland, ear canal, esophagus, eye, gallbladder, harderian gland, heart with aorta, large intestine (cecum, colon, rectum), small intestine (duodenum, jejunum, ileum), kidney, lacrimal gland, larynx, liver, lung, lymph nodes (mandibular and mesenteric), mammary gland (females only), mesentery, muscle, nose, ovary, pancreas, pancreatic islets, parathyroid gland, pharynx, pituitary gland, preputial gland, prostate gland, salivary gland, sciatic nerve, skin, spinal cord, spleen, stomach (forestomach and glandular), testis with epididymus and seminal vesicle, thymus, thyroid gland, tongue, trachea, urinary bladder, uterus, vagina, and Zymbal's gland.

4-Week Mechanistic Study
Cell Proliferation and Apoptosis Analyses
Additional groups of four male and four female mice were sacrificed after 4 weeks of exposure (October 7-November 5, 1996) to urethane, ethanol, and urethane/ethanol, and liver and lung samples were collected for cell proliferation analyses; liver samples were also used for apoptosis analyses.
Induction of Cytochromes P450 and P450 2E1, Glutathione Concentration, DNA Adduct Formation, and Urethane and Ethanol Serum Concentrations
Additional groups of four male and four female mice were sacrificed after 4 weeks of exposure (November 4-December 13, 1996) to urethane, ethanol, and urethane/ethanol. Liver and lung samples were collected for measurements of induction of cytochromes (P450 and P450 2E1) and glutathione; liver and lung samples were collected for measurements of DNA adduct concentrations; blood was collected from the retroorbital sinus for measurements of serum concentrations of urethane and ethanol.

Liver, lung, and body weights were measured in four mice per group, and feed and water consumption were measured in all 4-week study mice; results were combined.

Statistical Methods

Survival Analyses

The probability of survival was estimated by the product-limit procedure of Kaplan and Meier (1958) and is presented in the form of graphs. Animals found dead of other than natural causes were censored from the survival analyses; animals dying from natural causes were not censored. Statistical analyses for possible dose-related effects on survival used Cox's (1972) method for testing two groups for equality and Tarone's (1975) life table test to identify dose-related trends. All reported P values for the survival effects of urethane are one sided, and those for ethanol and the effect of ethanol on the carcinogenicity of urethane are two sided; the P values are unadjusted. P values < 0.05 were considered significant. P values > 0.05 and < 0.10 were considered marginally significant.

Calculation of Incidence

The incidences of neoplasms or nonneoplastic lesions are presented in Tables A1, A4, B1, B3, C1, C3, D1, D4, E1, E3, F1, and F3 as the numbers of animals bearing such lesions at a specific anatomic site and the numbers of animals with that site examined microscopically. For calculation of statistical significance, the incidences of most neoplasms (Tables A2a through A2e, B2, C2, D2a through D2e, E2, and F2) and all nonneoplastic lesions are given as the numbers of animals affected at each site examined microscopically. Tables A2a through A2e, B2, C2, D2a through D2e, E2, and F2 also give the survival-adjusted neoplasm rate for each group and each site-specific neoplasm. This survival-adjusted rate (based on the Poly-3 method described below) accounts for differential mortality by assigning a reduced risk of neoplasm, proportional to the third power of the fraction of time on study, to animals that do not reach terminal sacrifice.

Analysis of Neoplasm and Nonneoplastic Lesion Incidences

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

This method yields a lesion prevalence rate that depends only upon the choice of a shape parameter for a Weibull hazard function describing cumulative lesion incidence over time (Bailer and Portier, 1988). A value of k=3 was used in the analysis of site-specific lesions. This value was recommended by Bailer and Portier (1988) following an evaluation of neoplasm onset time distributions for a variety of site-specific neoplasms in control F344 rats and B6C3F$_1$ mice (Portier *et al.,* 1986). Bailer and Portier (1988) showed that the Poly-3 test gave valid results if the true value of k was anywhere in the range from 1 to 5. A further advantage of the Poly-3 method is that it does not require lesion lethality assumptions. Variation introduced by the use of risk weights, which reflect differential mortality, was accommodated by adjusting the variance of the Poly-3 statistic as recommended by Bieler and Williams (1993).

Tests of significance included pairwise comparisons of each exposed group with controls and a test for an overall exposure-related trend. Continuity-corrected Poly-3 tests (Haseman, 1984) were used in the analysis of neoplasm incidence, and reported P values are one sided for urethane and two sided for ethanol and the effect of ethanol on the carcinogenicity of urethane. Positive trends are reported with right-tailed P values. Negative trends are reported with left-tailed P values, with the letter N added to indicate a lower incidence as exposure increases P values < 0.05 were considered significant. P values > 0.05 and < 0.10 were considered marginally significant.

The relationship between treatment and nonneoplastic lesion severity was analyzed by the Jonckheere-Terpstra test (Jonckheere, 1954), which is based upon ranks and, therefore, distribution free. This test looks for monotonic trends. Unlike the Poly-3 test, it is not age adjusted, and animals that died early without nonneoplastic lesions or with less severe lesions were counted as though they had full opportunity to develop a more severe nonneoplastic lesion. The P values are one tailed (i.e., only increasing severity with dose will be significant). Pairwise comparisons were conducted using

Williams' modification (Williams, 1986) of Shirley's test (Shirley, 1977), which is based upon ranks and, therefore, distribution free. As with the Jonckheere-Terpstra test, this analysis detects monotonic differences and is not age adjusted. Because the test is monotonic, a mid-dose comparison cannot be significant unless all of the doses greater than it are also significant.

Analysis of Continuous Variables

For the 2-year study, body weights and feed and water consumption comparisons were made on a per cage basis on a subset of measurements sampled at 3-month intervals and were analyzed by analysis of variance (ANOVA); the cage body weight was calculated by averaging the individual animal weights. A mixed model approach (Brown and Prescott, 1999) to repeated measures analysis was used with the following fixed effects employed in the model: urethane concentration, ethanol concentration, and urethane-ethanol interaction term. ANOVA was also used to analyze liver and lung weight, terminal body weight, and the ratio of liver and lung weight to the terminal body weight. Only terminal sacrifice animals were included in this analysis.

For the 4-week study, body weights and feed and water consumption comparisons were made on a weekly basis using the mixed model approach described for the 2-year study. Terminal mean body and organ weights, cell proliferation indexes, concentrations of apoptosis, hepatic cytochromes (P450 and P450 2E1) and glutathione content, etheno DNA adduct concentrations, and serum urethane and ethanol were analyzed by ANOVA. Dunnett's (1955) two-sided test compared exposed group means to the control means. When necessary, data were transformed before the analysis to maintain homogeneous variances, a normal data distribution, or both. P values $<$ 0.05 were considered significant. P values $>$ 0.05 and $<$ 0.10 were considered marginally significant.

Quality Assurance Methods

The studies were conducted in compliance with Food and Drug Administration Good Laboratory Practice Regulations (21 CFR, Part 58). The Quality Assurance Unit of the National Center for Toxicological Research performed audits and inspections of protocols, procedures, data, and reports throughout the course of the studies. Separate audits covered completeness and accuracy of the pathology data, pathology specimens, final pathology tables, and a draft of this NTP Technical Report. Audit procedures and findings are presented in the reports and are on file at the NCTR. The audit findings were reviewed and assessed by the NCTR staff, and all comments were resolved or otherwise addressed during the preparation of this Technical Report.

RESULTS

4-Week Mechanistic Study

Results of the 4-week study are presented in Appendix G. Terminal group mean body weights were not affected by exposure to either urethane or ethanol (Table G1). Increasing the urethane concentration had no effect on water consumption by mice (Table G2). Increasing the ethanol concentration caused a significant decrease in water consumption by males (Table G2). Concentrations of 10, 30, and 90 ppm urethane resulted in average daily consumption of approximately 35, 110, and 315 µg urethane for males and 30, 80, and 245 µg for females. Concentrations of 2.5% and 5% ethanol resulted in average daily consumption of approximately 85 and 170 mg ethanol for males and 70 and 130 mg for females. Increasing the urethane concentration had no effect on feed consumption by mice (Table G3); increasing the ethanol concentration caused a significant exposure-related decrease in feed consumption by males.

Serum concentrations of urethane and ethanol were assessed. Urethane was detected in the serum of males and females exposed to 30 or 90 ppm urethane and 5% ethanol (Table G4); the concentration of urethane in other groups was similar to the detection limit of the assay. Ethanol was not detected in any of the samples. Liver and lung weights were not affected by either urethane or ethanol (Table G5). Increasing the ethanol concentration had no effect on the cell cycle distribution in the liver of males or females (Table G6). The percentage of G_0 cells was decreased and the percentage of G_1 cells was increased in the liver of females exposed to 30 or 90 ppm urethane (Table G6); the percentage of these cells were unchanged in males. The percent of apoptotic cells in the liver was affected by urethane in males, and the effect was significant in the 10 and 30 ppm groups (Table G6); ethanol had no effect on apoptosis in either sex. The percent of PCNA-labeling was decreased in the lung of males and females exposed to 30 or 90 ppm urethane; increasing the ethanol concentration had no effect on the percent of PCNA-labeling in males or females (Table G7). Total cytochrome P450 content, cytochrome P450 2E1 activity, and glutathione content in the liver of males and females were not affected by urethane (Table G8). Increasing the concentration of ethanol caused an exposure-related increase in cytochrome P450 2E1 activity and an exposure-related decrease in glutathione content in females (Table G8); these parameters in females exposed to 2.5% or 5% ethanol were significantly greater or less than those in the controls. Etheno-dA adduct concentrations in hepatic DNA were significantly increased by exposure to urethane and decreased by exposure to ethanol (Table G9); in lung DNA, neither urethane nor ethanol affected etheno-dA or etheno-dC adduct concentrations.

2-Year Study

Survival

Estimates of 2-year survival probabilities for male and female mice exposed to increasing concentrations of urethane and 0%, 2.5%, or 5% ethanol are shown in Tables 2, 3, and 4 and in Kaplan-Meier survival curves (Figures 3 and 4). When analyses were conducted within each exposure concentration of ethanol, significant exposure-related decreases in survival were observed as a function of urethane concentration (Tables 2, 3, and 4). Pairwise comparisons indicated that survival of males exposed to 90 ppm and females exposed to 30 or 90 ppm urethane and 0% ethanol was significantly less than that of the controls (Table 2). In addition, survival of males exposed to 90 ppm and females exposed to 10 ppm or greater urethane and 2.5% ethanol was significantly less than that of the controls (Table 3); survival of males exposed to 30 or 90 ppm and females exposed to 90 ppm urethane and 5% ethanol was significantly decreased (Table 4).

Estimates of 2-year survival probabilities for male and female mice exposed to increasing concentrations of ethanol and 0, 10, 30, or 90 ppm urethane are shown in Table 5 and in Kaplan-Meier survival curves (Figures 5 and 6). When analyses were conducted within each exposure concentration of urethane, a significant exposure-related increase in survival occurred in males exposed to 0 ppm urethane (Table 5). Pairwise comparisons indicated that survival of mice exposed to 2.5% ethanol and 90 ppm urethane and of males exposed to 5% ethanol and 0 ppm urethane was significantly greater than that of the controls (Table 5).

TABLE 2
Survival of Mice in the 2-Year Drinking Water Study of Urethane and 0% Ethanol

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
Male				
Animals initially in study	48	48	48	48
Moribund	2	8	4	11
Natural deaths	19	14	18	29
Animals surviving to study termination	27	26	26	8
Percent probability of survival at end of study[a]	56	54	54	17
Mean survival (days)[b]	667	655	697	626
Survival analysis[c]	P=0.001	P=0.375	P=0.460	P=0.001
Female				
Animals initially in study	48	48	48	48
Moribund	1	3	5	18
Natural deaths	9	8	16	29
Animals surviving to study termination	38	37	27	1
Percent probability of survival at end of study	79	77	56	2
Mean survival (days)	747	740	706	628
Survival analysis	P=0.001	P=0.390	P=0.006	P=0.001

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

Table 3
Survival of Mice in the 2-Year Drinking Water Study of Urethane and 2.5% Ethanol

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
Male				
Animals initially in study	48	48	48	48
Moribund	10	5	7	9
Natural deaths	6	13	16	23
Animals surviving to study termination	32	30	25	16
Percent probability of survival at end of study[a]	67	62	52	33
Mean survival (days)[b]	703	711	657	673
Survival analysis[c]	P=0.001	P=0.390	P=0.078	P=0.002
Female				
Animals initially in study	48	48	48	48
Accidental deaths[d]	4	4	0	0
Moribund	1	4	11	9
Natural deaths	4	7	18	31
Animals surviving to study termination	39	33	19	8
Percent probability of survival at end of study	89	75	40	17
Mean survival (days)	758	733	681	663
Survival analysis	P=0.001	P=0.043	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 control column, and the results of the life table pairwise comparisons (Cox, 1972) with the controls are in the exposed group columns.
[d] Censored from survival analyses

Table 4
Survival of Mice in the 2-Year Drinking Water Study of Urethane and 5% Ethanol

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
Male				
Animals initially in study	48	48	48	48
Moribund	5	6	6	15
Natural deaths	7	13	17	21
Animals surviving to study termination	36	29	25	12
Percent probability of survival at end of study[a]	75	62	52	25
Mean survival (days)[b]	736	687	676	654
Survival analysis[c]	P=0.001	P=0.062	P=0.007	P=0.001
Female				
Animals initially in study	48	48	48	48
Accidental deaths[d]	4	0	0	0
Moribund	6	4	4	11
Natural deaths	7	12	17	33
Animals surviving to study termination	31	32	27	4
Percent probability of survival at end of study	70	67	56	8
Mean survival (days)	741	713	712	645
Survival analysis	P=0.001	P=0.330	P=0.064	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 control column, and the results of the life table pairwise comparisons (Cox, 1972) with the controls are in the exposed group columns.
[d] Censored from survival analyses

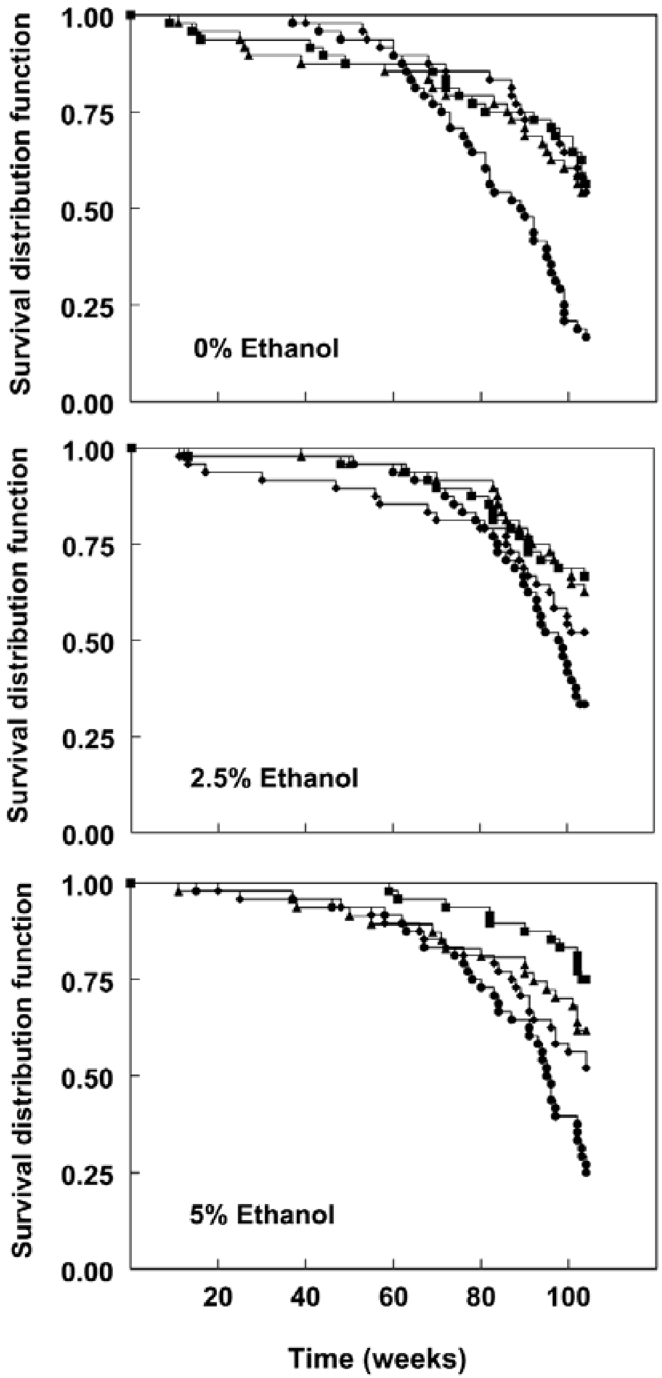


FIGURE 3
Kaplan-Meier Survival Curves for Male Mice Exposed to Urethane and 0%, 2.5%, or 5% Ethanol in Drinking Water for 2 Years (■=0 ppm; ▲=10 ppm; ◆=30 ppm; ●=90 ppm)

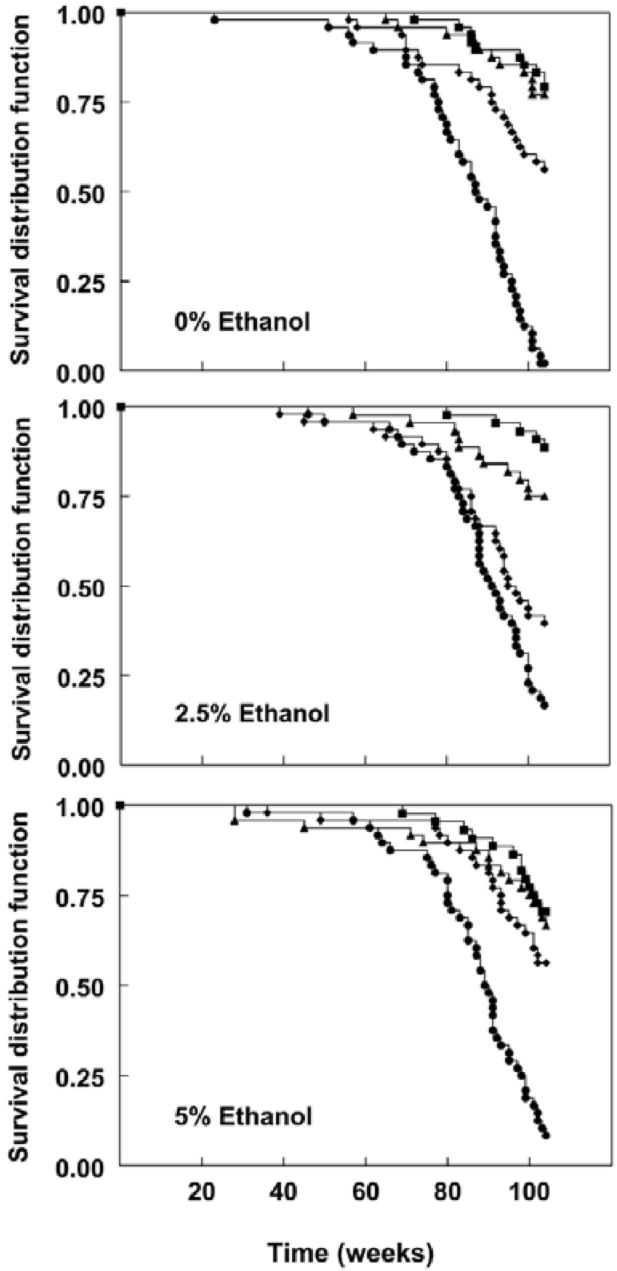


FIGURE 4
Kaplan-Meier Survival Curves for Female Mice Exposed to Urethane and 0%, 2.5%, or 5% Ethanol in Drinking Water for 2 Years (■=0 ppm; ▲=10 ppm; ◆=30 ppm; ●=90 ppm)

Table 5
Survival Analysis of Mice Exposed to Ethanol and 0, 10, 30, or 90 ppm Urethane in Drinking Water for 2 Years[a]

	Urethane (ppm)	0% Ethanol	2.5% Ethanol	5% Ethanol
Male				
Survival analysis[b]				
	0	P=0.043N	P=0.315N	P=0.043N
	10	P=0.408N	P=0.330N	P=0.422N
	30	P=0.732N	P=0.651	P=0.739
	90	P=0.147N	P=0.023N	P=0.151N
Female				
Survival analysis				
	0	P=0.311	P=0.215N	P=0.329
	10	P=0.265	P=0.774	P=0.271
	30	P=0.916N	P=0.101	P=0.917N
	90	P=0.273N	P=0.023N	P=0.221N

[a] The number of animals initially in study; the number of accidental deaths, moribund, and natural deaths; animals surviving to study termination; percent probability of survival at end of study; and mean survival are presented in Tables 2, 3, and 4; P values are two sided.

[b] The result of the life table trend test (Tarone, 1975) is in the 0% ethanol column, and the results of the life table pairwise comparisons (Cox, 1972) with 0% ethanol are in the 2.5% and 5% ethanol columns. A negative trend or a lower mortality in an exposure group is indicated by **N**.

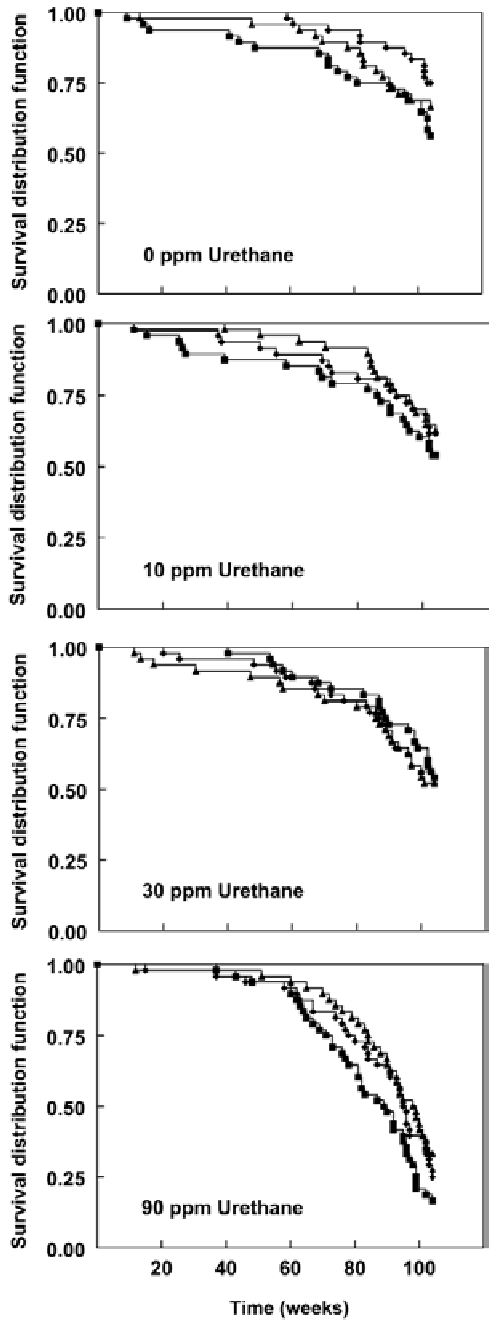


FIGURE 5
Kaplan-Meier Survival Curves for Male Mice Exposed to Ethanol and 0, 10, 30, or 90 ppm Urethane in Drinking Water for 2 Years (■=0%; ▲=2.5%; ◆=5%)

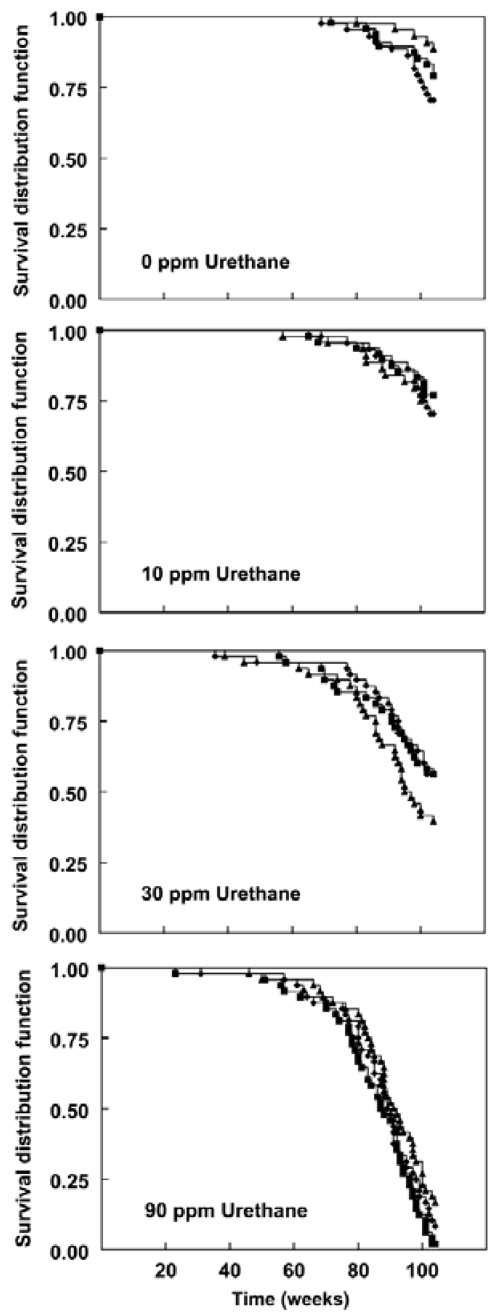


FIGURE 6
Kaplan-Meier Survival Curves for Female Mice Exposed to Ethanol and 0, 10, 30, or 90 ppm Urethane in Drinking Water for 2 Years (■=0%; ▲=2.5%; ◆=5%)

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

Mean body weights of mice exposed to increasing concentrations of urethane and 0%, 2.5%, or 5% ethanol showed evidence of urethane-induced reductions in body weights, especially in female mice (Figures 7 and 8). Mean body weights of mice exposed to 90 ppm urethane and 0%, 2.5%, or 5% ethanol were generally decreased during the last 24 weeks of the study; in addition, females exposed to 10 or 30 ppm urethane and 2.5% ethanol or 0, 10, or 30 ppm urethane and 5% ethanol also had generally reduced body weights during this time period. Urethane, but not ethanol, caused an exposure-related decrease in terminal body weights of mice; terminal body weights were significantly decreased in males and females exposed to 90 ppm urethane and in females exposed to 30 ppm urethane and 2.5% or 5% ethanol (Table H1). Mean body weights of mice exposed to increasing concentrations of ethanol and 0, 10, 30, or 90 ppm urethane were generally unchanged throughout the study (Figures 9 and 10).

Water consumption by mice exposed to increasing concentrations of urethane and 0%, 2.5%, or 5% ethanol was unchanged throughout the study (Tables J1 through J6; Figures 11 and 12). Concentrations of 10, 30, and 90 ppm urethane resulted in average daily consumption of approximately 40, 115, and 360 µg urethane for males and 35, 105, and 325 µg for females. Water consumption by mice exposed to increasing concentrations of ethanol and 0, 10, 30, or 90 ppm urethane was generally decreased throughout the study (Figures 13 and 14). This ethanol-induced reduction in water consumption was more marked in males than in females. Concentrations of 2.5% and 5% ethanol resulted in average daily consumption of approximately 100 and 180 mg ethanol for males and 80 and 155 mg for females.

Feed consumption by mice exposed to increasing concentrations of urethane and 0%, 2.5%, or 5% ethanol was unchanged (Tables K1 through K6; Figures 15 and 16). Feed consumption by mice exposed to increasing concentrations of ethanol and 0, 10, 30, or 90 ppm urethane was generally decreased, and a negative trend occurred in males and females (Figures 17 and 18). There were no clinical findings related to exposure to urethane or ethanol.

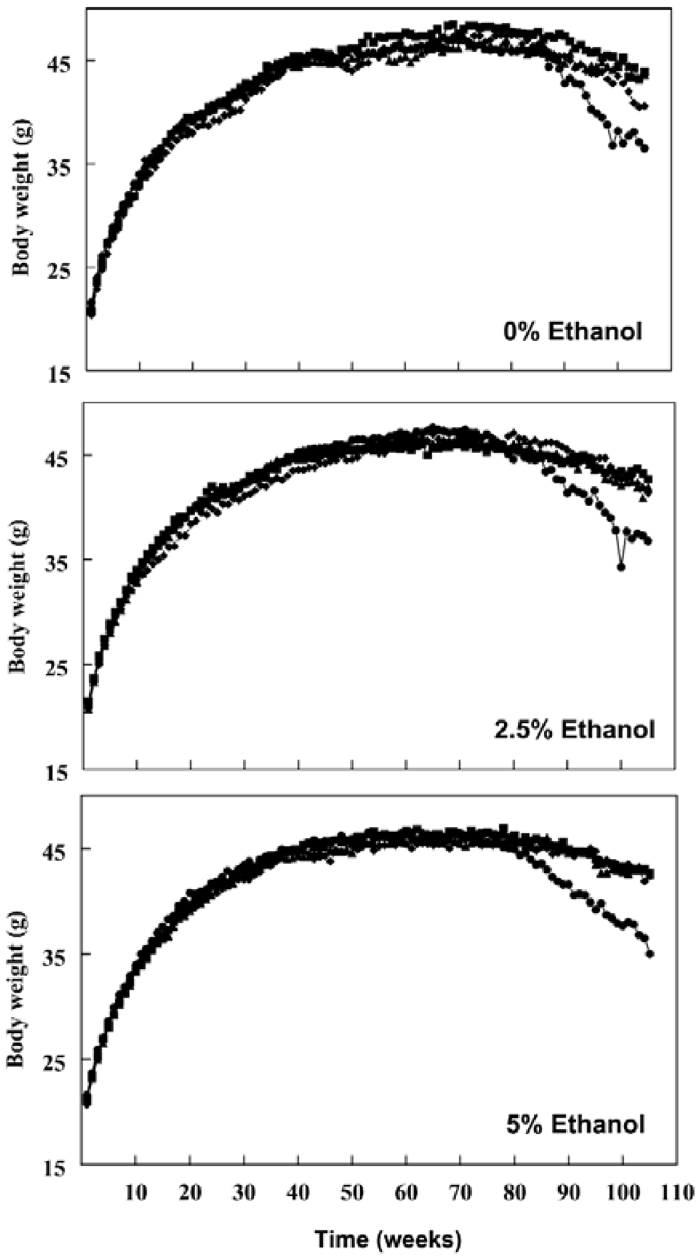


FIGURE 7
Growth Curves for Male Mice Exposed to Urethane and 0%, 2.5%, or 5% Ethanol in Drinking Water for 2 Years (■=0 ppm; ▲=10 ppm; ◆=30 ppm; ●=90 ppm)

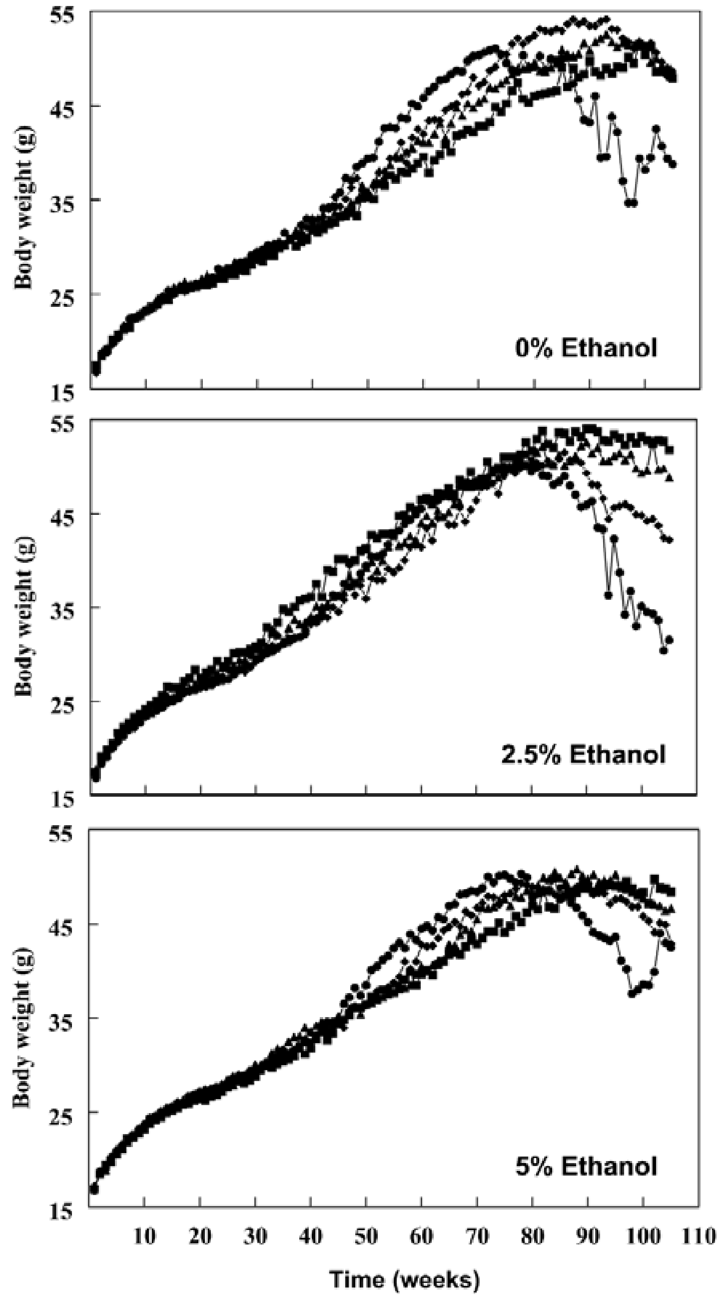


FIGURE 8
Growth Curves for Female Mice Exposed to Urethane and 0%, 2.5%, or 5% Ethanol in Drinking Water for 2 Years (■=0 ppm; ▲=10 ppm; ◆=30 ppm; ●=90 ppm)

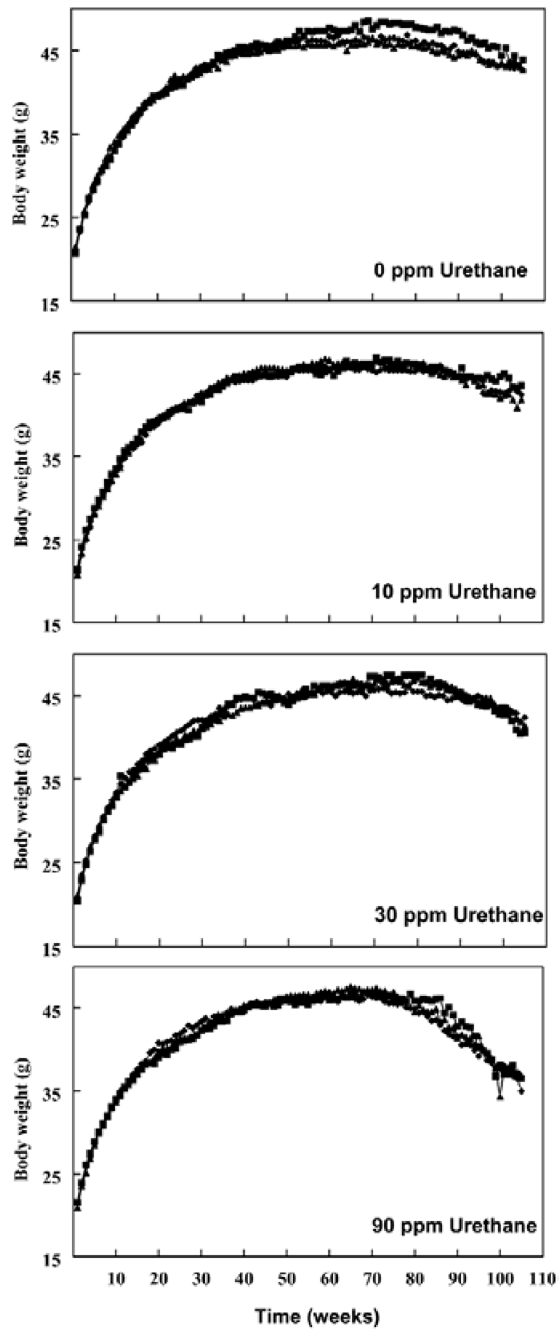


Figure 9
Growth Curves for Male Mice Exposed to Ethanol and 0, 10, 30, or 90 ppm Urethane in Drinking Water for 2 Years (■=0%; ▲=2.5%; ◆=5%)

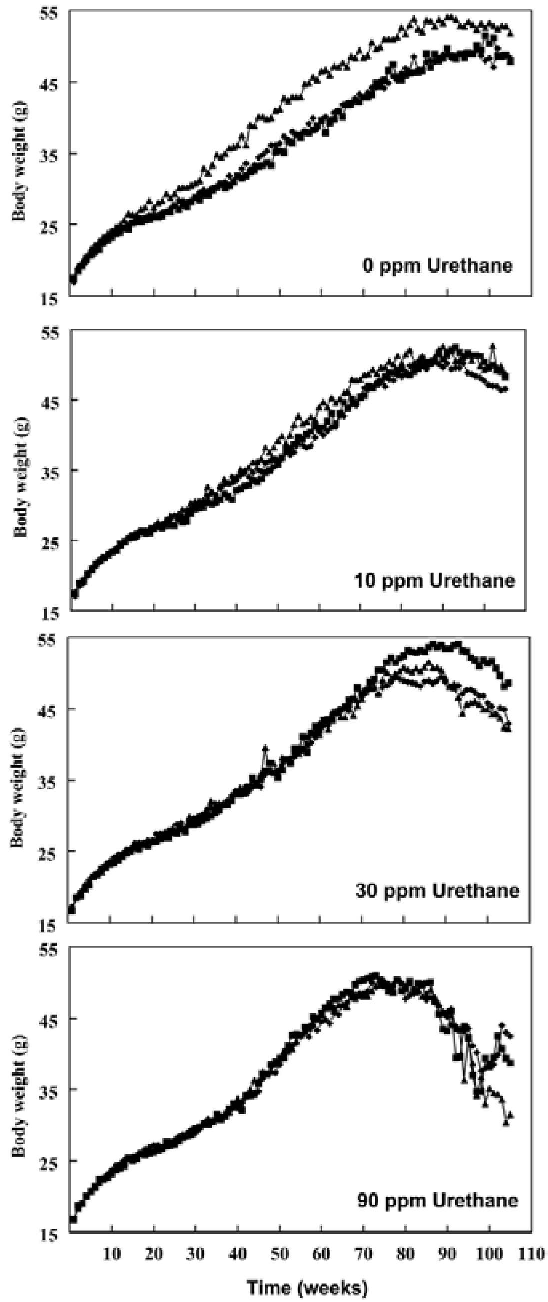


FIGURE 10
Growth Curves for Female Mice Exposed to Ethanol and 0, 10, 30, or 90 ppm Urethane in Drinking Water for 2 Years (■=0%; ▲=2.5%; ◆=5%)

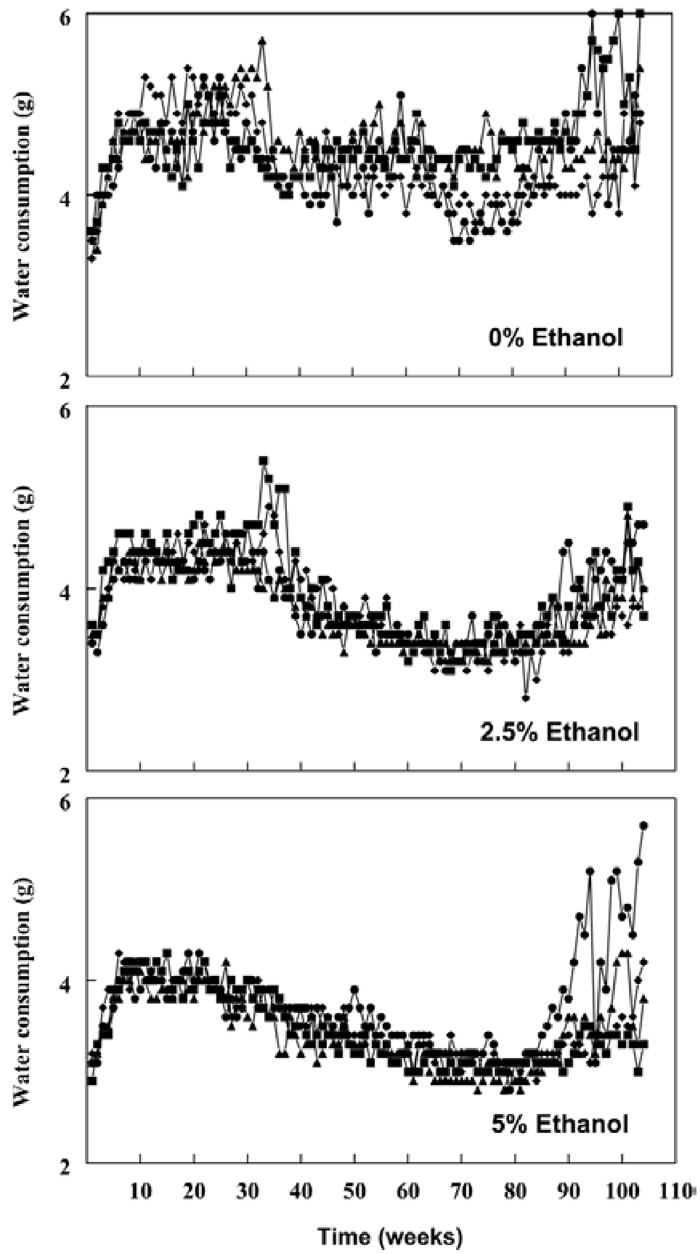


FIGURE 11
Water Consumption by Male Mice Exposed to Urethane and 0%, 2.5%, or 5% Ethanol in Drinking Water for 2 Years (■=0 ppm; ▲=10 ppm; ◆=30 ppm; ●=90 ppm)

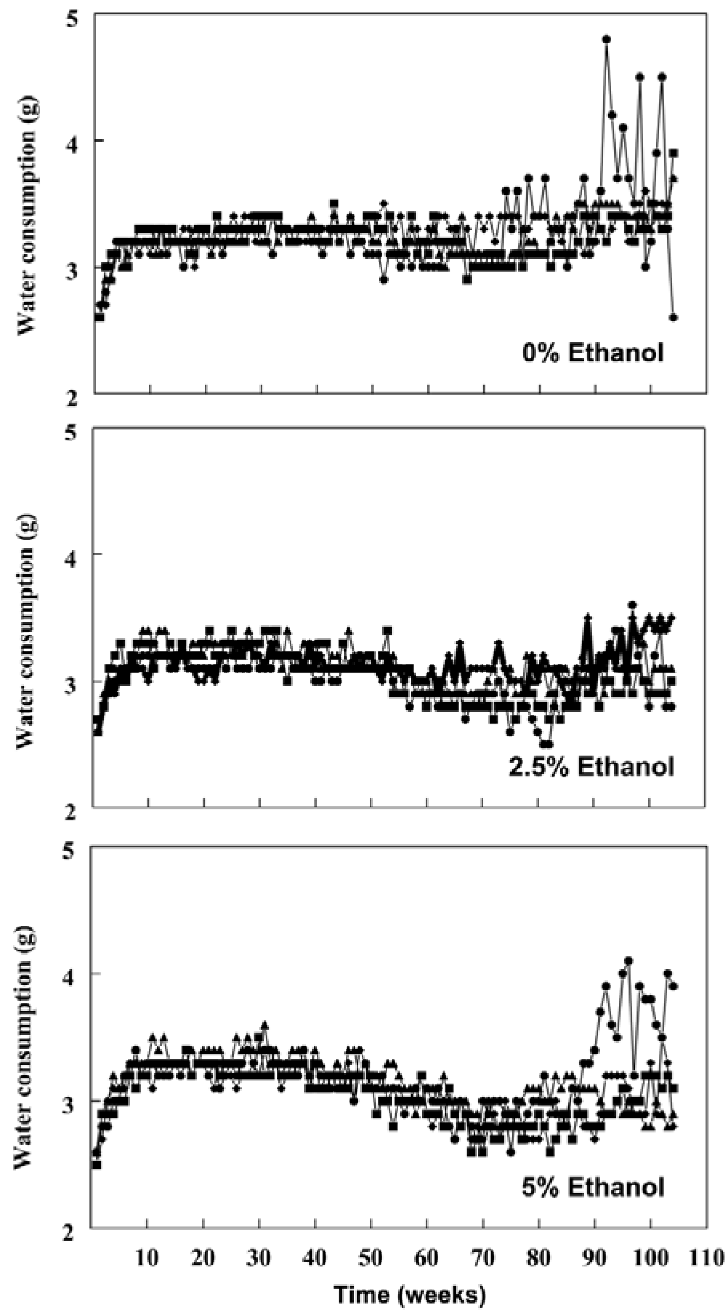


FIGURE 12
Water Consumption by Female Mice Exposed to Urethane and 0%, 2.5%, or 5% Ethanol in Drinking Water for 2 Years (■=0 ppm; ▲=10 ppm; ◆=30 ppm; ●=90 ppm)

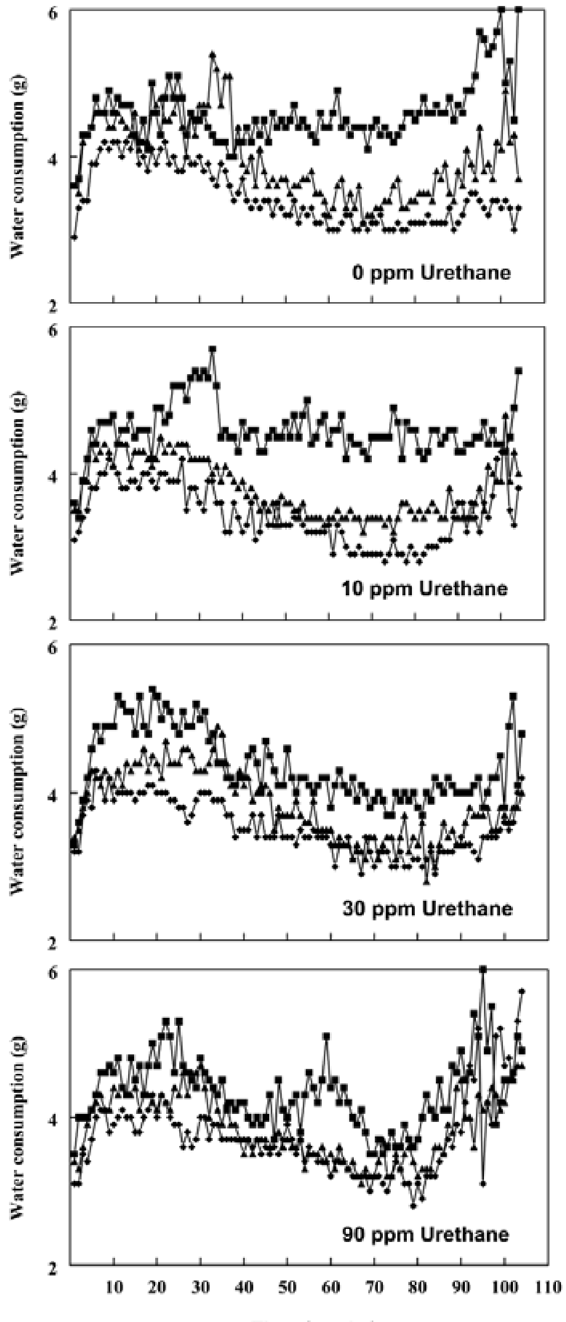


FIGURE 13
Water Consumption by Male Mice Exposed to Ethanol and 0, 10, 30, or 90 ppm Urethane in Drinking Water for 2 Years (■=0%; ▲=2.5%; ◆=5%)

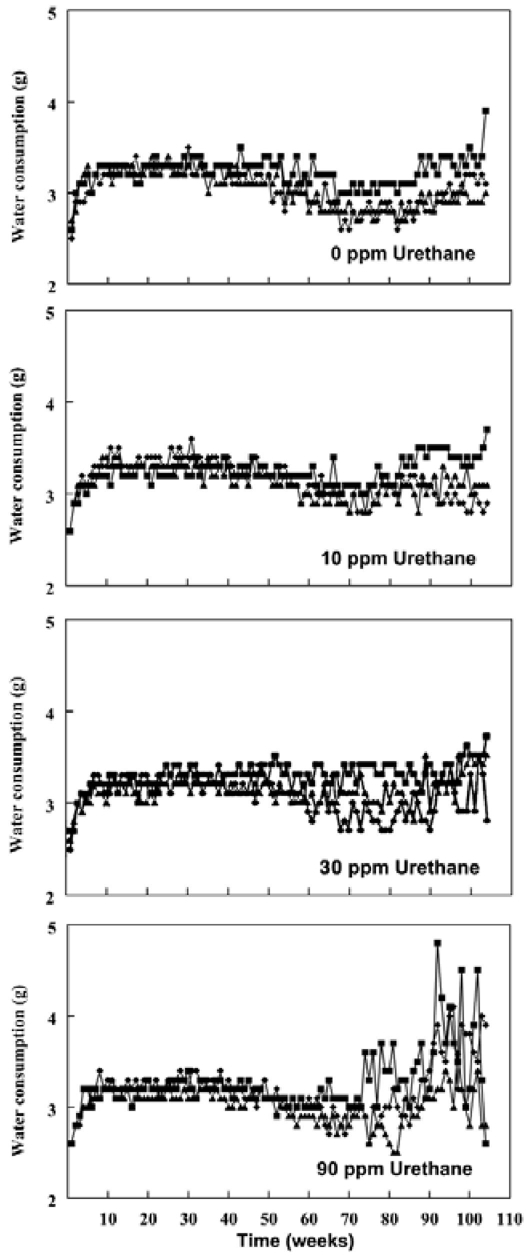


FIGURE 14
Water Consumption by Female Mice Exposed to Ethanol and 0, 10, 30, or 90 ppm Urethane in Drinking Water for 2 Years (■=0%; ▲=2.5%; ◆=5%)

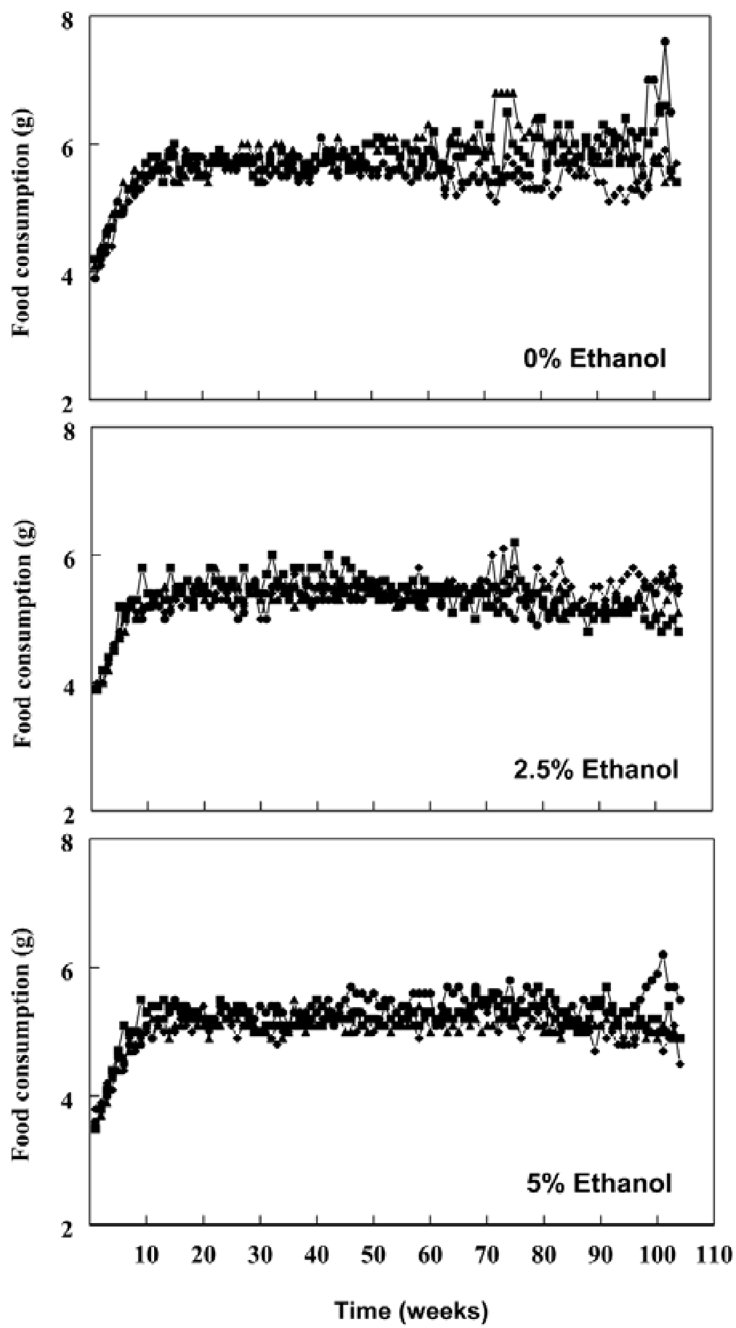


FIGURE 15
Feed Consumption by Male Mice Exposed to Urethane and 0%, 2.5%, or 5% Ethanol in Drinking Water for 2 Years (■=0 ppm; ▲=10 ppm; ◆=30 ppm; ●=90 ppm)

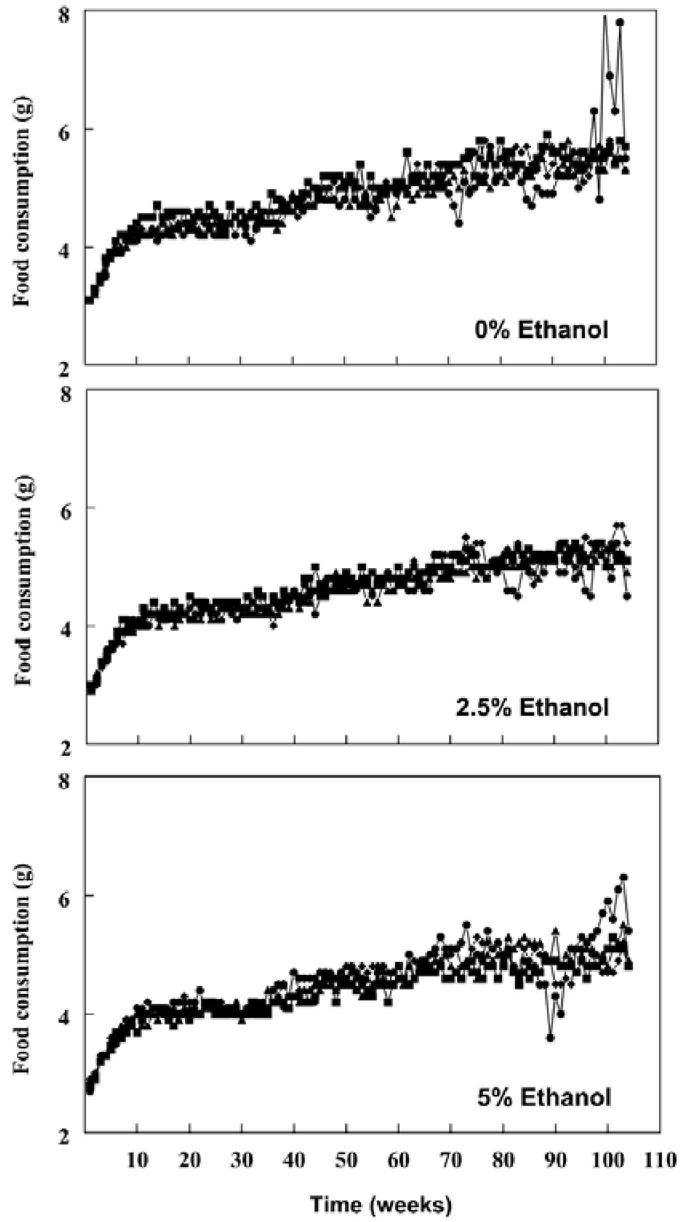


FIGURE 16
Feed Consumption by Female Mice Exposed to Urethane and 0%, 2.5%, or 5% Ethanol in Drinking Water for 2 Years (■=0 ppm; ▲=10 ppm; ◆=30 ppm; ●=90 ppm)

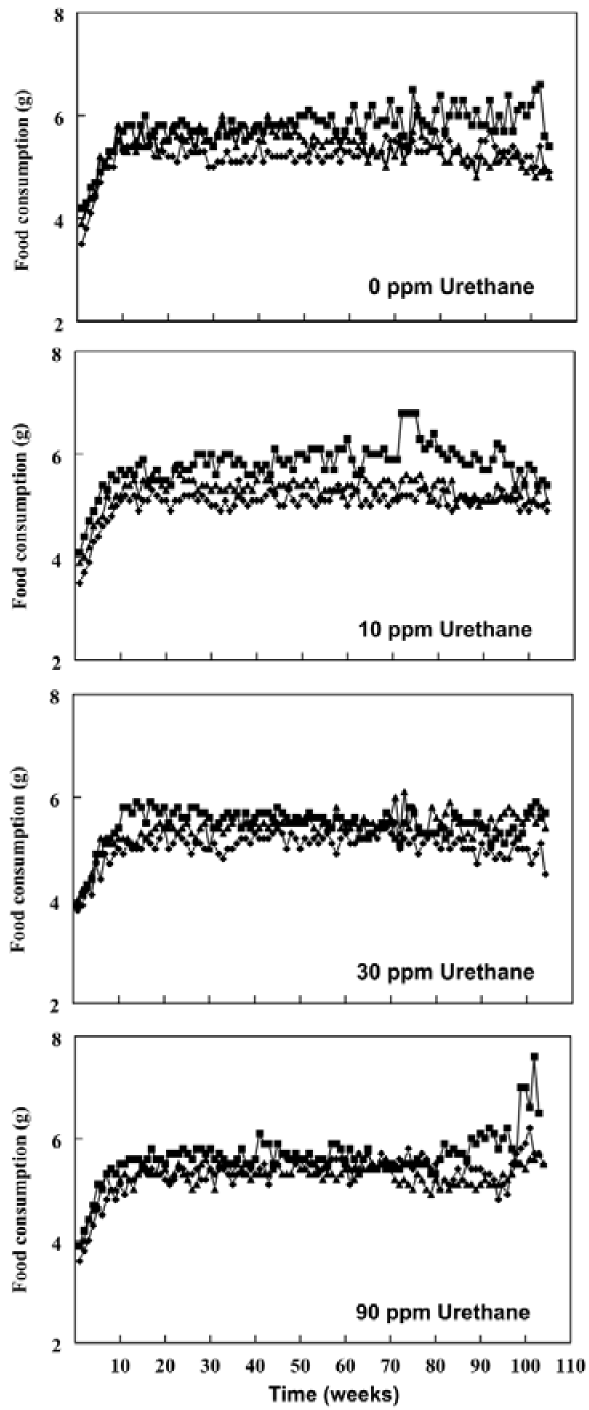


FIGURE 17
Feed Consumption by Male Mice Exposed to Ethanol and 0, 10, 30, or 90 ppm Urethane in Drinking Water for 2 Years (■=0%; ▲=2.5%; ◆=5%)

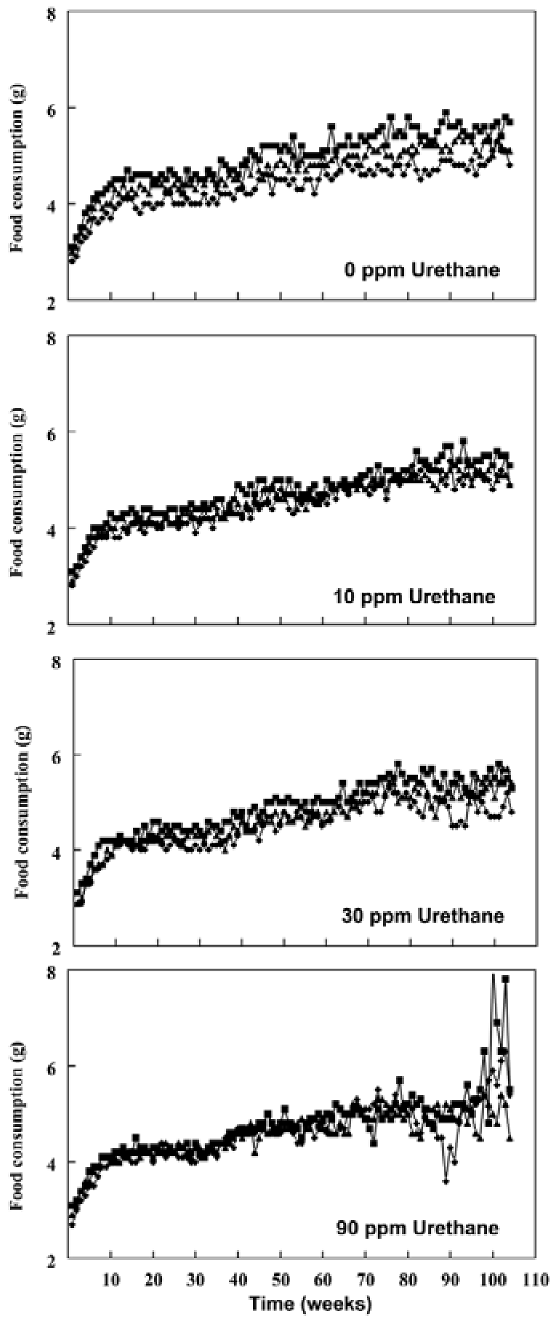


FIGURE 18
Feed Consumption by Female Mice Exposed to Ethanol and 0, 10, 30, or 90 ppm Urethane in Drinking Water for 2 Years (■=0%; ▲=2.5%; ◆=5%)

Pathology and Statistical Analyses

This section describes the statistically significant or biologically noteworthy changes in the incidences of hemangiosarcoma (all sites) and neoplasms and/or nonneoplastic lesions of the liver, lung, harderian gland, mammary gland, heart, ovary, uterus, forestomach, skin, and spleen. Summaries of the incidences of neoplasms and nonneoplastic lesions, statistical analyses of primary neoplasms that occurred with an incidence of at least 5% in at least one animal group, and historical incidences for most neoplasms mentioned in this section are presented in Appendixes A, B, and C for male mice and Appendixes D, E, and F for female mice.

Liver: Exposure to increasing concentrations of urethane and 0%, 2.5%, or 5% ethanol yielded no evidence that urethane affected liver weights in exposed mice; however, exposure to increasing concentrations of ethanol and 0, 10, 30, or 90 ppm urethane caused an exposure-related decrease in liver weights of males (Table H1). The incidences of hemangiosarcoma of the liver in mice exposed to 90 ppm urethane and 0%, 2.5%, or 5% ethanol were significantly greater than those in mice exposed to 0 ppm urethane (Tables 6, A2a, B2, C2, D2a, E2, and F2; Figure 19) and exceeded the historical ranges in controls for hemangiosarcoma (all sites) [male: 7/474 (1.5%), range 0%-4%; female: 6/518 (1.2%), range 0%-2%; Tables A3a and D3a]. The incidences of hemangiosarcoma in mice exposed to increasing concentrations of ethanol and 0, 10, 30, or 90 ppm urethane were not affected by exposure to ethanol (Tables A2b through A2e and D2b through D2e; Figure 19). The diagnosis of hemangiosarcoma was based on the proliferation of elongated, flattened, spindle-shaped or polyhedral endothelial cells that formed vascular spaces, solid nodules, or sheets of cells that replaced hepatic parenchyma. In organizing thrombi, normal-appearing endothelial cells penetrated only the superficial layers of fibrin in the thrombus and did not invade or replace hepatic parenchyma. In livers having large thrombi in areas of angiectasis, it was difficult to differentiate hemangiosarcoma from organizing thrombi.

In mice exposed to increasing concentrations of urethane and 0%, 2.5%, or 5% ethanol, the incidences of hepatocellular adenoma and hepatocellular adenoma or carcinoma (combined) in males and females exposed to 30 or 90 ppm urethane and 0% ethanol, in males exposed to 90 ppm urethane and 2.5% ethanol, and in females exposed to 30 or 90 ppm urethane and 2.5% or 5% ethanol were significantly increased (Tables 6, A2a, B2, D2a, E2, and F2; Figure 20). The incidences of hepatocellular adenoma and hepatocellular carcinoma in males exposed to 30 or 90 ppm urethane and 0% ethanol were at the upper end of the historical control ranges; the incidences of hepatocellular adenoma or carcinoma (combined) in these groups slightly exceeded the historical range (Tables 6 and A3b). The incidences of hepatocellular adenoma and hepatocellular adenoma or carcinoma (combined) in females exposed to urethane and 0% ethanol exceeded the historical control ranges (Tables 6 and D3b).

The incidences of hepatocellular adenoma and hepatocellular adenoma or carcinoma (combined) occurred with positive trends in males exposed to increasing concentrations of ethanol and 0 ppm urethane, and the incidence of hepatocellular adenoma was significantly increased in the 5% ethanol group (Figure 20; Table A2b).

Hepatocellular adenomas were nodular lesions that obviously compressed adjacent parenchyma. Hepatocytes composing these adenomas were larger than normal hepatocytes and were arranged without a lobular pattern. In some adenomas, there were a few small bile ducts, but in most adenomas, bile ducts were absent. A distinctive feature of the adenomas was sinusoidal ectasia that varied greatly in severity. Increased numbers of hematopoietic cells were usually present in the dilated vascular spaces. In severe cases of angiectasis within adenomas, there was often thrombus formation and necrosis of hepatocytes both within the adenoma and sometimes in adjacent nonneoplastic parenchyma. Differentiation between hepatocellular adenoma and a large eosinophilic focus (also induced by urethane administration and characterized by angiectasis) was made on the basis of size, the severity of compression of adjacent parenchyma, absence of lobular architecture and bile ducts from adenomas, and slight cellular atypia and pleomorphism in adenomas. The histomorphology of these adenomas differed from spontaneously occurring hepatocellular adenomas in $B6C3F_1$ mice described by Harada *et al.* (1999). Spontaneous hepatocellular adenomas lack angiectasis with hematopoietic cell infiltration, and the hepatocytes are usually slightly smaller with more cytoplasmic basophilia.

Incidences of several nonneoplastic lesions were significantly increased in mice exposed to increasing concentrations of urethane and 0%, 2.5%, or 5% ethanol (Tables 6, A4, B3, C3, D4, E3, and F3).

Table 6
Incidences of Neoplasms and Nonneoplastic Lesions of the Liver in Mice in the 2-Year Drinking Water Study of Urethane, Ethanol, and Urethane/Ethanol

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
Male				
0% Ethanol				
Number Examined Microscopically	46	47	46	44
Eosinophilic Focus[a]	6	7	19**	28**
Angiectasis	0	4*	6**	17**
Regeneration	0	1	2	1
Hemangiosarcoma				
Overall rate[b]	1/46 (2.2%)	2/47 (4.3%)	5/46 (10.9%)	13/44 (29.5%)
Poly-3 test[c]	P=0.001	P=0.489	P=0.118	P=0.001
Hepatocellular Adenoma, Multiple	2	3	4	7
Hepatocellular Adenoma (includes multiple)[d]				
Overall rate	7/46 (15.2%)	13/47 (27.7%)	17/46 (37.0%)	17/44 (38.6%)
Poly-3 test	P=0.009	P=0.077	P=0.025	P=0.003
Hepatocellular Carcinoma, Multiple	1	0	1	1
Hepatocellular Carcinoma (includes multiple)[e]	7	6	9	9
Hepatocellular Adenoma or Carcinoma[f]				
Overall rate	12/46 (26.1%)	18/47 (38.3%)	24/46 (52.2%)	23/44 (52.3%)
Poly-3 test	P=0.007	P=0.095	P=0.020	P=0.002
2.5% Ethanol				
Number Examined Microscopically	47	48	46	48
Eosinophilic Focus	6	3	17**	22**
Angiectasis	0	0	7**	16**
Regeneration	0	1	1	9**
Hemangiosarcoma				
Overall rate	3/47 (6.4%)	4/48 (8.3%)	3/46 (6.5%)	11/48 (22.9%)
Poly-3 test	P=0.002	P=0.514	P=0.604	P=0.013
Hepatocellular Adenoma, Multiple	2	2	4	11*
Hepatocellular Adenoma (includes multiple)	12	15	16	24**
Hepatocellular Carcinoma, Multiple	1	2	0	0
Hepatocellular Carcinoma (includes multiple)	6	5	5	4
Hepatocellular Adenoma or Carcinoma				
Overall rate	16/47 (34.0%)	19/48 (39.6%)	17/46 (37.0%)	24/48 (50.0%)
Poly-3 test	P=0.019	P=0.339	P=0.294	P=0.023

TABLE 6
Incidences of Neoplasms and Nonneoplastic Lesions of the Liver in Mice in the 2-Year Drinking Water Study of Urethane, Ethanol, and Urethane/Ethanol

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
Male (continued)				
5% Ethanol				
Number Examined Microscopically	48	46	48	48
Eosinophilic Focus	10	9	18*	25**
Angiectasis	1	1	8**	19**
Regeneration	0	0	3*	5**
Hemangiosarcoma				
Overall rate	2/48 (4.2%)	2/46 (4.3%)	4/48 (8.3%)	13/48 (27.1%)
Poly-3 test	P=0.001	P=0.638	P=0.260	P=0.001
Hepatocellular Adenoma, Multiple	2	3	3	3
Hepatocellular Adenoma (includes multiple)	19	9	16	12
Hepatocellular Carcinoma	7	9	2	9
Hepatocellular Adenoma or Carcinoma				
Overall rate	25/48 (52.1%)	16/46 (34.8%)	17/48 (35.4%)	18/48 (37.5%)
Poly-3 test	P=0.482N	P=0.140N	P=0.227N	P=0.365N
Female				
0% Ethanol				
Number Examined Microscopically	48	47	47	47
Eosinophilic Focus	3	14**	32**	20**
Angiectasis	0	3*	10**	24**
Thrombosis	0	1	1	11**
Necrosis				
Minimal	0 (0.0%)[h]	1 (2.1%)	2 (4.3%)	0 (0.0%)
Mild	3 (6.3%)	1 (2.1%)	1 (2.1%)	5 (10.6%)
Moderate	1 (2.1%)	2 (4.3%)	2 (4.3%)	8 (17.0%)
Monotonic trend test[g]	P=0.003	P=0.485	P=0.423	P=0.003
Regeneration	0	0	1	2
Hemangiosarcoma				
Overall rate	0/48 (0.0%)	0/47 (0.0%)	1/47 (2.1%)	7/47 (14.9%)
Poly-3 test	P=0.001	—[i]	P=0.471	P=0.001
Hepatocellular Adenoma, Multiple	2	2	9*	16**
Hepatocellular Adenoma (includes multiple)[j]	5	10	19**	18**
Hepatocellular Carcinoma	0	1	2	1
Hepatocellular Adenoma or Carcinoma[k]				
Overall rate	5/48 (10.4%)	11/47 (23.4%)	20/47 (42.6%)	19/47 (40.4%)
Poly-3 test	P=0.001	P=0.071	P=0.001	P=0.001

Table 6
Incidences of Neoplasms and Nonneoplastic Lesions of the Liver in Mice in the 2-Year Drinking Water Study of Urethane, Ethanol, and Urethane/Ethanol

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
Female (continued)				
2.5% Ethanol				
Number Examined Microscopically	47	47	47	46
Eosinophilic Focus	2	20**	21**	28**
Angiectasis	2	5	7*	20**
Thrombosis	1	0	4	9**
Necrosis				
Minimal	3 (6.4%)	2 (4.3%)	1 (2.1%)	2 (4.3%)
Mild	2 (4.3%)	1 (2.1%)	2 (4.3%)	9 (19.6%)
Moderate	0 (0.0%)	0 (0.0%)	2 (4.3%)	6 (13.0%)
Marked	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.2%)
Monotonic trend test	P<0.001	P=0.771	P=0.554	P<0.001
Regeneration	0	0	0	2*
Hemangiosarcoma				
Overall rate	1/47 (2.1%)	2/47 (4.3%)	0/47 (0.0%)	7/46 (15.2%)
Poly-3 test	P=0.001	P=0.470	P=0.553N	P=0.007
Hepatocellular Adenoma, Multiple	2	5	9*	14**
Hepatocellular Adenoma (includes multiple)	6	5	15**	23**
Hepatocellular Carcinoma	1	0	3	1
Hepatocellular Adenoma or Carcinoma				
Overall rate	7/47 (14.9%)	5/47 (10.6%)	16/47 (34.0%)	23/46 (50.0%)
Poly-3 test	P=0.001	P=0.441N	P=0.003	P=0.001
5% Ethanol				
Number Examined Microscopically	48	47	48	48
Eosinophilic Focus	2	26**	25**	21**
Angiectasis	2	1	5	22**
Thrombosis	0	0	1	8**
Necrosis				
Minimal	0 (0.0%)	1 (2.1%)	1 (2.1%)	2 (4.2%)
Mild	0 (0.0%)	1 (2.1%)	2 (4.2%)	8 (16.7%)
Moderate	0 (0.0%)	0 (0.0%)	0 (0.0%)	6 (12.5%)
Marked	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.1%)
Monotonic trend test	P<0.001	P=0.075	P=0.056	P<0.001
Regeneration	0	0	0	3**

Table 6
Incidences of Neoplasms and Nonneoplastic Lesions of the Liver in Mice in the 2-Year Drinking Water Study of Urethane, Ethanol, and Urethane/Ethanol

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
Female (continued)				
5% Ethanol (continued)				
Number Examined Microscopically	48	47	48	48
Hemangiosarcoma				
Overall rate	0/48 (0.0%)	0/47 (0.0%)	0/48 (0.0%)	6/48 (12.5%)
Poly-3 test	P=0.001	—	—	P=0.004
Hepatocellular Adenoma, Multiple	0	2	11**	14**
Hepatocellular Adenoma (includes multiple)	3	6	16**	16**
Hepatocellular Carcinoma, Multiple	0	0	0	1
Hepatocellular Carcinoma (includes multiple)	0	1	0	1
Hepatocellular Adenoma or Carcinoma				
Overall rate	3/48 (6.3%)	7/47 (14.9%)	16/48 (33.3%)	17/48 (35.4%)
Poly-3 test	P=0.001	P=0.127	P=0.001	P=0.001

* Significantly different (P≤0.05) from the control group by the Poly-3 (neoplasms) or Williams' (nonneoplastic lesions) test
** P≤0.01
[a] Number of animals with lesion
[b] Number of animals with neoplasm per number of animals with liver examined microscopically
[c] Beneath the control incidence (0 ppm urethane) is the P value associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and that exposed group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice. A negative trend or a lower incidence in an exposed group is indicated by **N**.
[d] Historical incidence for control groups in NCTR studies (mean): 89/470 (18.9%), range 13%-38%
[e] Historical incidence: 50/470 (10.6%), range 7%-21%
[f] Historical incidence: 129/470 (27.4%), range 19%-50%
[g] Beneath the control incidence is the overall monotonic trend in severity with exposure level tested using the Jonckheere-Terpstra test statistic. Beneath the exposed group incidence are the P values corresponding to pairwise monotonic tests of severity with exposure concentration using the Williams' modification of Shirley's nonparametric test for a monotonic dose response.
[h] Percentage of animals with lesion of given severity
[i] Value of statistic cannot be computed.
[j] Historical incidence: 21/515 (4.1%), range 0%-11%
[k] Historical incidence: 29/515 (5.6%), range 0%-11%

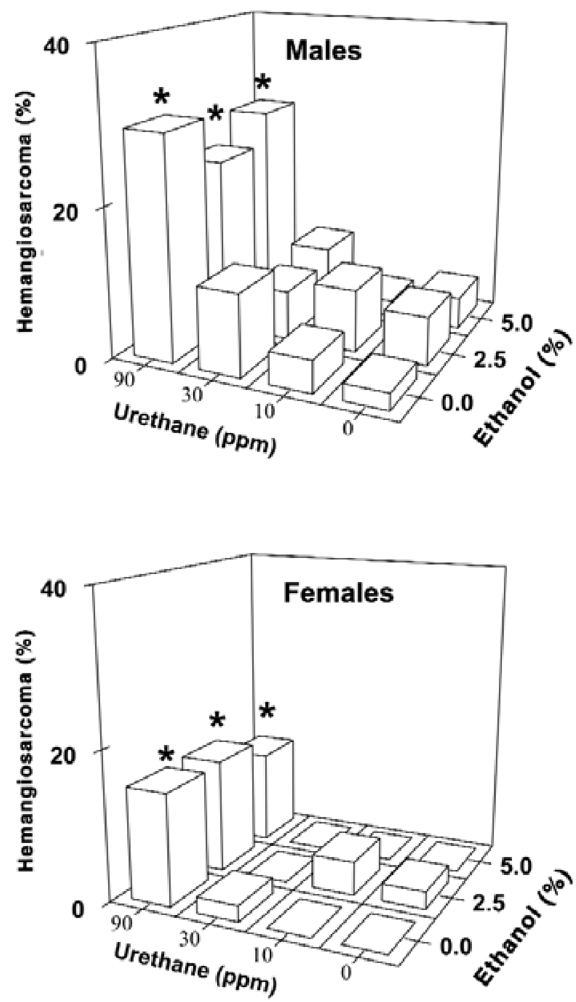


FIGURE 19
Incidences of Hemangiosarcoma of the Liver in Mice Exposed to Urethane and 0%, 2.5%, or 5% Ethanol in Drinking Water for 2 Years
[*=Significantly increased compared to group exposed to 0 ppm urethane and the same (i.e., 0%, 2.5%, or 5%) concentration of ethanol]

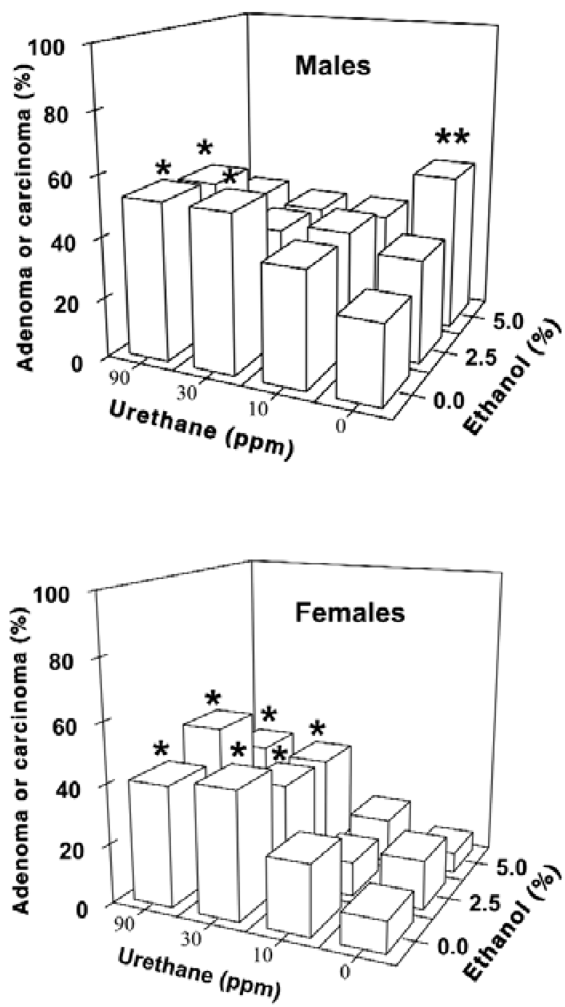


FIGURE 20
Incidences of Hepatocellular Adenoma or Carcinoma of the Liver in Mice Exposed to Urethane and 0%, 2.5%, or 5% Ethanol in Drinking Water for 2 Years
[*=Significantly increased compared to group exposed to 0 ppm urethane and the same (i.e., 0%, 2.5%, or 5%) concentration of ethanol; **=Marginally increased compared to group exposed to 0 ppm urethane and 0% ethanol]

Eosinophilic foci consisted of focal areas in which hepatocytes were larger than normal because of increased amounts of eosinophilic cytoplasm. The eosinophilic foci differed from eosinophilic foci usually seen in $B6C3F_1$ mice (Harada *et al.*, 1999) because the sinusoids within the foci were often dilated and contained increased numbers of hematopoietic cells. In a few foci, the cytoplasm of hepatocytes was vacuolated (clear cell focus) and in others, cells with both vacuolated and eosinophilic cytoplasm were present (mixed cell foci).

While sinusoidal dilatation was a consistent component of hepatocellular adenomas and eosinophilic foci, the vascular component of these lesions was not documented separately. However, in a number of animals, foci of angiectasis consisting of focal areas of sinusoidal dilatation lined by a single layer of essentially normal endothelial cells were present without morphologic alteration of adjacent hepatocytes. In these cases, angiectasis was coded. Hematopoietic cells were usually numerous and prominent within foci of angiectasis. Often the hepatic parenchyma adjacent to larger areas of angiectasis was either atrophic, necrotic, or there was a complete absence of hepatocytes. In areas lacking hepatocytes, there were orderly sinusoidal channels composed of condensed reticular hepatic framework lined by viable essentially normal endothelial cells. Thrombus formation was frequently present in larger areas of angiectasis. At the periphery of large thrombi, there were usually increased numbers of plump spindle-shaped endothelial cells and a few fibroblasts infiltrating the superficial layers of fibrin. There were often large, irregular areas of hepatocellular necrosis adjacent to large areas of angiectasis and thrombosis. Liver necrosis that had no lobular orientation was most likely due to intrahepatic circulatory disturbances caused by lesions in the microvasculature rather than to direct chemical toxicity.

Regeneration was present in some animals with extensive areas of liver necrosis. It was often difficult to differentiate areas of regeneration from hepatocellular adenoma. Regeneration usually accompanied large areas of hepatocellular necrosis and consisted of nodular proliferations of slightly enlarged hepatocytes. Angiectasis, which was very prominent in urethane-induced eosinophilic foci and hepatocellular adenomas, was not a prominent feature in regenerative nodules. In areas of regeneration, the lobular architecture was usually present but distorted. Portal areas were fewer and less distinct than in normal livers, and the hepatocytes lacked the atypia and pleomorphism that was usually present in hepatocellular adenomas.

Lung: Lung weights of mice exposed to 90 ppm urethane and 0%, 2.5%, or 5% ethanol were generally greater than those of mice exposed to 0 ppm urethane; the increases were significant in 90 ppm males and females exposed to 0% and 2.5% ethanol, respectively (Table H1). Incidences of alveolar/bronchiolar neoplasms increased in males and females exposed to increasing concentrations of urethane and 0%, 2.5%, or 5% ethanol, and the incidences of these neoplasms in the 30 and 90 ppm urethane groups were significantly increased except in males exposed to 30 ppm urethane and 5% ethanol (Tables 7, A2a, B2, C2, D2a, E2, and F2; Figure 21). The incidences of alveolar/bronchiolar adenoma or carcinoma were also significantly increased in males exposed to 10 ppm urethane and 0% ethanol and in females exposed to 10 ppm urethane and 5% ethanol. Both single and multiple alveolar/bronchiolar adenoma or carcinoma occurred. In mice exposed to increasing concentrations of urethane and 0% ethanol, the incidences of these lesions generally exceeded the historical control ranges in males exposed to 10, 30, or 90 ppm and in females exposed to 0, 10, 30, or 90 ppm urethane (Tables 7, A3c, and D3c).

The incidences of alveolar/bronchiolar adenoma or carcinoma (combined) occurred with positive trends in females exposed to increasing concentrations of ethanol and 10 ppm urethane, and the incidence was significantly increased in females exposed to 5% ethanol (Figure 21 and Table D2c). Incidences of alveolar/bronchiolar adenoma occurred with negative trends in males exposed to increasing concentrations of ethanol and 10 or 30 ppm urethane, and the incidences were significantly decreased in males exposed to 5% ethanol (Tables A2c and A2d). In addition, the incidence of alveolar/bronchiolar adenoma or carcinoma (combined) was significantly decreased in males exposed to 5% ethanol and 30 ppm urethane (Figure 21 and Table A2d).

Multiple alveolar/bronchiolar adenomas were coded when more than one alveolar/bronchiolar adenoma was present in the lung of a mouse. Multiple alveolar/bronchiolar carcinoma was coded when alveolar/bronchiolar carcinomas were present in different lung lobes and situated in a way that local invasion or intrapulmonary metastasis appeared unlikely. The histomorphology of urethane-induced benign and malignant lung tumors was similar to that of spontaneously occurring lung tumors in mice (Dixon *et al.*, 1999).

Table 7
Incidences of Neoplasms of the Lung in Mice in the 2-Year Drinking Water Study of Urethane, Ethanol, and Urethane/Ethanol

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
Male				
0% Ethanol				
Number Examined Microscopically	48	48	47	48
Alveolar/bronchiolar Adenoma, Multiple[a]	1	2	7*	20**
Alveolar/bronchiolar Adenoma (includes multiple)[b]				
Overall rate[c]	4/48 (8.3%)	17/48 (35.4%)	22/47 (46.8%)	34/48 (70.8%)
Poly-3 test[d]	P=0.001	P=0.001	P=0.001	P=0.001
Alveolar/bronchiolar Carcinoma, Multiple	0	0	1	1
Alveolar/bronchiolar Carcinoma (includes multiple)[e]				
Overall rate	1/48 (2.1%)	1/48 (2.1%)	9/47 (19.1%)	9/48 (18.8%)
Poly-3 test	P=0.001	P=0.753	P=0.010	P=0.002
Alveolar/bronchiolar Adenoma or Carcinoma[f]				
Overall rate	5/48 (10.4%)	18/48 (37.5%)	29/47 (61.7%)	37/48 (77.1%)
Poly-3 test	P=0.001	P=0.001	P=0.001	P=0.001
2.5% Ethanol				
Number Examined Microscopically	48	48	47	48
Alveolar/bronchiolar Adenoma, Multiple	1	2	8*	24**
Alveolar/bronchiolar Adenoma (includes multiple)				
Overall rate	10/48 (20.8%)	16/48 (33.3%)	19/47 (40.4%)	35/48 (72.9%)
Poly-3 test	P=0.001	P=0.124	P=0.010	P=0.001
Alveolar/bronchiolar Carcinoma, Multiple	0	0	1	4*
Alveolar/bronchiolar Carcinoma (includes multiple)				
Overall rate	2/48 (4.2%)	3/48 (6.3%)	8/47 (17.0%)	24/48 (50.0%)
Poly-3 test	P=0.001	P=0.513	P=0.029	P=0.001
Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rate	11/48 (22.9%)	19/48 (39.6%)	24/47 (51.1%)	43/48 (89.6%)
Poly-3 test	P=0.001	P=0.062	P=0.001	P=0.001

TABLE 7
Incidences of Neoplasms of the Lung in Mice in the 2-Year Drinking Water Study of Urethane, Ethanol, and Urethane/Ethanol

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
Male (continued)				
5% Ethanol				
Number Examined Microscopically	48	48	48	48
Alveolar/bronchiolar Adenoma, Multiple	1	1	3	14**
Alveolar/bronchiolar Adenoma (includes multiple)				
Overall rate	6/48 (12.5%)	8/48 (16.7%)	9/48 (18.8%)	33/48 (68.8%)
Poly-3 test	P=0.001	P=0.288	P=0.189	P=0.001
Alveolar/bronchiolar Carcinoma, Multiple	0	0	0	2
Alveolar/bronchiolar Carcinoma (includes multiple)				
Overall rate	5/48 (10.4%)	4/48 (8.3%)	5/48 (10.4%)	17/48 (35.4%)
Poly-3 test	P=0.001	P=0.578	P=0.531	P=0.001
Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rate	11/48 (22.9%)	11/48 (22.9%)	14/48 (29.2%)	40/48 (83.3%)
Poly-3 test	P=0.001	P=0.457	P=0.190	P=0.001
Female				
0% Ethanol				
Number Examined Microscopically	48	48	48	47
Alveolar/bronchiolar Adenoma, Multiple	0	0	4*	17*
Alveolar/bronchiolar Adenoma (includes multiple)[g]				
Overall rate	4/48 (8.3%)	6/48 (12.5%)	17/48 (35.4%)	29/47 (61.7%)
Poly-3 test	P=0.001	P=0.356	P=0.001	P=0.001
Alveolar/bronchiolar Carcinoma, Multiple	0	0	3	13**
Alveolar/bronchiolar Carcinoma (includes multiple)[h]				
Overall rate	2/48 (4.2%)	4/48 (8.3%)	13/48 (27.1%)	19/47 (40.4%)
Poly-3 test	P=0.001	P=0.324	P=0.001	P=0.001
Alveolar/bronchiolar Adenoma or Carcinoma[i]				
Overall rate	6/48 (12.5%)	8/48 (16.7%)	28/48 (58.3%)	39/47 (83.0%)
Poly-3 test	P=0.001	P=0.365	P=0.001	P=0.001

Table 7
Incidences of Neoplasms of the Lung in Mice in the 2-Year Drinking Water Study of Urethane, Ethanol, and Urethane/Ethanol

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
Female (continued)				
2.5% Ethanol				
Number Examined Microscopically	47	47	48	48
Alveolar/bronchiolar Adenoma, Multiple	0	3	4*	18**
Alveolar/bronchiolar Adenoma (includes multiple)				
Overall rate	5/47 (10.6%)	10/47 (21.3%)	16/48 (33.3%)	28/48 (58.3%)
Poly-3 test	P=0.001	P=0.103	P=0.001	P=0.001
Alveolar/bronchiolar Carcinoma, Multiple	0	0	2	12**
Alveolar/bronchiolar Carcinoma (includes multiple)				
Overall rate	0/47 (0.0%)	2/47 (4.3%)	6/48 (12.5%)	23/48 (47.9%)
Poly-3 test	P=0.001	P=0.219	P=0.007	P=0.001
Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rate	5/47 (10.6%)	11/47 (23.4%)	21/48 (43.8%)	38/48 (79.2%)
Poly-3 test	P=0.001	P=0.064	P=0.001	P=0.001
5% Ethanol				
Number Examined Microscopically	48	48	48	48
Alveolar/bronchiolar Adenoma, Multiple	1	2	3	22**
Alveolar/bronchiolar Adenoma (includes multiple)				
Overall rate	5/48 (10.4%)	10/48 (20.8%)	18/48 (37.5%)	30/48 (62.5%)
Poly-3 test	P=0.001	P=0.103	P=0.001	P=0.001
Alveolar/bronchiolar Carcinoma, Multiple	0	2	2	15**
Alveolar/bronchiolar Carcinoma (includes multiple)				
Overall rate	1/48 (2.1%)	7/48 (14.6%)	9/48 (18.8%)	23/48 (47.9%)
Poly-3 test	P=0.001	P=0.024	P=0.005	P=0.001
Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rate	5/48 (10.4%)	17/48 (35.4%)	24/48 (50.0%)	37/48 (77.1%)
Poly-3 test	P=0.001	P=0.001	P=0.001	P=0.001

* Significantly different (P≤0.05) from the control group by the Poly-3 test
** P≤0.01
[a] Number of animals with neoplasm
[b] Historical incidence for control groups in NCTR studies (mean): 71/473 (15.0%), range 8%-27%
[c] Number of animals with neoplasm per number of animals with lung examined microscopically
[d] Beneath the control incidence (0 ppm urethane) is the P value associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and that exposed group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice.
[e] Historical incidence: 11/473 (2.3%), range 0%-8%
[f] Historical incidence: 82/473 (17.3%), range 11%-31%
[g] Historical incidence: 22/515 (4.3%), range 2%-6%
[h] Historical incidence: 3/515 (0.6%), range 0%-4%
[i] Historical incidence: 25/515 (4.9%), range 2%-11%

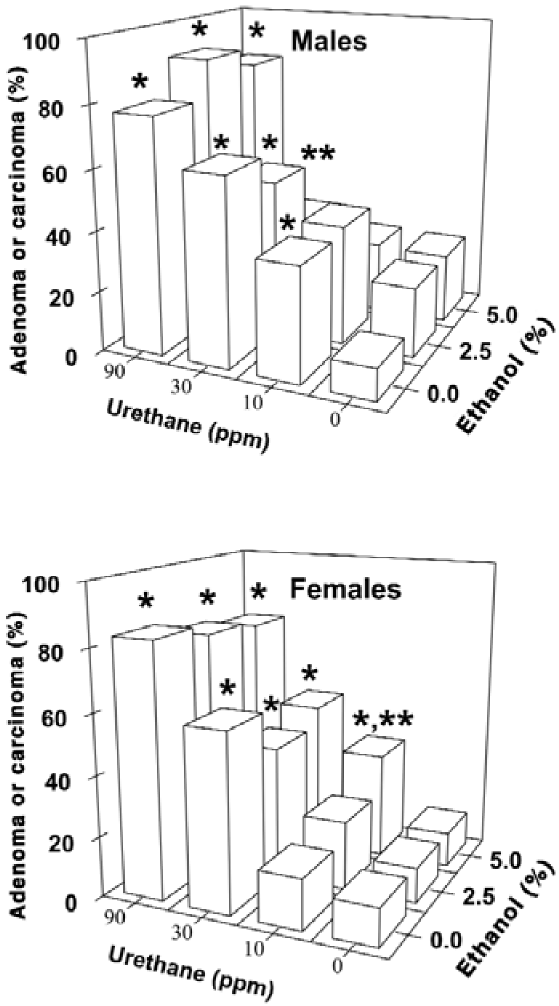


FIGURE 21
Incidences of Alveolar/bronchiolar Adenoma or Carcinoma (Combined) in Mice Exposed to Urethane and 0%, 2.5%, or 5% Ethanol in Drinking Water for 2 Years
[*=Significantly increased compared to group exposed to 0 ppm urethane and the same (i.e., 0%, 2.5%, or 5%) concentration of ethanol; **=Significantly different from the group exposed to the same concentration of urethane and 0% ethanol]

Harderian Gland: Incidences of harderian gland neoplasms increased in mice exposed to increasing concentrations of urethane and 0%, 2.5%, or 5% ethanol (Tables 8, A2a, B2, C2, D2a, E2, and F2; Figure 22). The incidences of harderian gland adenoma and carcinoma were generally increased in mice exposed to 10, 30, or 90 ppm urethane and 0%, 2.5%, or 5% ethanol; in addition, the incidences of harderian gland adenoma or carcinoma (combined) were significantly increased in all urethane-exposed groups except in females exposed to 10 ppm urethane and 2.5% ethanol. The incidences of these harderian gland neoplasms in mice exposed to 10, 30, or 90 ppm urethane and 0% ethanol exceeded the historical control ranges (Tables 8, A3d, and D3d). Multiplicity in the case of harderian gland neoplasms was indicated by the occurrence of adenomas or carcinomas in both harderian glands (bilateral) in the same animal.

In males exposed to increasing concentrations of ethanol and 0, 10, 30, or 90 ppm urethane, exposure-related decreased incidences of harderian gland adenoma and adenoma or carcinoma (combined) were noted in the 30 ppm groups; the decrease was significant for the combined neoplasm incidence in males exposed to 30 ppm urethane and 5% ethanol (Tables A2b through A2e; Figure 22). In females, no consistent effect of ethanol on harderian gland neoplasms was noted (Tables D2b through D2e; Figure 22).

Mammary Gland: Incidences of adenoacanthoma, adenocarcinoma, and adenoacanthoma or adenocarcinoma (combined) increased in females exposed to increasing concentrations of urethane and 0%, 2.5%, or 5% ethanol (Tables 9, D2a, E2, and F2; Figure 23). The incidences of these neoplasms were significantly increased in females exposed to 90 ppm urethane and 0% or 5% ethanol. The incidences of adenocarcinoma and adenoacanthoma or adenocarcinoma (combined) in females exposed to 30 or 90 ppm urethane and 2.5% ethanol were significantly increased. Adenoacanthoma occurred only in females exposed to urethane or to urethane and ethanol. The incidences of these neoplasms in females exposed to increasing concentrations of urethane and 0% ethanol exceeded the historical control ranges (Tables 9 and D3e); the incidence of adenocarcinoma in females exposed to 0 ppm urethane and 0% ethanol also exceeded the historical range.

In females exposed to increasing concentrations of ethanol and 0, 10, 30, or 90 ppm urethane, the incidences of adenoacanthoma and adenocarcinoma were similar to those in females exposed to 0% ethanol (Figure 23; Tables D2b through D2e).

Growth patterns of the adenocarcinomas were either the tubular or tubulo-alveolar type. In adenoacanthomas, the growth pattern was similar to the adenocarcinomas, but at least 25% or more of the tumor consisted of squamous metaplasia. The adenoacanthomas and adenocarcinomas were malignant; a few neoplasms of each type metastasized to the lung.

Heart: The incidences of hemangiosarcoma were significantly increased in males exposed to 90 ppm urethane and 0%, 2.5%, or 5% ethanol (Tables 10, A2a, B2, and C2; Figure 24). The incidence of hemangiosarcoma was increased in females exposed to 90 ppm urethane and 2.5% ethanol and significantly increased in females exposed to 90 ppm urethane and 5% ethanol (Tables 10 and F2; Figure 24) and exceeded the historical control ranges for hemangiosarcoma (all sites) [male: 7/474 (1.5%), range 0%-4%; female: 6/518 (1.2%), range 0%-2%; Tables A3a and D3a]. The incidences of hemangiosarcoma of the heart occurred only in groups exposed to urethane.

Increasing the concentration of ethanol had no effect on the incidences of hemangiosarcoma of the heart in males exposed to 0, 10, 30, or 90 ppm urethane or in females exposed to 0, 10, or 30 ppm urethane (Tables A1, A2e, B1, C1, D1, E1, and F1). In females, increasing the ethanol concentration in the 90 ppm urethane group caused an exposure-related increase in the incidence of hemangiosarcoma, and the increase in the 5% ethanol group was significant (Figure 24 and Table D2e).

Incidences of endothelial hyperplasia and angiectasis increased in mice exposed to increasing concentrations of urethane and 0%, 2.5%, or 5% ethanol (Tables 10, A4, B3, C3, D4, E3, and F3). Endothelial hyperplasia in males and angiectasis in males and females occurred only in urethane-exposed groups.

Exposure to increasing concentrations of ethanol and 0, 10, 30, or 90 ppm urethane generally had no effect on the incidence of endothelial hyperplasia or angiectasis in males or females (Tables 10, A4, B3, C3, D4, E3, and F3).

TABLE 8
Incidences of Neoplasms of the Harderian Gland in Mice in the 2-Year Drinking Water Study of Urethane, Ethanol, and Urethane/Ethanol

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
Male				
0% Ethanol				
Number Examined Microscopically	47	47	47	47
Adenoma, Bilateral[a]	0	1	4*	7*
Adenoma (includes bilateral)[b]				
Overall rate[c]	3/47 (6.4%)	11/47 (23.4%)	25/47 (53.2%)	28/47 (59.6%)
Poly-3 test[d]	P=0.001	P=0.013	P=0.001	P=0.001
Carcinoma, Bilateral	0	0	1	2
Carcinoma (includes bilateral)[e]				
Overall rate	0/47 (0.0%)	1/47 (2.1%)	7/47 (14.9%)	16/47 (34.0%)
Poly-3 test	P=0.001	P=0.493	P=0.011	P=0.001
Adenoma or Carcinoma[b]				
Overall rate	3/47 (6.4%)	12/47 (25.5%)	30/47 (63.8%)	38/47 (80.9%)
Poly-3 test	P=0.001	P=0.006	P=0.001	P=0.001
2.5% Ethanol				
Number Examined Microscopically	48	48	47	48
Adenoma, Bilateral	0	1	4*	8*
Adenoma (includes bilateral)				
Overall rate	6/48 (12.5%)	14/48 (29.2%)	21/47 (44.7%)	27/48 (56.3%)
Poly-3 test	P=0.001	P=0.034	P=0.001	P=0.001
Carcinoma, Bilateral	0	0	0	3
Carcinoma (includes bilateral)				
Overall rate	0/48 (0.0%)	0/48 (0.0%)	1/47 (2.1%)	16/48 (33.3%)
Poly-3 test	P=0.001	—[f]	P=0.476	P=0.001
Adenoma or Carcinoma				
Overall rate	6/48 (12.5%)	14/48 (29.2%)	21/47 (44.7%)	38/48 (79.2%)
Poly-3 test	P=0.001	P=0.034	P=0.001	P=0.001

Table 8
Incidences of Neoplasms of the Harderian Gland in Mice in the 2-Year Drinking Water Study of Urethane, Ethanol, and Urethane/Ethanol

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
Male (continued)				
5% Ethanol				
Number Examined Microscopically	47	48	48	45
Adenoma, Bilateral	0	0	3	10**
Adenoma (includes bilateral)				
Overall rate	5/47 (10.6%)	12/48 (25.0%)	15/48 (31.3%)	26/45 (57.8%)
Poly-3 test	P=0.001	P=0.034	P=0.004	P=0.001
Carcinoma, Bilateral	0	0	0	3
Carcinoma (includes bilateral)				
Overall rate	0/47 (0.0%)	2/48 (4.2%)	2/48 (4.2%)	10/45 (22.2%)
Poly-3 test	P=0.001	P=0.215	P=0.210	P=0.001
Adenoma or Carcinoma				
Overall rate	5/47 (10.6%)	14/48 (29.2%)	17/48 (35.4%)	35/45 (77.8%)
Poly-3 test	P=0.001	P=0.010	P=0.001	P=0.001
Female				
0% Ethanol				
Number Examined Microscopically	48	48	48	48
Adenoma, Bilateral	0	0	0	1
Adenoma (includes bilateral)[g]				
Overall rate	3/48 (6.3%)	10/48 (20.8%)	8/48 (16.7%)	21/48 (43.8%)
Poly-3 test	P=0.001	P=0.033	P=0.070	P=0.001
Carcinoma, Bilateral	0	0	0	4*
Carcinoma (includes bilateral)[h]				
Overall rate	0/48 (0.0%)	1/48 (2.1%)	11/48 (22.9%)	11/48 (22.9%)
Poly-3 test	P=0.001	P=0.495	P=0.001	P=0.001
Adenoma or Carcinoma[i]				
Overall rate	3/48 (6.3%)	11/48 (22.9%)	19/48 (39.6%)	30/48 (62.5%)
Poly-3 test	P=0.001	P=0.018	P=0.001	P=0.001

TABLE 8
Incidences of Neoplasms of the Harderian Gland in Mice in the 2-Year Drinking Water Study of Urethane, Ethanol, and Urethane/Ethanol

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
Female (continued)				
2.5% Ethanol				
Number Examined Microscopically	47	47	46	47
Adenoma, Bilateral	0	0	0	3
Adenoma (includes bilateral)				
Overall rate	2/47 (4.3%)	3/47 (6.4%)	9/46 (19.6%)	19/47 (40.4%)
Poly-3 test	P=0.001	P=0.461	P=0.007	P=0.001
Carcinoma, Bilateral	0	0	0	4*
Carcinoma (includes bilateral)				
Overall rate	1/47 (2.1%)	3/47 (6.4%)	6/46 (13.0%)	16/47 (34.0%)
Poly-3 test	P=0.001	P=0.276	P=0.024	P=0.001
Adenoma or Carcinoma				
Overall rate	3/47 (6.4%)	5/47 (10.6%)	15/46 (32.6%)	35/47 (74.5%)
Poly-3 test	P=0.001	P=0.311	P=0.001	P=0.001
5% Ethanol				
Number Examined Microscopically	48	48	46	46
Adenoma, Bilateral	0	0	0	6*
Adenoma (includes bilateral)				
Overall rate	4/48 (8.3%)	7/48 (14.6%)	6/46 (13.0%)	20/46 (43.5%)
Poly-3 test	P=0.001	P=0.226	P=0.294	P=0.001
Carcinoma, Bilateral	0	1	1	0
Carcinoma (includes bilateral)				
Overall rate	1/48 (2.1%)	11/48 (22.9%)	7/46 (15.2%)	10/46 (21.7%)
Poly-3 test	P=0.011	P=0.001	P=0.017	P=0.001
Adenoma or Carcinoma				
Overall rate	5/48 (10.4%)	18/48 (37.5%)	13/46 (28.3%)	29/46 (63.0%)
Poly-3 test	P=0.001	P=0.001	P=0.013	P=0.001

* Significantly different ($P \leq 0.05$) from the control group by the Poly-3 test
** $P \leq 0.01$
[a] Number of animals with neoplasm
[b] Historical incidence for control groups in NCTR studies (mean): 25/325 (7.7%), range 2%-11%
[c] Number of animals with neoplasm per number of animals with harderian gland examined microscopically
[d] Beneath the control incidence (0 ppm urethane) is the P value associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and that exposed group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice.
[e] Historical incidence: 0/325
[f] Value of statistic cannot be computed.
[g] Historical incidence: 21/368 (5.7%), range 3%-9%
[h] Historical incidence: 3/368 (0.8%), range 1%-2%
[i] Historical incidence: 23/368 (6.3%), range 4%-9%

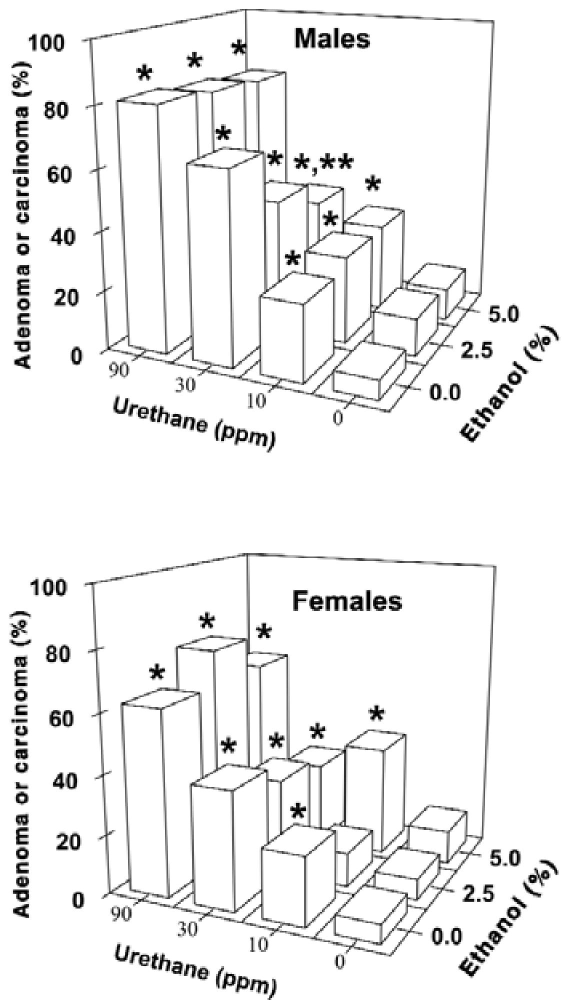


FIGURE 22
Incidences of Adenoma or Carcinoma (Combined) of the Harderian Gland in Mice Exposed to Urethane and 0%, 2.5%, or 5% Ethanol in Drinking Water for 2 Years
[*=Significantly increased compared to group exposed to 0 ppm urethane and the same (i.e., 0%, 2.5%, or 5%) concentration of ethanol; **=Significantly decreased compared to group exposed to 30 ppm urethane and 0% ethanol)

TABLE 9
Incidences of Neoplasms of the Mammary Gland in Female Mice in the 2-Year Drinking Water Study of Urethane, Ethanol, and Urethane/Ethanol

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
0% Ethanol				
Adenoacanthoma[a]				
Overall rate[b]	0/47 (0.0%)	1/46 (2.2%)	1/46 (2.2%)	11/48 (22.9%)
Poly-3 test[c]	P=0.001	P=0.492	P=0.476	P=0.001
Adenocarcinoma[d]				
Overall rate	4/47 (8.5%)	3/46 (6.5%)	3/46 (6.5%)	11/48 (22.9%)
Poly-3 test	P=0.001	P=0.524N	P=0.564N	P=0.007
Adenoacanthoma or Adenocarcinoma[d]				
Overall rate	4/47 (8.5%)	4/46 (8.7%)	4/46 (8.7%)	22/48 (45.8%)
Poly-3 test	P=0.001	P=0.622	P=0.582	P=0.001
2.5% Ethanol				
Adenoacanthoma				
Overall rate	0/47 (0.0%)	0/45 (0.0%)	2/48 (4.2%)	3/47 (6.4%)
Poly-3 test	P=0.017	—[e]	P=0.188	P=0.071
Adenocarcinoma				
Overall rate	4/47 (8.5%)	3/45 (6.7%)	11/48 (22.9%)	14/47 (29.8%)
Poly-3 test	P=0.001	P=0.568N	P=0.015	P=0.001
Adenoacanthoma or Adenocarcinoma				
Overall rate	4/47 (8.5%)	3/45 (6.7%)	12/48 (25.0%)	16/47 (34.0%)
Poly-3 test	P=0.001	P=0.568N	P=0.007	P=0.001
5% Ethanol				
Adenoacanthoma				
Overall rate	0/47 (0.0%)	0/48 (0.0%)	1/48 (2.1%)	9/45 (20.0%)
Poly-3 test	P=0.001	—	P=0.483	P=0.001
Adenocarcinoma				
Overall rate	3/47 (6.4%)	4/48 (8.3%)	6/48 (12.5%)	15/45 (33.3%)
Poly-3 test	P=0.001	P=0.476	P=0.214	P=0.001
Adenoacanthoma or Adenocarcinoma				
Overall rate	3/47 (6.4%)	4/48 (8.3%)	7/48 (14.6%)	23/45 (51.1%)
Poly-3 test	P=0.001	P=0.476	P=0.134	P=0.001

[a] Historical incidence for control groups in NCTR studies: 0/179
[b] Number of animals with neoplasm per number of animals with mammary gland examined microscopically
[c] Beneath the control incidence (0 ppm urethane) is the P value associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and that exposed group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice. A lower incidence in an exposed group is indicated by **N**.
[d] Historical incidence (mean): 2/179 (1.1%), range 1%-2%
[e] Value of statistic cannot be computed.

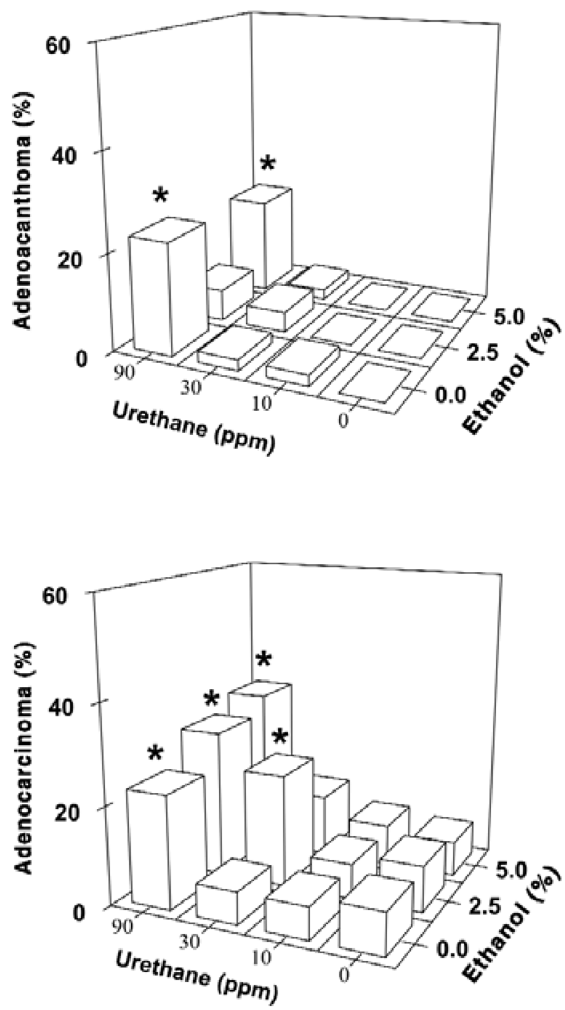


FIGURE 23
Incidences of Adenoacanthoma and Adenocarcinoma of the Mammary Gland in Female Mice Exposed to Urethane and 0%, 2.5%, or 5% Ethanol in Drinking Water for 2 Years
[*=Significantly increased compared to group exposed to 0 ppm urethane and the same (i.e., 0%, 2.5%, or 5%) concentration of ethanol]

TABLE 10
Incidences of Neoplasms and Nonneoplastic Lesions of the Heart in Mice in the 2-Year Drinking Water Study of Urethane, Ethanol, and Urethane/Ethanol

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
Male				
0% Ethanol				
Number Examined Microscopically	48	48	47	48
Hyperplasia, Endothelium				
Minimal[a]	0 (0.0%)[c]	0 (0.0%)	2 (4.3%)	5 (10.4%)
Mild	0 (0.0%)	0 (0.0%)	2 (4.3%)	3 (6.3%)
Moderate	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.1%)
Monotonic trend test[b]	P<0.001	—[d]	P=0.007	P<0.001
Angiectasis				
Minimal	0 (0.0%)	1 (2.1%)	1 (2.1%)	8 (16.7%)
Mild	0 (0.0%)	0 (0.0%)	1 (2.1%)	3 (6.3%)
Monotonic trend test	P<0.001	P=0.159	P=0.087	P<0.001
Hemangiosarcoma				
Overall rate[e]	0/48 (0.0%)	0/48 (0.0%)	1/47 (2.1%)	5/48 (10.4%)
Poly-3 test[f]	P=0.001	—	P=0.508	P=0.016
2.5% Ethanol				
Number Examined Microscopically	48	48	47	48
Hyperplasia, Endothelium				
Minimal	0 (0.0%)	1 (2.1%)	1 (2.1%)	5 (10.4%)
Mild	0 (0.0%)	0 (0.0%)	2 (4.3%)	4 (8.3%)
Moderate	0 (0.0%)	0 (0.0%)	1 (2.1%)	0 (0.0%)
Monotonic trend test	P<0.001	P=0.159	P=0.013	P<0.001
Angiectasis				
Minimal	0 (0.0%)	0 (0.0%)	3 (6.4%)	5 (10.4%)
Mild	0 (0.0%)	0 (0.0%)	1 (2.1%)	4 (8.3%)
Moderate	0 (0.0%)	0 (0.0%)	3 (6.4%)	2 (4.2%)
Marked	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (4.2%)
Monotonic trend test	P<0.001	—	P<0.001	P<0.001
Hemangiosarcoma				
Overall rate	0/48 (0.0%)	0/48 (0.0%)	2/47 (4.3%)	4/48 (8.3%)
Poly-3 test	P=0.007	—	P=0.211	P=0.049
5% Ethanol				
Number Examined Microscopically	47	48	48	48
Hyperplasia, Endothelium				
Minimal	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.1%)
Mild	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.1%)
Monotonic trend test	P=0.029	—	—	P=0.028
Angiectasis				
Minimal	0 (0.0%)	0 (0.0%)	1 (2.1%)	3 (6.3%)
Mild	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (4.2%)
Monotonic trend test	P=0.002	—	P=0.133	P=0.002
Hemangiosarcoma				
Overall rate	0/47 (0.0%)	0/48 (0.0%)	1/48 (2.1%)	4/48 (8.3%)
Poly-3 test	P=0.003	—	P=0.470	P=0.035

Table 10
Incidences of Neoplasms and Nonneoplastic Lesions of the Heart in Mice in the 2-Year Drinking Water Study of Urethane, Ethanol, and Urethane/Ethanol

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
Female				
0% Ethanol				
Number Examined Microscopically	48	48	48	48
Hyperplasia, Endothelium				
Minimal	0 (0.0%)	0 (0.0%)	1 (2.1%)	3 (6.3%)
Mild	1 (2.1%)	0 (0.0%)	2 (4.2%)	3 (6.3%)
Monotonic trend test	P=0.005	P=0.841	P=0.130	P=0.014
Hemangiosarcoma	0	0	1	0
2.5% Ethanol				
Number Examined Microscopically	47	47	48	48
Hyperplasia, Endothelium				
Minimal	0 (0.0%)	0 (0.0%)	3 (6.3%)	4 (8.3%)
Mild	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (6.3%)
Moderate	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.1%)
Monotonic trend test	P<0.001	—	P=0.020	P<0.001
Angiectasis				
Minimal	0 (0.0%)	0 (0.0%)	1 (2.1%)	2 (4.2%)
Mild	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (4.2%)
Monotonic trend test	P=0.004	—	P=0.134	P=0.006
Hemangiosarcoma	0	0	0	3
5% Ethanol				
Number Examined Microscopically	47	48	48	47
Hyperplasia, Endothelium				
Minimal	0 (0.0%)	0 (0.0%)	2 (4.2%)	5 (10.6%)
Mild	0 (0.0%)	0 (0.0%)	1 (2.1%)	7 (14.9%)
Moderate	0 (0.0%)	1 (2.1%)	0 (0.0%)	2 (4.3%)
Monotonic trend test	P<0.001	P=0.161	P=0.039	P<0.001
Angiectasis				
Minimal	0 (0.0%)	0 (0.0%)	1 (2.1%)	1 (2.1%)
Mild	0 (0.0%)	0 (0.0%)	2 (4.2%)	3 (6.4%)
Monotonic trend test	P=0.005	—	P=0.019	P=0.017
Hemangiosarcoma				
Overall rate	0/47 (0.0%)	0/48 (0.0%)	0/48 (0.0%)	6/47 (12.8%)
Poly-3 test	P=0.001	—	—	P=0.004

[a] Number of animals with lesion
[b] Beneath the control incidence is (0 ppm urethane) the overall monotonic trend in severity with exposure level tested using the Jonckheere-Terpstra test statistic. Beneath the exposed group incidence are the P values corresponding to pairwise monotonic tests of severity with exposure concentration using the Williams' modification of Shirley's nonparametric test for a monotonic dose response.
[c] Percentage of animals with lesion of given severity
[d] Value of statistic cannot be computed.
[e] Number of animals with neoplasm per number of animals with heart examined microscopically
[f] Beneath the control incidence is the P value associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and that exposed group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice.

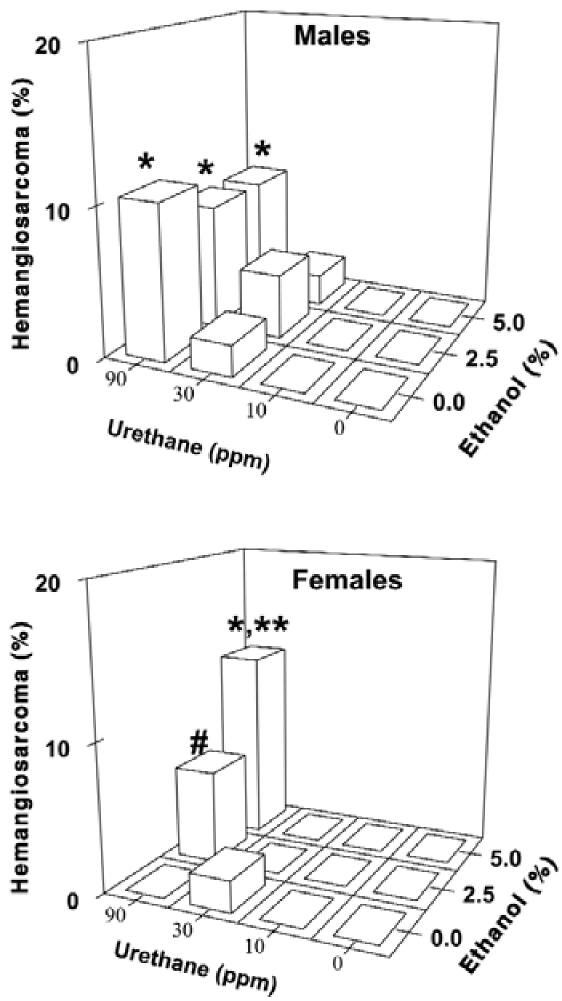


FIGURE 24
Incidences of Hemangiosarcoma of the Heart in Mice Exposed to Urethane and 0%, 2.5%, or 5% Ethanol in Drinking Water for 2 Years
[*=Significantly increased compared to group exposed to 0 ppm urethane and the same (i.e., 0%, 2.5%, or 5%) concentration of ethanol; **=Significantly increased compared to group exposed to 90 ppm urethane and 0% ethanol; #=Marginally increased compared to group exposed to 0 ppm urethane and 2.5% ethanol]

The endothelial hyperplasia and angiectasis were morphologically different, though possibly related, and involved the microvasculature of the heart. Endothelial hyperplasia was characterized by increased numbers of slightly enlarged hyperchromatic nuclei in the capillary endothelium between individual cardiac muscle fibers. Most endothelial hyperplastic lesions were focal changes that varied greatly in size, and the size of the lesion was the primary determination for severity grades. Angiectasis consisted of focal dilatation of vascular spaces in the myocardium. The dilated spaces were lined by a single layer of essentially normal endothelial cells, and the size of the angiectatic foci was the basis for severity grade.

Ovary and Uterus: The incidences of granulosa cell tumors (benign or malignant) occurred with positive trends in females exposed to increasing concentrations of urethane and 0%, 2.5%, or 5% ethanol (Tables 11, D2a, E2, and F2; Figure 25). The incidences of these neoplasms were significantly increased in females exposed to 90 ppm urethane and 0% ethanol and in females exposed to 30 ppm urethane and 5% ethanol. Marginally increased incidences occurred in females exposed to 30 or 90 ppm urethane and 2.5% ethanol and in females exposed to 90 ppm urethane and 5% ethanol. The incidences of these ovarian tumors generally exceeded the historical control ranges in females exposed to 30 or 90 ppm urethane and 0%, 2.5%, or 5% ethanol (Tables 11 and D3f).

In females exposed to increasing concentrations of urethane and 0%, 2.5%, or 5% ethanol, hemangiosarcoma of the uterus occurred in eight urethane-exposed females. None of the increased incidences were significant (Tables 11, D1, E1, F1), but the incidence in females exposed to 90 ppm urethane and 0% ethanol exceeded the historical control range for hemangiosarcoma (all sites) [6/518 (1.2%), range 0%-2%; Table D3a].

Incidences of ovarian and uterine neoplasms were not affected by exposure to increasing concentrations of ethanol and 0, 10, 30, or 90 ppm urethane (Tables 11, D1, D2d, and D2e).

In the uterus of females exposed to increasing concentrations of urethane and 0% or 2.5% ethanol, incidences of angiectasis (dilated vascular spaces lined by a single layer of essentially normal endothelial cells) and thrombosis occurred with positive trends, and the incidences in females exposed to 30 or 90 ppm urethane were significantly increased (Tables 11, D4, and E3). Hemorrhage from large areas of uterine angiectasis was the cause of death in five females (one exposed to 30 ppm and four exposed to 90 ppm urethane).

The incidences of uterine angiectasis and thrombosis were generally not affected by increasing concentrations of ethanol and 0, 10, 30, or 90 ppm urethane except for a slight ethanol-induced increase in females exposed to 0 ppm urethane (Tables 11, D4, E3, and F3).

Angiectasis was differentiated from hemangiosarcoma by the presence of proliferating endothelial cells that formed irregular vascular spaces in hemangiosarcomas. In angiectasis, endothelial cells were sometimes slightly enlarged but were arranged in orderly fashion forming a single cell layer that lined dilated vascular spaces. Thrombus formation was frequent in larger areas of angiectasis. At the periphery of large thrombi, there were usually increased numbers of plump spindle-shaped endothelial cells and a few fibroblasts infiltrating the superficial layers of fibrin.

Forestomach: The incidences of squamous cell papilloma or carcinoma (combined) occurred with a positive trend in males exposed to increasing concentrations of urethane and 0% ethanol, and the incidence in the 90 ppm group was significantly increased (0 ppm, 0/46; 10 ppm, 2/47; 30 ppm, 3/44; 90 ppm, 5/45) (Figure 26 and Table A2a). The incidences of this neoplasm in males were not affected by exposure to increasing concentrations of ethanol and 0, 10, 30, or 90 ppm urethane (Tables A2b through A2e). The incidences of this neoplasm in all urethane-exposed groups of males exceeded the historical control range [2/458 (0.4%), range 0%-2%].

Table 11
Incidences of Neoplasms and Nonneoplastic Lesions of the Reproductive System in Female Mice in the 2-Year Drinking Water Study of Urethane, Ethanol, and Urethane/Ethanol

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
0% Ethanol				
Ovary[a]	48	46	46	39
Benign Granulosa Cell Tumor[b,c]	0	0	2	3*
Malignant Granulosa Cell Tumor[d]	0	0	0	3*
Benign or Malignant Granulosa Cell Tumor[d]				
Overall rate[e]	0/48 (0.0%)	0/46 (0.0%)	2/46 (4.3%)	5/39 (12.8%)
Poly-3 test[f]	P=0.001	—[g]	P=0.203	P=0.004
Uterus	48	47	48	46
Angiectasis				
Minimal	0 (0.0%)[i]	2 (4.3%)	0 (0.0%)	0 (0.0%)
Mild	0 (0.0%)	0 (0.0%)	1 (2.1%)	2 (4.3%)
Moderate	0 (0.0%)	1 (2.1%)	4 (8.3%)	2 (4.3%)
Marked	0 (0.0%)	1 (2.1%)	1 (2.1%)	3 (6.5%)
Monotonic trend test[h]	P=0.003	P=0.020	P=0.009	P=0.005
Thrombosis				
Moderate	0 (0.0%)	0 (0.0%)	3 (6.3%)	1 (2.2%)
Marked	0 (0.0%)	1 (2.1%)	1 (2.1%)	3 (6.5%)
Monotonic trend test	P=0.010	P=0.156	P=0.016	P=0.028
Hemangiosarcoma	0	0	0	2
2.5% Ethanol				
Ovary				
Benign Granulosa Cell Tumor				
Overall rate	0/47 (0.0%)	0/46 (0.0%)	3/47 (6.4%)	3/48 (6.3%)
Poly-3 test	P=0.023	—	P=0.080	P=0.073
Uterus	47	47	48	48
Angiectasis				
Mild	1 (2.1%)	2 (4.3%)	2 (4.2%)	5 (10.4%)
Moderate	0 (0.0%)	0 (0.0%)	4 (8.3%)	3 (6.3%)
Marked	0 (0.0%)	0 (0.0%)	1 (2.1%)	1 (2.1%)
Monotonic trend test	P<0.001	P=0.280	P=0.009	P=0.004
Thrombosis				
Mild	0 (0.0%)	0 (0.0%)	2 (4.2%)	0 (0.0%)
Moderate	0 (0.0%)	0 (0.0%)	2 (4.2%)	4 (8.3%)
Marked	0 (0.0%)	0 (0.0%)	1 (2.1%)	2 (4.2%)
Monotonic trend test	P=0.001	—	P=0.003	P=0.005
Hemangiosarcoma	0	0	1	1

Table 11
Incidences of Neoplasms and Nonneoplastic Lesions of the Reproductive System in Female Mice in the 2-Year Drinking Water Study of Urethane, Ethanol, and Urethane/Ethanol

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
5% Ethanol				
Ovary	46	47	46	45
Benign Granulosa Cell Tumor	0	0	5*	3
Malignant Granulosa Cell Tumor	0	0	1	0
Benign or Malignant Granulosa Cell Tumor				
Overall rate	0/46 (0.0%)	0/47 (0.0%)	6/46 (13.0%)	3/45 (6.7%)
Poly-3 test	P=0.022	—	P=0.011	P=0.064
Uterus	48	48	47	45
Angiectasis				
Mild	1 (2.1%)	0 (0.0%)	6 (12.8%)	2 (4.4%)
Moderate	1 (2.1%)	0 (0.0%)	2 (4.3%)	3 (6.7%)
Marked	2 (4.2%)	2 (4.2%)	0 (0.0%)	1 (2.2%)
Monotonic trend test	P=0.093	P=0.789	P=0.116	P=0.207
Thrombosis				
Moderate	0 (0.0%)	0 (0.0%)	2 (4.3%)	3 (6.7%)
Marked	1 (2.1%)	2 (4.2%)	0 (0.0%)	1 (2.2%)
Monotonic trend test	P=0.080	P=0.280	P=0.347	P=0.083
Hemangiosarcoma	0	2	1	1

[a] Number of animals with ovary or uterus examined microscopically
[b] Number of animals with lesion
[c] Historical incidence for control groups in NCTR studies: 0/504
[d] Historical incidence (mean): 1/504 (0.2%), range 0%-1%
[e] Number of animals with neoplasm per number of animals with ovary examined microscopically
[f] Beneath the control incidence (0 ppm urethane) is the P value associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and that exposed group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice.
[g] Value of statistic cannot be computed.
[h] Beneath the control incidence is the overall monotonic trend in severity with exposure level tested using the Jonckheere-Terpstra test statistic. Beneath the exposed group incidence are the P values corresponding to pairwise monotonic tests of severity with exposure concentration using the Williams' modification of Shirley's nonparametric test for a monotonic dose response.
[i] Percentage of animals with lesion of given severity

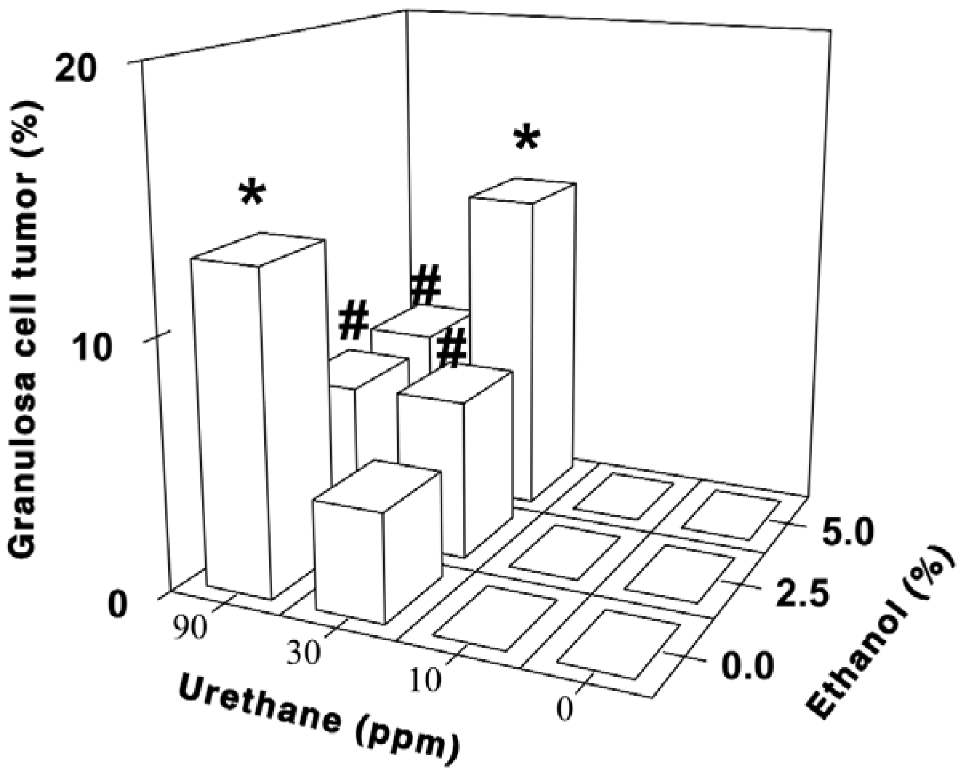


FIGURE 25
Incidences of Granulosa Cell Tumor of the Ovary in Female Mice Exposed to Urethane and 0%, 2.5%, or 5% Ethanol in Drinking Water for 2 Years
[*=Significantly increased compared to group exposed to 0 ppm urethane and the same (i.e., 0%, 2.5%, or 5%) concentration of ethanol; #=Marginally increased compared to group exposed to 0 ppm urethane and the same (i.e., 0%, 2.5%, or 5%) concentration of ethanol]

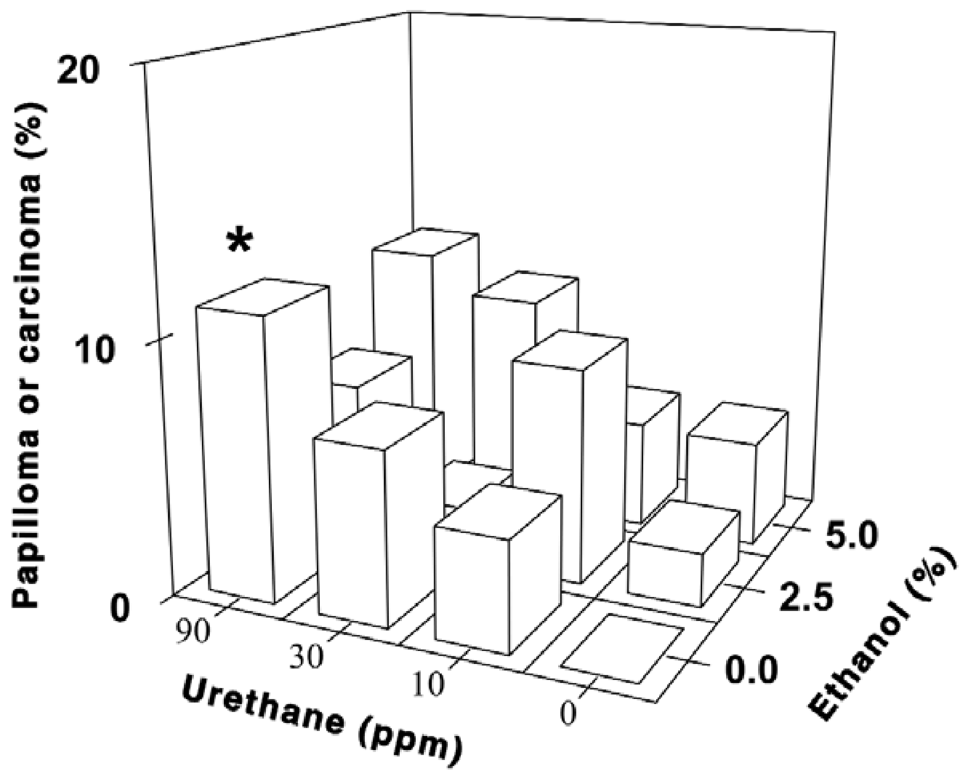


FIGURE 26
Incidences of Squamous Cell Papilloma or Carcinoma (Combined) of the Forestomach in Male Mice Exposed to Urethane and 0%, 2.5%, or 5% Ethanol in Drinking Water for 2 Years
(*=Significantly increased compared to group exposed to 0 ppm urethane and 0% ethanol)

Skin: Increasing the concentration of urethane, in the presence of 0%, 2.5%, or 5% ethanol, caused a dose-dependent increase in squamous cell papilloma or carcinoma of the skin of male B6C3F$_1$ mice, with the incidence being significant at 30 and 90 ppm urethane in the presence of 2.5% ethanol and at 90 ppm urethane in the presence of 0% and 5% ethanol (Tables 12, D1, and E1; Figure 27). Varying the ethanol concentration, at a constant level of urethane, did not affect the tumor incidence. Likewise, urethane did not affect the incidence of squamous cell papilloma or carcinoma in female B6C3F$_1$ mice (not shown).

Urethane caused slight increases in the incidences of hemangiosarcoma of the skin in females exposed to 0% ethanol (0 ppm, 0/48; 10 ppm, 0/48; 30 ppm, 0/46; 90 ppm, 2/48) or 2.5% ethanol (0/47, 0/47, 0/48, 2/47) (Tables D1 and E1); these increases were considered to be exposure-related. The incidences of this neoplasm in females exposed to 90 ppm urethane and 0% or 2.5% ethanol exceeded the historical control range for hemangiosarcoma (all sites) [6/518 (1.2%), range 0%-2%; Table D3a].

Spleen: Incidences of hemangiosarcoma of the spleen increased in males exposed to increasing concentrations of urethane and 2.5% ethanol and in females exposed to increasing concentrations of urethane and 0% or 2.5% ethanol (Tables 13, A2a, B2, D2a, and E2). The incidence of this neoplasm in females exposed to 90 ppm urethane and 0% ethanol was significantly increased, and the incidences in males and females were considered to be exposure-related. The incidences of this neoplasm in mice exposed to 90 ppm urethane and 0% or 2.5% ethanol exceeded the historical control ranges for hemangiosarcoma (all sites) [male: 7/474 (1.5%), range 0%-4%; female: 6/518 (1.2%), range 0%-2%; Tables A3a and D3a].

In addition to the liver, heart, and spleen in males and females and the uterus and skin in females, incidences of hemangiosarcoma occurred in many different organs in mice including the bone, bone marrow, mesentery, lung, and kidney of males and females, the pancreas, forestomach, preputial gland, seminal vesicle, and mandibular, mesenteric, and inguinal lymph node of males, and the adrenal cortex, skeletal muscle, and ovary of females (Tables A1, B1, C1, D1, E1, and F1). However, the incidences of this neoplasm in these organs were not exposure concentration related.

Table 12
Incidences of Squamous Cell Papilloma or Carcinoma (Combined) of the Skin in Male B6C3F$_1$ Mice in the 2-Year Drinking Water Study of Urethane, Ethanol, and Urethane/Ethanol

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
0% Ethanol				
Squamous Cell Papilloma or Carcinoma[a]				
Overall rate[b]	0/47 (0.0%)	1/48 (2.1%)	3/47 (6.4%)	6/48 (12.5%)
Poly-3 test[c]	P=0.001	P=0.497	P=0.127	P=0.007
2.5% Ethanol				
Squamous Cell Papilloma or Carcinoma				
Overall rate	0/48 (0.0%)	1/48 (2.1%)	4/46 (8.7%)	7/47 (14.9%)
Poly-3 test	P=0.001	P=0.503	P=0.043	P=0.005
5% Ethanol				
Squamous Cell Papilloma or Carcinoma				
Overall rate	0/48 (0.0%)	2/47 (4.3%)	0/48 (0.0%)	7/45 (15.6%)
Poly-3 test	P=0.001	P=0.211	—[d]	P=0.002

[a] Historical incidence for control groups in NCTR studies: 0/468
[b] Number of animals with neoplasm per number of animals with skin examined microscopically
[c] Beneath the control incidence (0 ppm urethane) is the P value associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and that exposed group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice.
[d] Value of statistic cannot be computed.

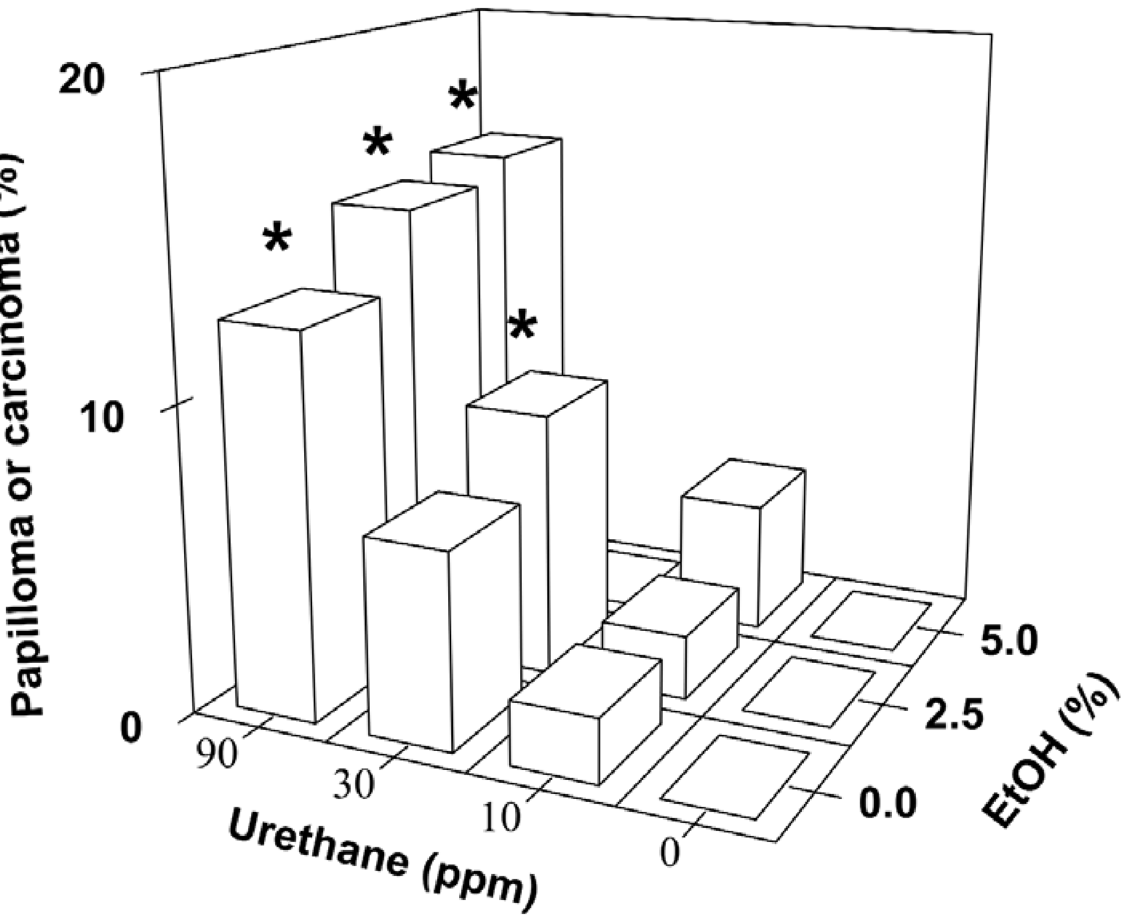


Figure 27
Incidences of Squamous Cell Papilloma or Carcinoma (Combined) of the Skin in Male Mice Exposed to Urethane and 0%, 2.5%, or 5% Ethanol in Drinking Water for 2 Years
(*=Significantly increased compared to group exposed to 0 ppm urethane and 0% ethanol)

TABLE 13
Incidence of Hemangiosarcoma of the Spleen in Mice in the 2-Year Drinking Water Study of Urethane, Ethanol, and Urethane/Ethanol

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
Male				
0% Ethanol				
Hemangiosarcoma				
Overall rate[a]	2/44 (4.5%)	2/46 (4.3%)	2/45 (4.4%)	5/42 (11.9%)
Poly-3 test[b]	P=0.051	P=0.692	P=0.681N	P=0.120
2.5% Ethanol				
Hemangiosarcoma				
Overall rate	0/46 (0.0%)	0/46 (0.0%)	1/46 (2.2%)	3/46 (6.5%)
Poly-3 test	P=0.015	—[c]	P=0.478	P=0.099
5% Ethanol				
Hemangiosarcoma	0/48	1/46	0/46	1/45
Female				
0% Ethanol				
Hemangiosarcoma				
Overall rate	0/48 (0.0%)	0/45 (0.0%)	1/47 (2.1%)	4/46 (8.7%)
Poly-3 test	P=0.001	—	P=0.471	P=0.021
2.5% Ethanol				
Hemangiosarcoma				
Overall rate	0/47 (0.0%)	0/46 (0.0%)	0/46 (0.0%)	3/46 (6.5%)
Poly-3 test	P=0.005	—	—	P=0.069
5% Ethanol				
Hemangiosarcoma	0/48	1/47	0/48	1/45

[a] Number of animals with neoplasm per number of animals examined microscopically
[b] Beneath the control incidence (0 ppm urethane) is the P value associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and that exposed group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice. A lower incidence in an exposed group is indicated by **N**.
[c] Value of statistic cannot be computed.

DISCUSSION AND CONCLUSIONS

Survival, Body Weights, and Water and Feed Consumption

In the current 2-year study, survival of mice significantly decreased as the urethane content of the drinking water was increased, and the decrease was more pronounced in females than in males. In a drinking water study conducted by Inai *et al.* (1991), survival of male B6C3F$_1$ mice exposed to 600 ppm urethane for 70 weeks was decreased, but survival of those exposed to 0.6, 3, 6, or 60 ppm urethane was not decreased; the mice were killed after 70 weeks of exposure. In the present study, decreases in survival were evident after approximately 80 weeks of exposure. A similar decrease in survival of NMRI mice exposed to concentrations up to 12.5 mg urethane/kg body weight per day in drinking water began at approximately 85 weeks into the study (Schmähl *et al.*, 1977); that exposure concentration is similar to the 90 ppm urethane concentration used in the current 2-year study.

Survival of female mice was not affected by ethanol in the current 2-year study. However, in male mice, there was a marginal exposure-related increase in survival as a function of the ethanol concentration, and male mice exposed to 5% ethanol in the absence of urethane survived significantly longer than males that did not receive ethanol. Schmidt *et al.* (1987) also reported an increase in survival of male C57BL/10J mice administered 7.5% ethanol, but there was no effect on survival at 3.5% ethanol, and there was a decrease in survival of mice at 15% ethanol.

In the current 2-year study, water consumption was affected by ethanol, but not urethane. Specifically, as the concentration of ethanol increased, the fluid intake by mice decreased. Concomitant with the decrease in fluid intake, there was a decrease in feed consumption as the ethanol concentration (but not urethane) in drinking water increased, which resulted in similar caloric intake among the exposed groups. Based upon a caloric content of 4.5 kcal/g for NIH-31 diet (Lewis, 1996, personal communication) and 7.11 kcal/g for ethanol (Mayes, 1996), male mice that received 0%, 2.5%, or 5% ethanol in the current 2-year study consumed 25.5, 24.7, or 24.4 kcal/day, respectively, while female mice consumed 21.8, 21.3, or 21.2 kcal/day, respectively.

A decrease in the mean fluid intake occurred in 14- to 160-week-old male C57BL/10J mice administered 12% ethanol in drinking water (Schmidt *et al.*, 1987); however, no decrease occurred in mice given 3.5% or 7.5% ethanol. The Schmidt *et al.* (1987) study differed from the current 2-year study in a number of ways, including the strain of mouse, exposure period, and number of mice per cage. In another study, feed consumption by Sprague-Dawley rats was not affected by 1% ethanol in a semisynthetic liquid diet (Holmberg and Ekström, 1995). When the ethanol content was increased to 3%, exposed male rats decreased their feed intake compared to the control rats that received an isocaloric glucose diet, whereas the opposite trend occurred in female rats.

In the current 2-year study, mean body weights of mice were affected by urethane beginning at approximately 92 weeks (males) and 56 weeks (females). These changes probably reflected the exposure-related changes in survival due to the induction of neoplasia that occurred after increasing the urethane content of the drinking water. Body weights were not affected by ethanol, which is similar to what occurred in male C57BL/10J mice during lifetime exposure of up to 12% ethanol (Schmidt *et al.*, 1987). In contrast, there was a significant decrease in the body weights of Sprague-Dawley rats exposed to 3% ethanol in a semisynthetic liquid diet (Holmberg and Ekström, 1995).

Mice in the current 2-year study adjusted their caloric intake by decreasing their feed consumption as the ethanol content of the drinking water increased. This observation is important because the spontaneous incidence of certain tumors in mice is related to body weight (Seilkop, 1995; Haseman *et al.*, 1997); it should be noted, however, that while the total calories consumed were nearly identical among the groups in the current study, there was a decreasing trend in males and females as the ethanol content increased. This suggests that the mice utilized the calories obtained from ethanol more efficiently than those obtained from the NIH-31 diet, an interpretation supported by the fact that only about 80% of the NIH-31 diet is metabolically available (Lewis, 1996, personal communication).

Although ethanol did not affect the body weights of mice in the current 2-year study, the body weights of mice in all exposure groups were substantially greater than those of B6C3F$_1$ mice typically used at the National Center for Toxicological Research (NCTR). This was particularly true for female mice, which weighed nearly 50 g at the end of the study compared to the typical 35 g in other NCTR studies (Turturro and Hart, 1986; Culp *et al.*, 1998; Culp, personal communication). This trend was less pronounced in males; nonetheless, males in the current 2-year study weighed approximately 10% more than is typically seen in NCTR studies. Comparisons of current study results to historical control results must be conducted with caution because of the relationship between the spontaneous incidences of certain tumors to body weight (Seilkop, 1995; Haseman *et al.*, 1997).

The mice in the current 2-year study were fed pelleted NIH-31 diet. When compared to another bioassay conducted at the NCTR using the same feed (experiment E0503) (Turturro and Hart, 1986), the amount of feed consumed by the mice in the two studies was nearly identical. A major difference between these two studies is that while the mice in the current study were housed four per cage, the mice in study E0503 were housed singly. In other recent NCTR bioassays (studies E2127 and E6722) (Culp *et al.*, 1998; Culp, personal communication), group-housed female B6C3F$_1$ mice also received NIH-31 meal. The mice in those studies showed weight gains similar to those in study E0503; however, feed consumption in studies E2127 and E6722 was only 75% of that observed in the current 2-year study and study E0503. From these data, we concluded that singly-housed mice have greater energy requirements than group-housed mice, and thus require more food to maintain the same weight. It also appears that feed consumption by group-housed mice fed pelleted NIH-31 diet in the current 2-year study was greater than that by group-housed mice fed NIH-31 meal in previous NCTR studies, and that this greater feed consumption by mice in the current 2-year study was responsible for the increased body weight.

In Schmidt *et al.* (1987), water consumption by the group-housed males was substantially less than that by the males housed singly. Body weights of both groups were nearly identical; however, because feed consumption was not reported, it is difficult to make comparisons to the current 2-year study. As noted earlier, mice in the Schmidt *et al.* (1987) study did not decrease fluid intake even after they received 3.5% or 7% ethanol in contrast to the decrease that occurred in the current 2-year study. This difference may be due to the greater energy requirements to maintain the body weight of the singly housed mice.

Urethane Carcinogenesis

The liver in mice is a common tumor target of urethane (Mirvish, 1968; IARC, 1974; Dragani *et al.*, 1984), although this is not always the case (Inai *et al.*, 1991). Hepatocellular adenomas and carcinomas are thought to arise from the sequential metabolism of urethane to vinyl carbamate and vinyl carbamate epoxide (Ribovich *et al.*, 1982). In support of this, vinyl carbamate has been shown to induce more hepatocellular carcinomas than urethane (Dahl *et al.*, 1980), and vinyl carbamate epoxide is more hepatocarcinogenic than vinyl carbamate (Park *et al.*, 1993). DNA adducts indicative of vinyl carbamate epoxide have been detected in liver DNA of mice treated with urethane, vinyl carbamate, and vinyl carbamate epoxide (Fernando *et al.*, 1996). In addition, hepatocellular adenomas and carcinomas induced by urethane and vinyl carbamate in B6C3F$_1$ mice have a characteristic increase in CAA to CTA mutations at codon 61 of the H-*ras* oncogene when compared to the CAA to AAA mutations typically found in spontaneous tumors (Wiseman *et al.*, 1986; Dragani *et al.*, 1991; Maronpot *et al.*, 1995; Watson *et al.*, 1995). Such a mutation is consistent with the formation of 1,N^6-ethenodeoxyadenosine, which is known to lead to transversion mutations from dA to dT (Levine *et al.*, 2000).

In the absence of urethane and ethanol in the current 2-year study, the incidences of hepatocellular adenoma or carcinoma (combined) were 26.1% in males and 10.4% in females. The incidence in these control males was similar to the incidences in other studies conducted at the NCTR. However, the incidence of this neoplasm in control females was greater than the historical mean, but still within the historical control range. The high spontaneous liver neoplasm incidence in female mice was probably a reflection of their increased body weight (Seilkop, 1995; Haseman *et al.*, 1997).

Urethane, in the absence of ethanol, caused exposure-related increases in the incidences of hepatocellular adenoma or carcinoma (combined) in males and females in the current 2-year study. These increased incidences could have been due to increases in the concentrations of 1,N^6-ethenodeoxyadenosine in hepatic DNA, such as that recorded in the current 4-week study. Compared to other carcinogens administered chronically (Beland and Poirier, 1993), however, the increase in 1,N^6-ethenodeoxyadenosine was rather modest (approximately 25%); nonetheless, it was consistent with that reported by Fernando *et al.*, (1996) who administered 250 nmol urethane/g body weight per day to adult B6C3F$_1$ mice. Mice given 90 ppm urethane in the current 2-year study consumed approximately 90 nmol/g per day.

The LC-ES MS/MS method used to conduct the DNA adduct analyses in current 4-week study was designed to detect 1,N^6-ethenodeoxyadenosine and 3,N^4-ethenodeoxycytidine. Two other DNA adducts, 3,N^2-ethenodeoxyguanosine and 7-(2-oxoethyl)-deoxyguanosine, are also formed upon the metabolic activation of urethane. While these adducts could be involved in the tumorigenicity of urethane, the fact that a CAA to CTA transversion in codon 61 of the H-*ras* protooncogene, which is typically observed in hepatocellular tumors induced by urethane (Dragani *et al.*, 1991), suggests that 1,N^6-ethenodeoxyadenosine would make a substantially greater contribution.

Female mice exposed to urethane in the current 4-week study had a fourfold increase in the percentage of hepatocytes in the G1 phase of the cell cycle; this change did not occur in males. The fact that female mice had a greater relative increase in the incidence of hepatocellular neoplasms suggests that the formation of 1,N^6-ethenodeoxyadenosine, coupled with the greater rate of cell replication, contributed to the neoplasm response.

In addition to the increased incidences of hepatocellular adenoma and hepatocellular carcinoma, urethane caused exposure-related increases in the incidences of liver hemangiosarcoma in the current 2-year study; the increases were significant in mice exposed to 90 ppm urethane. Urethane also caused significant increases in the incidences of hemangiosarcoma of the heart and the incidence of angiectasis, which may represent a proliferative or potentially preneoplastic lesion preceding hemangiosarcoma, was increased by urethane in both liver and heart. Hemangiosarcomas are rare in B6C3F$_1$ mice; the control incidences in all organs in studies conducted at the NCTR are 1.5% in males and 1.2% in females. The mechanism for the induction of hemangiosarcoma is not known, but liver and heart hemangiosarcomas were also observed by Inai *et al.* (1991), who found a significant increase in the incidence in male mice exposed to 600 ppm urethane in the drinking water. In the current 2-year study and in the Inai *et al.* (1991) study, the formation of hemangiosarcoma appeared to be markedly nonlinear. In the Inai *et al.* (1991) study, a significantly increased incidence of hemangiosarcoma occurred only in the 600 ppm group; in the current 2-year study, a significant increase occurred only in the 90 ppm group. With other carcinogens, similar exposure responses have been attributed to carcinogen-induced toxicity at higher concentrations, with a concomitant increase in cell replication (Cohen and Ellwein, 1990, 1992, 1995; Culp *et al.*, 2000). In preliminary NCTR studies, the levels of 8-oxodeoxyguanosine, 1,N^6-ethenodeoxyadenosine, and 3,N^4-ethen- odeoxycytidine were substantially higher in liver endothelial cells than in hepatocytes; however, the levels were not dramatically affected by the presence of urethane (Hamilton, Doerge, and Beland, unpublished data). Although these data need to be confirmed, they support the concept that the incidence of hemangiosarcoma may result from enhanced cell proliferation due to toxicity that occurs at high doses of urethane.

In the absence of urethane and ethanol in the current 2-year study, the incidences of alveolar/bronchiolar adenoma or carcinoma (combined) were 10.4% in males and 12.5% in females. The incidence in males was at the low end of the historical control range in studies conducted at the NCTR; the incidence in females exceeded the historical control range. The occurrence of lung tumors in female B6C3F$_1$ mice is not related to body weight (Seilkop, 1995; Haseman *et al.*, 1997); thus, the increased spontaneous incidence of these neoplasms cannot be explained by the increased body weights of female control mice in the current 2-year study.

Urethane caused an exposure-related increase in the incidences of alveolar/bronchiolar adenoma or carcinoma (combined) in males and females. In the absence of ethanol, a statistically significant increase in alveolar/brnchiolar adenoma or carcinoma (combined) was detected at 10 ppm in male mice (37.5%) and 30 ppm in female mice (58.3%), and the incidence reached 77.1% in males and 83.0% in females at 90 ppm urethane. Inai *et al.* (1991) also found an increase in the incidences of alveolar/bronchiolar adenoma or carcinoma in male B6C3F$_1$ mice; the incidences were 68.0% and 95.5% at 60 and 600 ppm urethane, respectively. They did not detect an increase in tumors at 6 ppm; in addition, no carcinomas occurred in mice exposed to 60 ppm urethane and only a low incidence (13.6%) in mice exposed to 600 ppm. In contrast, the incidences of alveolar/bronchiolar carcinoma were only slightly less than those of alveolar/bronchiolar adenoma in males and females in the current 2-year study.

A urethane-induced formation of alveolar/bronchiolar adenoma or carcinoma (combined) in male B6C3F$_1$ mice was associated with activation of the K-*ras* protooncogene, which occurs in approximately 50% of the tumors (Kawano *et al.*, 1995). A CAA to CTA transversion in codon 61 was the major mutation detected (62% of the mutations). Codon 61 CAA to CGA transversion (21%) and codon 12 GGT to GAT (18%) transition mutations were detected to a lesser extent. K-*ras* mutations were found in approximately 30% of spontaneous tumors in male B6C3F$_1$ mice, and the majority of mutations (73%) involved dG transitions and transversions at codons 12 and 13 (Sills *et al.*, 1999; Hayashi *et al.*, 2001). A comparison of these data suggests that the interaction of urethane metabolites with dA is involved in lung tumor initiation. This interpretation is supported by the high prevalence of K-*ras* mutations in lung tumors induced by vinyl carbamate in various C57BL/6J hybrids; the majority involved codon 61 CAA to CGA transition and CAA to CTA transversion mutations (Massey *et al.*, 1995). Nonetheless, the administration of urethane did not affect the levels of 1,*N*^{6}-ethenodeoxyadenosine or 3,*N*^{4}-ethenodeoxycytidine in lung DNA. Furthermore, Fernando *et al.* (1996) reported only a modest (and probably statistically insignificant) increase in 1,*N*^{6}-ethenodeoxyadenosine and no change in the levels of 3,*N*^{4}-ethenodeoxycytidine in adult male B6C3F$_1$ mice treated with urethane. Although the levels of 1,*N*^{6}-ethenodeoxyadenosine and 3,*N*^{4}-ethenodeoxycytidine were not increased after treatment with urethane in the current 4-week study, there was a significant decrease in PCNA labeling. This suggests that there was urethane-induced DNA damage and that progression through the cell cycle was arrested until the damage could be repaired.

In the current 2-year study, urethane caused increased incidences of adenocarcinoma and adenoacanthoma of the mammary gland in females; these are rare neoplasms in B6C3F$_1$ mice. In studies conducted at the NCTR, the spontaneous incidences were 1.1% for adenocarcinoma and 0% for adenoacanthoma. Similar to the NCTR historical control data, mammary gland adenoacanthoma did not occur in control mice (0 ppm urethane and 0% ethanol) in the current study; however, the incidence of adenocarcinoma (8.5%) exceeded the historical control incidence. As noted previously, female mice in the current 2-year study weighed considerably more than B6C3F$_1$ mice used at the NCTR. The incidence of mammary gland neoplasms is related to body weight in F344 rats; although, this does not appear to be the case with B6C3F$_1$ mice (Seilkop, 1995; Haseman *et al.*, 1997). Nonetheless, the incidence of mammary gland adenocarcinoma in 90 ppm females in the current study exceeded the control incidence by a factor of three, which supports the observations of Tannenbaum and Silverstone (1958) and Della Porta *et al.* (1967), who reported the induction of mammary gland carcinoma in female B6C3F$_1$ mice after administration of urethane by various routes. Adenocarcinomas and adenoacanthomas were also reported in other strains of mice (Tannenbaum and Silverstone, 1958; Tannenbaum and Maltoni, 1962; Della Porta *et al.*,1967; Imai *et al.*, 1982, 1984).

In the current 2-year study, urethane induced high incidences of harderian gland adenoma and carcinoma in males and females, and the increases occurred in a relatively linear manner. In control mice, the incidences of adenoma or carcinoma (combined) (6.4% in males and 6.3% in females) were similar to those in controls from other studies conducted at the NCTR. The induction of harderian gland neoplasms was previously reported in B6C3F$_1$ mice (Tannenbaum and Silverstone, 1958; Della Porta *et al.*, 1967; Vesselinovitch *et al.*, 1971) as well as in other strains of mice (Della Porta *et al.*, 1963, 1967; Deringer, 1965; Klein, 1966) exposed to urethane.

In the current 2-year study, urethane also caused significant increases in the incidences of granulosa cell tumors of the ovary in female mice and of squamous cell papilloma or carcinoma (combined) of the forestomach and skin in males. The incidence of granulosa cell tumor of the ovary in 30 ppm females exceeded the incidence in historical controls, as did the forestomach neoplasm incidence in 10 ppm males.

The spectrum of tumors induced by urethane in the current study (i.e., increased incidences of liver, lung, and harderian gland neoplasms and hemangiosarcoma of the liver and heart in both sexes, forestomach neoplasms in males, and mammary gland and ovarian neoplasms in females) is very similar to what has been observed previously in B6C3F$_1$ mice exposed to 1,3-butadiene and isoprene (reviewed by Melnick and Sills, 2001). As with urethane, both of these compounds are thought to be metabolized to reactive epoxide intermediates, and this appears to be catalyzed primarily by cytochrome P450 2E1 (Bogaards *et al.*, 1996; Jackson *et al.*, 2000).

Ethanol Carcinogenesis

Equivocal results have been obtained in previous studies that assessed the carcinogenicity of ethanol in mice. Horie *et al.* (1965) administered 14% or 43% ethanol in the drinking water to CF_1 mice for 5 days per week and found low incidences of forestomach papilloma, malignant lymphoma, and lung adenoma in the 43% ethanol group; however, the lack of a control group make these data difficult to interpret. The same criticism applies to studies in which ddN mice were exposed to 19.5% ethanol in the drinking water 5 days per week (Kuratsune *et al.*, 1971) and C57Bl mice were treated with 200 µL of 40% ethanol by gavage twice weekly (Griciute *et al.*, 1981). In other studies, exposure to 12% ethanol in the drinking water decreased the latency of mammary gland tumors in female C3H/St mice (Schrauzer *et al.*, 1979). Likewise, the incidence of liver sarcoma was increased in C57Bl/10J mice exposed to 7.5% or 12% ethanol in the drinking water compared to those exposed to 0% or 3.5% ethanol (Schmidt *et al.*, 1987). In the current 2-year study, male $B6C3F_1$ mice exposed to ethanol had exposure-related increases in the incidences of hepatocellular adenoma and hepatocellular adenoma or carcinoma (combined); the incidences were significantly increased in the 5% ethanol group. A similar trend did not occur in female mice.

As noted in the Introduction of this Technical Report, ethanol is metabolized through oxidation to acetaldehyde, a process that is catalyzed primarily by alcohol dehydrogenase, and to a lesser extent, cytochrome P450 and catalase (IARC, 1988). Acetaldehyde reacts with the exocyclic amine of deoxyguanosine to form a Schiff base, which can be reduced to give N^2-ethyldeoxyguanosine (Fang and Vaca, 1995, 1997; Matsuda *et al.*, 1999; Terashima *et al.*, 2001). N^2-Ethyldeoxyguanosine has been detected in hepatic DNA from male C57Bl/6 mice administered 10% ethanol in drinking water for 5 weeks (Fang and Vaca, 1995); a potential criticism of this study is a lack of control mice, therefore, it is not clear whether the adduct detected was due solely to the oxidation of ethanol to acetaldehyde. In another study, female BD_6 rats were given 5% ethanol in the drinking water for 8 months (Izzotti *et al.*, 1998). When assessed by ^{32}P-postlabeling analyses, treatment-related DNA adducts were not detected in the esophagus, liver, lung, or heart after exposure to ethanol; however, the chromatographic conditions were such that the detection of N^2-ethyldeoxyguanosine would be quite unlikely. In the current 4-week study, the presence of N^2-ethyldeoxyguanosine in hepatic DNA was assessed using the method described by Fang and Vaca (1995). N^2-Ethyldeoxyguanosine was not detected in any of the samples with a detection limit of 6 adducts/10^8 nucleotides (Fang and Beland, unpublished observation).

The Effect of Ethanol on the Carcinogenicity of Urethane

Ethanol increased the activity of certain carcinogens in mice; for example, treating male and female C57Bl mice with ethanol and *N*-nitrosodimethylamine by gavage resulted in the induction of aesthesioneuroepithelioma, a tumor that did not occur in the absence of ethanol (Griciute *et al.*, 1981). Likewise, the coadministration of ethanol and *N*-nitrosodimethylamine in male strain A mice increased the incidence and multiplicity of lung tumors (Anderson, 1988; Anderson *et al.*, 1992). A similar ethanol-induced enhancement of tumorigenicity occurred with other *N*-nitrosamines, including *N*-nitrosodiethylamine (Griciute *et al.*, 1984; Anderson *et al.*, 1993), *N*-nitrosodi-*n*-propylamine (Griciute *et al.*, 1984), and *N*-nitrosopyrrolidine (Anderson *et al.*, 1993). The mechanism for the enhancement in carcinogenicity has been attributed to ethanol inhibiting the hepatic first-pass metabolism of the carcinogen, which increases exposure to extrahepatic organs, the sites of increased tumorigenesis (Anderson *et al.*, 1995). This mechanism is supported by the decreased rates of carcinogen clearance and increased DNA adduct formation in extrahepatic tissues (Anderson *et al.*, 1986, 1994). In addition, ethanol induces cytochrome P450 2E1 (Forkert *et al.*, 1991), the enzyme responsible for the metabolism of many low molecular-weight compounds and for the activation of *N*-nitrosamines. These concepts appear to have a direct bearing on the results obtained in the current 2-year study.

In the current 4-week study, female mice exposed to ethanol (in the presence or absence of urethane) for 4 weeks had a significant increase in hepatic cytochrome P450 2E1, and the increase was 1.3- and 1.6-fold at 2.5% and 5% ethanol, respectively. Although somewhat modest, a similar magnitude of induction was reported by Forkert *et al.* (1991) who exposed male CD-1 mice to

10% ethanol in the drinking water for 2 weeks. Because urethane is metabolized to a reactive electrophile by cytochrome P450 2E1, these results suggest there could be an increased activation of the carcinogen upon coadministration of ethanol, at least in female B6C3F$_1$ mice.

Urethane was detected only in the serum from mice exposed to ethanol in the current 4-week study; thus, as with *N*-nitrosamines (Anderson *et al.*, 1986, 1994), the coadministration of ethanol appeared to decrease the first-pass hepatic clearance of urethane, with a concomitant increase in its systemic distribution. Consistent with a decrease in hepatic metabolism of urethane, there was a decrease in the level of etheno dA in liver DNA of mice treated with ethanol.

Furthermore, as was observed with *N*-nitrosodimethylamine (Anderson, 1988; Anderson *et al.*, 1992) and *N*-nitrosopyrrolidine (Anderson *et al.*, 1993), in female B6C3F$_1$ mice administered 10 ppm urethane, ethanol caused exposure-related increases in the incidences of alveolar/bronchiolar adenoma or carcinoma (combined) in the current 2-year study, and the increase was significant in females exposed to 10 ppm urethane and 5% ethanol. This trend was not evident in females exposed to 30 or 90 ppm urethane; however, these exposure concentrations resulted in appreciably higher neoplasm incidences in the absence of ethanol. In the current 2-year study in males, ethanol caused an exposure-related decrease in the incidence of alveolar/bronchiolar adenoma at 10 ppm urethane, and the decrease was significant in the 5% ethanol group. In males exposed to 30 ppm urethane, ethanol caused exposure-related decreases in the incidences of alveolar/bronchiolar adenoma and alveolar/bronchiolar adenoma or carcinoma (combined), and the decreases were, again, significant in males exposed to 5% ethanol.

In the current 2-year study, ethanol also increased the incidence of hemangiosarcoma of the heart in females exposed to 90 ppm urethane, but not in males. This finding is of interest because heart hemangiosarcomas are very rare in B6C3F$_1$ mice. Ethanol also caused exposure-related decreases in the incidences of harderian gland adenoma or carcinoma (combined) in males exposed to 30 ppm urethane; the decrease was significant in the 5% ethanol group. The reason for these sex-related differences in response in the lung, heart, and harderian gland is not known, but may be related to the fact that ethanol induced cytochrome P450 2E1 in females, but not males. It should also be noted that the changes in tumorigenicity of ethanol were modest and could have been due to normal biological variation; therefore, the current studies do not establish a definitive effect of ethanol on the carcinogenicity of urethane.

Ethanol increased the incidences of forestomach tumors in C55Bl mice treated with *N*-nitrosodiethylamine and *N*-nitrosodi-*n*-propylamine (Griciute *et al.*, 1984). Although forestomach neoplasms occurred in male B6C3F$_1$ mice exposed to urethane in the current 2-year study, the occurrence of these neoplasms was not affected by ethanol.

CONCLUSIONS

Under the conditions of this 2-year drinking water study, there was *clear evidence of carcinogenic activity** of urethane in male B6C3F$_1$ mice based on increased incidences of liver, lung, harderian gland, skin, and forestomach neoplasms and of hemangiosarcoma, primarily of the liver and heart. There was *clear evidence of carcinogenic activity* of urethane in female B6C3F$_1$ mice based on increased incidences of liver, lung, harderian gland, mammary gland, and ovarian neoplasms and of hemangiosarcoma, primarily of the liver and spleen. The occurrences of hemangiosarcoma of the spleen in males and of the uterus and skin in females may have been exposure related.

Exposure to urethane resulted in increased incidences of nonneoplastic lesions of the liver and heart in males and females and of the uterus in females.

The design of this 2-year drinking water study was inadequate to determine the carcinogenic activity of ethanol in male and female B6C3F$_1$ mice.

Overall, there was weak evidence of an interaction of ethanol on the carcinogenicity of urethane in B6C3F$_1$ mice. In males, increasing the ethanol concentration may have decreased the alveolar/bronchiolar and harderian gland adenoma or carcinoma responses to urethane. In females, increasing the ethanol concentration may have increased the incidence of hemangiosarcoma of the heart and alveolar/bronchiolar adenoma or carcinoma responses to urethane.

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* Explanation of Levels of Evidence of Carcinogenic Activity is on page 13. A summary of the Technical Reports Review Subcommittee comments and public discussion on this Technical Report appears on page 15.

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APPENDIX A
SUMMARY OF LESIONS IN MALE MICE IN THE 2-YEAR DRINKING WATER STUDY OF URETHANE, ETHANOL, AND URETHANE/ETHANOL

Table A1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Drinking Water Study of Urethane and 0% Ethanol[a]

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
Disposition Summary				
Animals initially in study	48	48	48	48
Early deaths				
Moribund	2	8	4	11
Natural deaths	19	14	18	29
Survivors				
Terminal sacrifice	27	26	26	8
Animals examined microscopically	48	48	47	48
Alimentary System				
Esophagus	(47)	(47)	(46)	(46)
Lymphoma malignant	2 (4%)			
Gallbladder	(35)	(38)	(36)	(23)
Lymphoma malignant			1 (3%)	
Intestine large, cecum	(39)	(37)	(40)	(31)
Lymphoma malignant			1 (3%)	
Intestine small, ileum	(37)	(37)	(35)	(26)
Lymphoma malignant		1 (3%)	2 (6%)	
Intestine small, jejunum	(39)	(39)	(37)	(24)
Carcinoma			1 (3%)	
Liver	(46)	(47)	(46)	(44)
Hemangiosarcoma	1 (2%)	2 (4%)	5 (11%)	13 (30%)
Hepatoblastoma		1 (2%)		
Hepatocellular adenoma	5 (11%)	10 (21%)	13 (28%)	10 (23%)
Hepatocellular adenoma, multiple	2 (4%)	3 (6%)	4 (9%)	7 (16%)
Hepatocellular carcinoma	6 (13%)	6 (13%)	8 (17%)	8 (18%)
Hepatocellular carcinoma, multiple	1 (2%)		1 (2%)	1 (2%)
Histiocytic sarcoma	1 (2%)	2 (4%)	5 (11%)	2 (5%)
Leukemia granulocytic				1 (2%)
Lymphoma malignant	3 (7%)	2 (4%)	3 (7%)	1 (2%)
Sarcoma, metastatic, skin				2 (5%)
Mesentery	(1)	(1)	(1)	(1)
Sarcoma, metastatic, skin				1 (100%)
Pancreas	(45)	(44)	(44)	(42)
Hemangiosarcoma			1 (2%)	
Histiocytic sarcoma	1 (2%)			
Leukemia granulocytic				1 (2%)
Lymphoma malignant	2 (4%)	1 (2%)	2 (5%)	
Salivary glands	(47)	(48)	(46)	(46)
Leukemia granulocytic				1 (2%)
Lymphoma malignant	3 (6%)	1 (2%)	3 (7%)	
Neoplasm NOS, metastatic, thymus	1 (2%)			
Sarcoma, metastatic, skin	1 (2%)			
Stomach, forestomach	(46)	(47)	(44)	(45)
Hemangiosarcoma				1 (2%)
Hemangiosarcoma, serosa				1 (2%)
Lymphoma malignant	1 (2%)			
Squamous cell carcinoma		1 (2%)		2 (4%)
Squamous cell papilloma		1 (2%)	3 (7%)	3 (7%)
Stomach, glandular	(43)	(43)	(44)	(42)
Carcinoma		1 (2%)		
Lymphoma malignant	1 (2%)		1 (2%)	
Sarcoma, metastatic, serosa, skin				1 (2%)
Tongue	(47)	(48)	(47)	(48)
Lymphoma malignant	2 (4%)			

Table A1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Drinking Water Study of Urethane and 0% Ethanol

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
Cardiovascular System				
Blood vessel	(47)	(46)	(47)	(45)
Lymphoma malignant		1 (2%)		
Heart	(48)	(48)	(47)	(48)
Alveolar/bronchiolar carcinoma, metastatic, lung			1 (2%)	
Hemangioma		1 (2%)	1 (2%)	
Hemangiosarcoma			1 (2%)	5 (10%)
Lymphoma malignant	2 (4%)		1 (2%)	
Neoplasm NOS, metastatic, thymus	1 (2%)			
Schwannoma malignant				1 (2%)
Endocrine System				
Adrenal gland, cortex	(44)	(44)	(44)	(44)
Adenoma	1 (2%)	1 (2%)		
Adenoma, subcapsular	1 (2%)	1 (2%)	1 (2%)	
Lymphoma malignant			2 (5%)	
Adrenal gland, medulla	(44)	(43)	(42)	(43)
Lymphoma malignant			1 (2%)	
Pheochromocytoma benign			2 (5%)	5 (12%)
Pheochromocytoma benign, bilateral				1 (2%)
Islets, pancreatic	(45)	(44)	(44)	(42)
Adenoma				1 (2%)
Pituitary gland	(35)	(42)	(39)	(38)
Lymphoma malignant			1 (3%)	
Thyroid gland	(46)	(46)	(46)	(45)
Adenoma, follicular cell	2 (4%)	2 (4%)		
Lymphoma malignant	2 (4%)		1 (2%)	
General Body System				
None				
Genital System				
Coagulating gland	(46)	(48)	(46)	(46)
Lymphoma malignant	2 (4%)		1 (2%)	
Epididymis	(47)	(48)	(46)	(44)
Leukemia granulocytic				1 (2%)
Lymphoma malignant	2 (4%)		1 (2%)	
Neoplasm NOS, metastatic, thymus	1 (2%)			
Preputial gland	(45)	(44)	(43)	(43)
Carcinoma			1 (2%)	
Lymphoma malignant	1 (2%)		1 (2%)	
Prostate	(46)	(45)	(45)	(45)
Lymphoma malignant	2 (4%)		2 (4%)	
Neoplasm NOS, metastatic, thymus	1 (2%)			
Seminal vesicle	(46)	(48)	(46)	(46)
Leukemia granulocytic				1 (2%)
Lymphoma malignant	2 (4%)		1 (2%)	
Testes	(47)	(48)	(46)	(46)
Lymphoma malignant			1 (2%)	1 (2%)

Table A1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Drinking Water Study of Urethane and 0% Ethanol

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
Hematopoietic System				
Bone marrow	(46)	(47)	(45)	(45)
Hemangiosarcoma	1 (2%)	1 (2%)		
Histiocytic sarcoma	1 (2%)	1 (2%)		1 (2%)
Leukemia granulocytic				1 (2%)
Lymphoma malignant	1 (2%)		1 (2%)	
Lymph node	(47)	(47)	(46)	(46)
Alveolar/bronchiolar carcinoma, metastatic, mediastinal, lung			1 (2%)	
Carcinoma, metastatic, pancreatic, stomach		1 (2%)		
Hepatoblastoma, metastatic, mediastinal, liver		1 (2%)		
Histiocytic sarcoma, lumbar		1 (2%)		
Leukemia granulocytic, iliac				1 (2%)
Leukemia granulocytic, inguinal				1 (2%)
Lymphoma malignant, axillary			2 (4%)	
Lymphoma malignant, inguinal			2 (4%)	
Lymphoma malignant, lumbar			2 (4%)	
Lymphoma malignant, mediastinal		1 (2%)		
Lymphoma malignant, pancreatic		1 (2%)		
Lymphoma malignant, renal		2 (4%)	3 (7%)	
Sarcoma, metastatic, axillary, skin	1 (2%)			
Lymph node, mandibular	(46)	(46)	(46)	(45)
Hemangiosarcoma	1 (2%)			
Leukemia granulocytic				1 (2%)
Lymphoma malignant	3 (7%)	1 (2%)	3 (7%)	1 (2%)
Neoplasm NOS	1 (2%)			
Lymph node, mesenteric	(43)	(47)	(43)	(38)
Hemangiosarcoma				1 (3%)
Histiocytic sarcoma	1 (2%)	2 (4%)	2 (5%)	1 (3%)
Leukemia granulocytic				1 (3%)
Lymphoma malignant	6 (14%)	3 (6%)	5 (12%)	2 (5%)
Neoplasm NOS, metastatic, thymus	1 (2%)			
Sarcoma		1 (2%)		
Spleen	(44)	(46)	(45)	(42)
Hemangioma			1 (2%)	1 (2%)
Hemangiosarcoma	2 (5%)	2 (4%)	2 (4%)	5 (12%)
Histiocytic sarcoma	1 (2%)	3 (7%)	3 (7%)	2 (5%)
Leukemia granulocytic				1 (2%)
Lymphoma malignant	9 (20%)	4 (9%)	5 (11%)	3 (7%)
Thymus	(32)	(29)	(35)	(27)
Alveolar/bronchiolar carcinoma, metastatic, lung			1 (3%)	
Lymphoma malignant	2 (6%)	2 (7%)	3 (9%)	
Neoplasm NOS	1 (3%)			
Sarcoma, metastatic, skin				1 (4%)
Sarcoma, metastatic, uncertain primary site	1 (3%)			
Integumentary System				
Mammary gland		(2)	(5)	(1)
Carcinoma				1 (100%)
Lymphoma malignant			1 (20%)	

Table A1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Drinking Water Study of Urethane and 0% Ethanol

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
Integumentary System (continued)				
Skin	(47)	(48)	(47)	(48)
Basal cell adenoma			2 (4%)	1 (2%)
Basal cell carcinoma		1 (2%)		1 (2%)
Fibroma		2 (4%)	3 (6%)	
Fibroma, multiple	1 (2%)			
Fibroma, tail				1 (2%)
Hemangioma		1 (2%)		1 (2%)
Hemangiosarcoma	1 (2%)			2 (4%)
Histiocytic sarcoma	1 (2%)		1 (2%)	
Histiocytic sarcoma, multiple	1 (2%)			
Lipoma				1 (2%)
Lymphoma malignant	1 (2%)		1 (2%)	1 (2%)
Neoplasm NOS				1 (2%)
Rhabdomyosarcoma, metastatic, skeletal muscle		1 (2%)		
Sarcoma	9 (19%)	7 (15%)	5 (11%)	9 (19%)
Sarcoma, multiple	1 (2%)	2 (4%)		5 (10%)
Squamous cell carcinoma			2 (4%)	1 (2%)
Squamous cell papilloma		1 (2%)	1 (2%)	3 (6%)
Squamous cell papilloma, multiple				2 (4%)
Musculoskeletal System				
Bone	(48)	(48)	(47)	(48)
Hemangiosarcoma, cranium				1 (2%)
Sarcoma, metastatic, sternum, uncertain primary site	1 (2%)			
Skeletal muscle	(48)	(48)	(47)	(48)
Alveolar/bronchiolar carcinoma, metastatic				1 (2%)
Alveolar/bronchiolar carcinoma, metastatic, diaphragm, lung				1 (2%)
Lymphoma malignant	1 (2%)		1 (2%)	
Neoplasm NOS, metastatic, thymus	1 (2%)			
Rhabdomyosarcoma	1 (2%)	1 (2%)		
Sarcoma				1 (2%)
Nervous System				
Brain, cerebellum	(48)	(47)	(44)	(46)
Lymphoma malignant	1 (2%)		1 (2%)	
Brain, cerebrum	(48)	(48)	(47)	(47)
Lymphoma malignant	1 (2%)		1 (2%)	
Respiratory System				
Larynx	(45)	(45)	(46)	(45)
Lymphoma malignant	2 (4%)			
Lung	(48)	(48)	(47)	(48)
Alveolar/bronchiolar adenoma	3 (6%)	15 (31%)	15 (32%)	14 (29%)
Alveolar/bronchiolar adenoma, multiple	1 (2%)	2 (4%)	7 (15%)	20 (42%)
Alveolar/bronchiolar carcinoma	1 (2%)	1 (2%)	8 (17%)	8 (17%)
Alveolar/bronchiolar carcinoma, multiple			1 (2%)	1 (2%)
Basal cell carcinoma, metastatic, skin		1 (2%)		

Table A1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Drinking Water Study of Urethane and 0% Ethanol

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
Respiratory System (continued)				
Lung (continued)	(48)	(48)	(47)	(48)
Hemangiosarcoma				1 (2%)
Hepatoblastoma, metastatic, liver		1 (2%)		
Hepatocellular carcinoma, metastatic, liver	4 (8%)		2 (4%)	1 (2%)
Hepatocellular carcinoma, metastatic, multiple, liver				1 (2%)
Histiocytic sarcoma		2 (4%)	2 (4%)	1 (2%)
Leukemia granulocytic				1 (2%)
Lymphoma malignant	3 (6%)		3 (6%)	
Neoplasm NOS	1 (2%)			
Neoplasm NOS, metastatic, thymus	1 (2%)			
Sarcoma, metastatic, skin	1 (2%)	2 (4%)	1 (2%)	3 (6%)
Schwannoma malignant, metastatic, lung				1 (2%)
Schwannoma malignant, metastatic, nose		1 (2%)		
Nose	(47)	(48)	(47)	(47)
Hemangioma, mucosa				1 (2%)
Lymphoma malignant	1 (2%)		1 (2%)	
Schwannoma malignant		1 (2%)		
Trachea	(47)	(47)	(46)	(46)
Lymphoma malignant	1 (2%)		1 (2%)	
Special Senses System				
Eye	(47)	(47)	(47)	(47)
Lymphoma malignant	1 (2%)			
Harderian gland	(47)	(47)	(47)	(47)
Adenoma	3 (6%)	10 (21%)	21 (45%)	21 (45%)
Adenoma, bilateral		1 (2%)	4 (9%)	7 (15%)
Carcinoma		1 (2%)	6 (13%)	14 (30%)
Carcinoma, bilateral			1 (2%)	2 (4%)
Lymphoma malignant	2 (4%)		1 (2%)	
Lacrimal gland	(47)	(47)	(44)	(47)
Leukemia granulocytic				1 (2%)
Lymphoma malignant	2 (4%)		1 (2%)	
Zymbal's gland	(45)	(45)	(45)	(45)
Basosquamous tumor benign			1 (2%)	
Lymphoma malignant	2 (4%)		1 (2%)	
Urinary System				
Kidney	(46)	(47)	(46)	(45)
Adenoma, renal tubule			1 (2%)	1 (2%)
Hemangiosarcoma				1 (2%)
Leukemia granulocytic				1 (2%)
Lymphoma malignant	2 (4%)	2 (4%)	2 (4%)	2 (4%)
Urinary bladder	(46)	(46)	(46)	(40)
Lymphoma malignant	1 (2%)	1 (2%)	1 (2%)	

Table A1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Drinking Water Study of Urethane and 0% Ethanol

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
Neoplasm Summary				
Total animals with primary neoplasms[b]	33	39	46	47
Total primary neoplasms	123	114	204	221
Total animals with benign neoplasms	17	29	41	45
Total benign neoplasms	19	51	80	101
Total animals with malignant neoplasms	27	30	37	43
Total malignant neoplasms	101	63	124	119
Total animals with metastatic neoplasms	7	6	5	8
Total metastatic neoplasms	16	8	6	12
Total animals with uncertain neoplasms-benign or malignant	2			1
Total uncertain neoplasms	3			1

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

TABLE A2a
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Drinking Water Study of Urethane and 0% Ethanol

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
Adrenal Medulla: Benign Pheochromocytoma				
Overall rate[a]	0/44 (0.0%)	0/43 (0.0%)	2/42 (4.8%)	6/43 (14.0%)
Adjusted rate[b]	0/35.9 (0.0%)	0/32.7 (0.0%)	2/36.1 (5.5%)	6/29.4 (20.4%)
Terminal rate[c]	0/27 (0.0%)	0/23 (0.0%)	0/23 (0.0%)	0/8 (0.0%)
First incidence (days)	—[e]	—	432	453
Poly-3 test[d]	P=0.001	—[f]	P=0.238	P=0.006
Harderian Gland: Adenoma				
Overall rate	3/47 (6.4%)	11/47 (23.4%)	25/47 (53.2%)	28/47 (59.6%)
Adjusted rate	3/38.0 (7.9%)	11/36.5 (30.1%)	25/41.2 (60.7%)	28/36.0 (77.8%)
Terminal rate	1/27 (3.7%)	7/26 (26.9%)	17/26 (65.4%)	8/8 (100.0%)
First incidence (days)	599	691	456	466
Poly-3 test	P=0.001	P=0.013	P=0.001	P=0.001
Harderian Gland: Carcinoma				
Overall rate	0/47 (0.0%)	1/47 (2.1%)	7/47 (14.9%)	16/47 (34.0%)
Adjusted rate	0/37.2 (0.0%)	1/35.9 (2.8%)	7/41.2 (17.0%)	16/35.7 (44.9%)
Terminal rate	0/27 (0.0%)	1/26 (3.8%)	2/26 (7.7%)	3/8 (37.5%)
First incidence (days)	—	765 (T)	510	453
Poly-3 test	P=0.001	P=0.493	P=0.011	P=0.001
Harderian Gland: Adenoma or Carcinoma				
Overall rate	3/47 (6.4%)	12/47 (25.5%)	30/47 (63.8%)	38/47 (80.9%)
Adjusted rate	3/38.0 (7.9%)	12/36.5 (32.8%)	30/43.3 (69.2%)	38/42.0 (90.6%)
Terminal rate	1/27 (3.7%)	8/26 (30.8%)	17/26 (65.4%)	8/8 (100.0%)
First incidence (days)	599	691	456	453
Poly-3 test	P=0.001	P=0.006	P=0.001	P=0.001
Heart: Hemangiosarcoma				
Overall rate	0/48 (0.0%)	0/48 (0.0%)	1/47 (2.1%)	5/48 (10.4%)
Adjusted rate	0/37.6 (0.0%)	0/36.3 (0.0%)	1/39.1 (2.6%)	5/31.0 (16.1%)
Terminal rate	0/27 (0.0%)	0/26 (0.0%)	0/26 (0.0%)	1/8 (12.5%)
First incidence (days)	—	—	754	453
Poly-3 test	P=0.001	—	P=0.508	P=0.016
Heart: Hemangioma or Hemangiosarcoma				
Overall rate	0/48 (0.0%)	1/48 (2.1%)	2/47 (4.3%)	5/48 (10.4%)
Adjusted rate	0/37.6 (0.0%)	1/36.3 (2.8%)	2/39.2 (5.1%)	5/31.0 (16.1%)
Terminal rate	0/27 (0.0%)	0/26 (0.0%)	0/26 (0.0%)	1/8 (12.5%)
First incidence (days)	—	754	724	453
Poly-3 test	P=0.004	P=0.493	P=0.246	P=0.016
Kidney: Adenoma, Hemangiosarcoma, or Leukemia Granulocytic				
Overall rate	0/46 (0.0%)	0/47 (0.0%)	1/46 (2.2%)	3/45 (6.7%)
Adjusted rate	0/36.8 (0.0%)	0/36.3 (0.0%)	1/38.9 (2.6%)	3/29.5 (10.2%)
Terminal rate	0/27 (0.0%)	0/26 (0.0%)	1/26 (3.8%)	0/8 (0.0%)
First incidence (days)	—	—	765 (T)	493
Poly-3 test	P=0.012	—	P=0.511	P=0.082
Liver: Hemangiosarcoma				
Overall rate	1/46 (2.2%)	2/47 (4.3%)	5/46 (10.9%)	13/44 (29.5%)
Adjusted rate	1/36.8 (2.7%)	2/35.6 (5.6%)	5/39.6 (12.6%)	13/31.1 (41.8%)
Terminal rate	1/27 (3.7%)	1/26 (3.8%)	3/26 (11.5%)	2/8 (25.0%)
First incidence (days)	765 (T)	754	510	493
Poly-3 test	P=0.001	P=0.489	P=0.118	P=0.001

Table A2a
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Drinking Water Study of Urethane and 0% Ethanol

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
Liver: Histiocytic Sarcoma				
Overall rate	1/46 (2.2%)	2/47 (4.3%)	5/46 (10.9%)	2/44 (4.5%)
Adjusted rate	1/36.8 (2.7%)	2/36.1 (5.5%)	5/39.3 (12.7%)	2/28.4 (7.1%)
Terminal rate	0/27 (0.0%)	0/26 (0.0%)	2/26 (7.7%)	0/8 (0.0%)
First incidence (days)	756	614	668	680
Poly-3 test	P=0.347	P=0.493	P=0.115	P=0.410
Liver: Hepatocellular Adenoma				
Overall rate	7/46 (15.2%)	13/47 (27.7%)	17/46 (37.0%)	17/44 (38.6%)
Adjusted rate	7/37.4 (18.7%)	13/36.1 (36.0%)	17/41.3 (41.2%)	17/33.8 (50.3%)
Terminal rate	6/27 (22.2%)	11/26 (42.3%)	9/26 (34.6%)	4/8 (50.0%)
First incidence (days)	541	662	456	453
Poly-3 test	P=0.009	P=0.077	P=0.025	P=0.003
Liver: Hepatocellular Carcinoma				
Overall rate	7/46 (15.2%)	6/47 (12.8%)	9/46 (19.6%)	9/44 (20.5%)
Adjusted rate	7/37.0 (18.9%)	6/36.0 (16.7%)	9/40.3 (22.3%)	9/30.0 (30.0%)
Terminal rate	5/27 (18.5%)	3/26 (11.5%)	5/26 (19.2%)	2/8 (25.0%)
First incidence (days)	712	665	542	580
Poly-3 test	P=0.135	P=0.521N	P=0.464	P=0.221
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rate	12/46 (26.1%)	18/47 (38.3%)	24/46 (52.2%)	23/44 (52.3%)
Adjusted rate	12/37.6 (31.9%)	18/36.6 (49.2%)	24/42.5 (56.5%)	23/35.2 (65.3%)
Terminal rate	9/27 (33.3%)	13/26 (50.0%)	13/26 (50.0%)	5/8 (62.5%)
First incidence (days)	541	662	456	453
Poly-3 test	P=0.007	P=0.095	P=0.020	P=0.002
Lung: Alveolar/bronchiolar Adenoma				
Overall rate	4/48 (8.3%)	17/48 (35.4%)	22/47 (46.8%)	34/48 (70.8%)
Adjusted rate	4/37.6 (10.6%)	17/38.4 (44.3%)	22/41.2 (53.4%)	34/39.5 (86.2%)
Terminal rate	4/27 (14.8%)	11/26 (42.3%)	16/26 (61.5%)	8/8 (100.0%)
First incidence (days)	765 (T)	511	456	293
Poly-3 test	P=0.001	P=0.001	P=0.001	P=0.001
Lung: Alveolar/bronchiolar Carcinoma				
Overall rate	1/48 (2.1%)	1/48 (2.1%)	9/47 (19.1%)	9/48 (18.8%)
Adjusted rate	1/37.7 (2.7%)	1/36.3 (2.8%)	9/40.5 (22.2%)	9/30.8 (29.2%)
Terminal rate	0/27 (0.0%)	1/26 (3.8%)	5/26 (19.2%)	3/8 (37.5%)
First incidence (days)	739	765 (T)	542	521
Poly-3 test	P=0.001	P=0.753	P=0.010	P=0.002
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rate	5/48 (10.4%)	18/48 (37.5%)	29/47 (61.7%)	37/48 (77.1%)
Adjusted rate	5/37.7 (13.3%)	18/38.4 (46.9%)	29/42.2 (68.8%)	37/40.4 (91.7%)
Terminal rate	4/27 (14.8%)	12/26 (46.2%)	20/26 (76.9%)	8/8 (100.0%)
First incidence (days)	739	511	456	293
Poly-3 test	P=0.001	P=0.001	P=0.001	P=0.001
Lymph Node (Mesenteric): Histiocytic Sarcoma				
Overall rate	1/43 (2.3%)	2/47 (4.3%)	2/43 (4.7%)	1/38 (2.6%)
Adjusted rate	1/35.2 (2.8%)	2/36.8 (5.4%)	2/36.8 (5.4%)	1/25.5 (3.9%)
Terminal rate	0/26 (0.0%)	0/26 (0.0%)	0/25 (0.0%)	0/8 (0.0%)
First incidence (days)	756	614	668	729
Poly-3 test	P=0.614	P=0.515	P=0.515	P=0.685

Table A2a
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Drinking Water Study of Urethane and 0% Ethanol

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
Skin: Squamous Cell Papilloma				
Overall rate	0/47 (0.0%)	1/48 (2.1%)	1/47 (2.1%)	5/48 (10.4%)
Adjusted rate	0/37.2 (0.0%)	1/36.6 (2.7%)	1/39.1 (2.6%)	5/30.4 (16.4%)
Terminal rate	0/27 (0.0%)	0/26 (0.0%)	0/26 (0.0%)	2/8 (25.0%)
First incidence (days)	—	662	762	453
Poly-3 test	P=0.002	P=0.497	P=0.510	P=0.016
Skin: Squamous Cell Papilloma or Squamous Cell Carcinoma				
Overall rate	0/47 (0.0%)	1/48 (2.1%)	3/47 (6.4%)	6/48 (12.5%)
Adjusted rate	0/37.2 (0.0%)	1/36.6 (2.7%)	3/39.1 (7.7%)	6/31.0 (19.4%)
Terminal rate	0/27 (0.0%)	0/26 (0.0%)	2/26 (7.7%)	2/8 (25.0%)
First incidence (days)	—	662	762	453
Poly-3 test	P=0.001	P=0.497	P=0.127	P=0.007
Skin: Squamous Cell Papilloma, Squamous Cell Carcinoma, Basal Cell Adenoma, or Basal Cell Carcinoma				
Overall rate	0/47 (0.0%)	1/48 (2.1%)	5/47 (10.6%)	8/48 (16.7%)
Adjusted rate	0/37.2 (0.0%)	1/36.6 (2.7%)	5/39.1 (12.8%)	8/31.8 (25.2%)
Terminal rate	0/27 (0.0%)	0/26 (0.0%)	3/26 (11.5%)	2/8 (25.0%)
First incidence (days)	—	662	746	453
Poly-3 test	P=0.001	P=0.497	P=0.034	P=0.001
Skin: Sarcoma				
Overall rate	10/47 (21.3%)	9/48 (18.8%)	5/47 (10.6%)	14/48 (29.2%)
Adjusted rate	10/38.7 (25.8%)	9/37.8 (23.8%)	5/39.9 (12.5%)	14/34.7 (40.3%)
Terminal rate	6/27 (22.2%)	5/26 (19.2%)	3/26 (11.5%)	1/8 (12.5%)
First incidence (days)	536	520	432	453
Poly-3 test	P=0.064	P=0.526N	P=0.111N	P=0.137
Skin: Fibroma or Sarcoma				
Overall rate	10/47 (21.3%)	11/48 (22.9%)	8/47 (17.0%)	15/48 (31.3%)
Adjusted rate	10/38.7 (25.8%)	11/37.8 (29.1%)	8/39.9 (20.0%)	15/35.0 (42.9%)
Terminal rate	6/27 (22.2%)	7/26 (26.9%)	6/26 (23.1%)	1/8 (12.5%)
First incidence (days)	536	520	432	453
Poly-3 test	P=0.064	P=0.472	P=0.366N	P=0.092
Skin: Hemangioma or Hemangiosarcoma				
Overall rate	1/47 (2.1%)	1/48 (2.1%)	0/47 (0.0%)	3/48 (6.3%)
Adjusted rate	1/37.2 (2.7%)	1/36.3 (2.8%)	0/39.0 (0.0%)	3/30.3 (9.9%)
Terminal rate	0/27 (0.0%)	1/26 (3.8%)	0/26 (0.0%)	1/8 (12.5%)
First incidence (days)	764	765 (T)	—	576
Poly-3 test	P=0.103	P=0.756	P=0.490N	P=0.235
Spleen: Hemangiosarcoma				
Overall rate	2/44 (4.5%)	2/46 (4.3%)	2/45 (4.4%)	5/42 (11.9%)
Adjusted rate	2/36.7 (5.4%)	2/36.5 (5.5%)	2/38.1 (5.2%)	5/28.1 (17.8%)
Terminal rate	1/27 (3.7%)	1/26 (3.8%)	1/26 (3.8%)	1/8 (12.5%)
First incidence (days)	757	691	724	548
Poly-3 test	P=0.051	P=0.692	P=0.681N	P=0.120
Spleen: Hemangioma or Hemangiosarcoma				
Overall rate	2/44 (4.5%)	2/46 (4.3%)	3/45 (6.7%)	6/42 (14.3%)
Adjusted rate	2/36.7 (5.4%)	2/36.5 (5.5%)	3/38.1 (7.9%)	6/28.9 (20.8%)
Terminal rate	1/27 (3.7%)	1/26 (3.8%)	2/26 (7.7%)	1/8 (12.5%)
First incidence (days)	757	691	724	483
Poly-3 test	P=0.021	P=0.692	P=0.517	P=0.065

Table A2a
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Drinking Water Study of Urethane and 0% Ethanol

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
Spleen: Histiocytic Sarcoma				
Overall rate	1/44 (2.3%)	3/46 (6.5%)	3/45 (6.7%)	2/42 (4.8%)
Adjusted rate	1/36.7 (2.7%)	3/36.7 (8.2%)	3/38.7 (7.8%)	2/27.5 (7.3%)
Terminal rate	0/27 (0.0%)	1/26 (3.8%)	0/26 (0.0%)	0/8 (0.0%)
First incidence (days)	756	614	643	680
Poly-3 test	P=0.423	P=0.304	P=0.324	P=0.401
Stomach (Forestomach): Squamous Cell Papilloma				
Overall rate	0/46 (0.0%)	1/47 (2.1%)	3/44 (6.8%)	3/45 (6.7%)
Adjusted rate	0/36.8 (0.0%)	1/36.5 (2.7%)	3/37.7 (7.9%)	3/29.3 (10.2%)
Terminal rate	0/27 (0.0%)	0/26 (0.0%)	3/26 (11.5%)	0/8 (0.0%)
First incidence (days)	—	691	765 (T)	646
Poly-3 test	P=0.058	P=0.499	P=0.122	P=0.081
Stomach (Forestomach): Squamous Cell Papilloma or Squamous Cell Carcinoma				
Overall rate	0/46 (0.0%)	2/47 (4.3%)	3/44 (6.8%)	5/45 (11.1%)
Adjusted rate	0/36.8 (0.0%)	2/37.2 (5.4%)	3/37.7 (7.9%)	5/29.6 (16.9%)
Terminal rate	0/27 (0.0%)	0/26 (0.0%)	3/26 (11.5%)	1/8 (12.5%)
First incidence (days)	—	537	765 (T)	646
Poly-3 test	P=0.011	P=0.239	P=0.122	P=0.015
All Organs: Hemangioma				
Overall rate	0/48 (0.0%)	2/48 (4.2%)	2/47 (4.3%)	3/48 (6.3%)
Adjusted rate	0/37.6 (0.0%)	2/36.3 (5.5%)	2/39.2 (5.1%)	3/30.1 (10.0%)
Terminal rate	0/27 (0.0%)	1/26 (3.8%)	1/26 (3.8%)	1/8 (12.5%)
First incidence (days)	—	754	724	483
Poly-3 test	P=0.097	P=0.229	P=0.246	P=0.082
All Organs: Hemangiosarcoma				
Overall rate	4/48 (8.3%)	4/48 (8.3%)	7/47 (14.9%)	19/48 (39.6%)
Adjusted rate	4/37.7 (10.6%)	4/36.6 (10.9%)	7/39.9 (17.5%)	19/34.5 (55.2%)
Terminal rate	1/27 (3.7%)	2/26 (7.7%)	4/26 (15.4%)	3/8 (37.5%)
First incidence (days)	739	691	510	453
Poly-3 test	P=0.001	P=0.628	P=0.292	P=0.001
All Organs: Hemangioma or Hemangiosarcoma				
Overall rate	4/48 (8.3%)	5/48 (10.4%)	9/47 (19.1%)	21/48 (43.8%)
Adjusted rate	4/37.7 (10.6%)	5/36.6 (13.7%)	9/40.1 (22.4%)	21/35.2 (59.7%)
Terminal rate	1/27 (3.7%)	3/26 (11.5%)	5/26 (19.2%)	4/8 (50.0%)
First incidence (days)	739	691	510	453
Poly-3 test	P=0.001	P=0.480	P=0.135	P=0.001
All Organs: Histiocytic Sarcoma				
Overall rate	3/48 (6.3%)	3/48 (6.3%)	6/47 (12.8%)	2/48 (4.2%)
Adjusted rate	3/38.3 (7.8%)	3/36.8 (8.1%)	6/39.9 (15.1%)	2/29.7 (6.7%)
Terminal rate	1/27 (3.7%)	1/26 (3.8%)	2/26 (7.7%)	0/8 (0.0%)
First incidence (days)	515	614	643	680
Poly-3 test	P=0.560N	P=0.645	P=0.259	P=0.615N
All Organs: Malignant Lymphoma				
Overall rate	9/48 (18.8%)	7/48 (14.6%)	6/47 (12.8%)	4/48 (8.3%)
Adjusted rate	9/37.7 (23.8%)	7/36.7 (19.1%)	6/40.3 (14.9%)	4/29.8 (13.4%)
Terminal rate	7/27 (25.9%)	6/26 (23.1%)	3/26 (11.5%)	2/8 (25.0%)
First incidence (days)	739	642	410	600
Poly-3 test	P=0.200N	P=0.414N	P=0.236N	P=0.222N

Table A2a
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Drinking Water Study of Urethane and 0% Ethanol

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
All Organs: Uncertain or Benign Neoplasms				
Overall rate	19/48 (39.6%)	29/48 (60.4%)	41/47 (87.2%)	45/48 (93.8%)
Adjusted rate	19/40.2 (47.2%)	29/39.0 (74.4%)	41/44.1 (92.9%)	45/45.8 (98.3%)
Terminal rate	14/27 (51.9%)	19/26 (73.1%)	25/26 (96.2%)	8/8 (100.0%)
First incidence (days)	541	511	432	293
Poly-3 test	P=0.001	P=0.009	P=0.001	P=0.001
All Organs: Malignant Neoplasms				
Overall rate	27/48 (56.3%)	30/48 (62.5%)	37/47 (78.7%)	43/48 (89.6%)
Adjusted rate	27/40.3 (67.1%)	30/40.4 (74.2%)	37/45.3 (81.7%)	43/44.0 (97.8%)
Terminal rate	17/27 (63.0%)	17/26 (65.4%)	19/26 (73.1%)	8/8 (100.0%)
First incidence (days)	515	520	410	453
Poly-3 test	P=0.001	P=0.319	P=0.090	P=0.001
All Organs: Uncertain, Benign, or Malignant Neoplasms				
Overall rate	33/48 (68.8%)	39/48 (81.3%)	46/47 (97.9%)	47/48 (97.9%)
Adjusted rate	33/42.1 (78.5%)	39/41.3 (94.3%)	46/46.1 (99.7%)	47/47.1 (99.8%)
Terminal rate	20/27 (74.1%)	24/26 (92.3%)	26/26 (100.0%)	8/8 (100.0%)
First incidence (days)	515	511	410	293
Poly-3 test	P=0.001	P=0.031	P=0.001	P=0.001

(T) Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals with tissue examined microscopically
[b] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the control incidence (0 ppm urethane) is the P value associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and that exposed group. The Poly-3 test accounts for the differential mortality in animals that do not reach terminal sacrifice. A negative trend or a lower incidence in an exposed group is indicated by **N**.
[e] Not applicable; no neoplasms in animal group
[f] Value of statistic cannot be computed.

Table A2b
Statistical Analysis of Primary Neoplasms in Male Mice Exposed to Ethanol and 0 ppm Urethane in Drinking Water for 2 Years

	0% Ethanol	2.5% Ethanol	5% Ethanol
Adrenal Cortex: Adenoma			
Overall rate[a]	2/44 (4.5%)	3/46 (6.5%)	3/46 (6.5%)
Adjusted rate[b]	2/35.9 (5.6%)	3/38.9 (7.7%)	3/41.9 (7.2%)
Terminal rate[c]	2/27 (7.4%)	3/31 (9.7%)	3/35 (8.6%)
First incidence (days)	765 (T)	765 (T)	765 (T)
Poly-3 test[d]	P=0.986	P=1.000	P=1.000
Adrenal Medulla: Benign Pheochromocytoma			
Overall rate	0/44 (0.0%)	2/44 (4.5%)	2/46 (4.3%)
Adjusted rate	0/35.9 (0.0%)	2/36.9 (5.4%)	2/41.9 (4.8%)
Terminal rate	0/27 (0.0%)	2/29 (6.9%)	2/35 (5.7%)
First incidence (days)	—[e]	765 (T)	765 (T)
Poly-3 test	P=0.449	P=0.485	P=0.556
Harderian Gland: Adenoma			
Overall rate	3/47 (6.4%)	6/48 (12.5%)	5/47 (10.6%)
Adjusted rate	3/38.0 (7.9%)	6/41.1 (14.6%)	5/42.9 (11.7%)
Terminal rate	1/27 (3.7%)	4/32 (12.5%)	5/35 (14.3%)
First incidence (days)	599	582	765 (T)
Poly-3 test	P=0.772	P=0.560	P=0.848
Liver: Hemangiosarcoma			
Overall rate	1/46 (2.2%)	3/47 (6.4%)	2/48 (4.2%)
Adjusted rate	1/36.8 (2.7%)	3/40.0 (7.5%)	2/44.6 (4.5%)
Terminal rate	1/27 (3.7%)	2/32 (6.3%)	1/36 (2.8%)
First incidence (days)	765 (T)	719	464
Poly-3 test	P=1.000	P=0.670	P=1.000
Liver: Hepatocellular Adenoma			
Overall rate	7/46 (15.2%)	12/47 (25.5%)	19/48 (39.6%)
Adjusted rate	7/37.4 (18.7%)	12/41.1 (29.2%)	19/44.6 (42.6%)
Terminal rate	6/27 (22.2%)	9/32 (28.1%)	16/36 (44.4%)
First incidence (days)	541	582	607
Poly-3 test	P=0.024	P=0.411	P=0.034
Liver: Hepatocellular Carcinoma			
Overall rate	7/46 (15.2%)	6/47 (12.8%)	7/48 (14.6%)
Adjusted rate	7/37.0 (18.9%)	6/40.9 (14.7%)	7/44.9 (15.6%)
Terminal rate	5/27 (18.5%)	3/32 (9.4%)	3/36 (8.3%)
First incidence (days)	712	607	447
Poly-3 test	P=0.835	P=0.843	P=0.918
Liver: Hepatocellular Adenoma or Carcinoma			
Overall rate	12/46 (26.1%)	16/47 (34.0%)	25/48 (52.1%)
Adjusted rate	12/37.6 (31.9%)	16/41.9 (38.2%)	25/45.6 (54.8%)
Terminal rate	9/27 (33.3%)	11/32 (34.4%)	19/36 (52.8%)
First incidence (days)	541	582	447
Poly-3 test	P=0.038	P=0.724	P=0.056
Lung: Alveolar/bronchiolar Adenoma			
Overall rate	4/48 (8.3%)	10/48 (20.8%)	6/48 (12.5%)
Adjusted rate	4/37.6 (10.6%)	10/40.8 (24.5%)	6/44.1 (13.6%)
Terminal rate	4/27 (14.8%)	8/32 (25.0%)	5/36 (13.9%)
First incidence (days)	765 (T)	614	710
Poly-3 test	P=0.966	P=0.187	P=0.944

Table A2b
Statistical Analysis of Primary Neoplasms in Male Mice Exposed to Ethanol and 0 ppm Urethane in Drinking Water for 2 Years

	0% Ethanol	2.5% Ethanol	5% Ethanol
Lung: Alveolar/bronchiolar Carcinoma			
Overall rate	1/48 (2.1%)	2/48 (4.2%)	5/48 (10.4%)
Adjusted rate	1/37.7 (2.7%)	2/40.1 (5.0%)	5/43.9 (11.4%)
Terminal rate	0/27 (0.0%)	2/32 (6.3%)	5/36 (13.9%)
First incidence (days)	739	765 (T)	765 (T)
Poly-3 test	P=0.165	P=1.000	P=0.280
Lung: Alveolar/bronchiolar Adenoma or Carcinoma			
Overall rate	5/48 (10.4%)	11/48 (22.9%)	11/48 (22.9%)
Adjusted rate	5/37.7 (13.3%)	11/40.8 (27.0%)	11/44.1 (25.0%)
Terminal rate	4/27 (14.8%)	9/32 (28.1%)	10/36 (27.8%)
First incidence (days)	739	614	710
Poly-3 test	P=0.296	P=0.216	P=0.294
Skin: Sarcoma			
Overall rate	10/47 (21.3%)	16/48 (33.3%)	12/48 (25.0%)
Adjusted rate	10/38.7 (25.8%)	16/43.1 (37.1%)	12/44.8 (26.8%)
Terminal rate	6/27 (22.2%)	9/32 (28.1%)	6/36 (16.7%)
First incidence (days)	536	582	607
Poly-3 test	P=1.000	P=0.389	P=1.000
Skin: Fibroma or Sarcoma			
Overall rate	10/47 (21.3%)	18/48 (37.5%)	13/48 (27.1%)
Adjusted rate	10/38.7 (25.8%)	18/43.1 (41.8%)	13/44.8 (29.0%)
Terminal rate	6/27 (22.2%)	11/32 (34.4%)	7/36 (19.4%)
First incidence (days)	536	582	607
Poly-3 test	P=0.953	P=0.195	P=0.935
Spleen: Hemangiosarcoma			
Overall rate	2/44 (4.5%)	0/46 (0.0%)	0/48 (0.0%)
Adjusted rate	2/36.7 (5.4%)	0/39.2 (0.0%)	0/43.9 (0.0%)
Terminal rate	1/27 (3.7%)	0/32 (0.0%)	0/36 (0.0%)
First incidence (days)	757	—	—
Poly-3 test	P=0.168	P=0.445	P=0.398
All Organs: Hemangioma			
Overall rate	0/48 (0.0%)	0/48 (0.0%)	3/48 (6.3%)
Adjusted rate	0/37.6 (0.0%)	0/40.1 (0.0%)	3/43.9 (6.8%)
Terminal rate	0/27 (0.0%)	0/32 (0.0%)	3/36 (8.3%)
First incidence (days)	—	—	765 (T)
Poly-3 test	P=0.086	—[f]	P=0.297
All Organs: Hemangiosarcoma			
Overall rate	4/48 (8.3%)	3/48 (6.3%)	3/48 (6.3%)
Adjusted rate	4/37.7 (10.6%)	3/40.3 (7.4%)	3/44.6 (6.7%)
Terminal rate	1/27 (3.7%)	2/32 (6.3%)	2/36 (5.6%)
First incidence (days)	739	719	464
Poly-3 test	P=0.690	P=0.929	P=0.819
All Organs: Hemangioma or Hemangiosarcoma			
Overall rate	4/48 (8.3%)	3/48 (6.3%)	6/48 (12.5%)
Adjusted rate	4/37.7 (10.6%)	3/40.3 (7.4%)	6/44.6 (13.4%)
Terminal rate	1/27 (3.7%)	2/32 (6.3%)	5/36 (13.9%)
First incidence (days)	739	719	464
Poly-3 test	P=0.767	P=0.929	P=0.956

Table A2b
Statistical Analysis of Primary Neoplasms in Male Mice Exposed to Ethanol and 0 ppm Urethane in Drinking Water for 2 Years

	0% Ethanol	2.5% Ethanol	5% Ethanol
All Organs: Histiocytic Sarcoma			
Overall rate	3/48 (6.3%)	1/48 (2.1%)	2/48 (4.2%)
Adjusted rate	3/38.3 (7.8%)	1/40.1 (2.5%)	2/44.9 (4.5%)
Terminal rate	1/27 (3.7%)	1/32 (3.1%)	0/36 (0.0%)
First incidence (days)	515	765 (T)	542
Poly-3 test	P=0.719	P=0.577	P=0.858
All Organs: Malignant Lymphoma			
Overall rate	9/48 (18.8%)	11/48 (22.9%)	12/48 (25.0%)
Adjusted rate	9/37.7 (23.8%)	11/41.0 (26.8%)	12/44.5 (27.0%)
Terminal rate	7/27 (25.9%)	9/32 (28.1%)	11/36 (30.6%)
First incidence (days)	739	614	542
Poly-3 test	P=0.866	P=0.965	P=0.945
All Organs: Benign Neoplasms			
Overall rate	19/48 (39.6%)	27/48 (56.3%)	30/48 (62.5%)
Adjusted rate	19/40.2 (47.2%)	27/42.4 (63.6%)	30/45.0 (66.6%)
Terminal rate	14/27 (51.9%)	21/32 (65.6%)	25/36 (69.4%)
First incidence (days)	541	582	607
Poly-3 test	P=0.088	P=0.190	P=0.103
All Organs: Malignant Neoplasms			
Overall rate	27/48 (56.3%)	31/48 (64.6%)	31/48 (64.6%)
Adjusted rate	27/40.3 (67.1%)	31/44.7 (69.4%)	31/47.5 (65.2%)
Terminal rate	17/27 (63.0%)	19/32 (59.4%)	20/36 (55.6%)
First incidence (days)	515	513	447
Poly-3 test	P=0.924	P=1.000	P=1.000
All Organs: Benign or Malignant Neoplasms			
Overall rate	33/48 (68.8%)	41/48 (85.4%)	42/48 (87.5%)
Adjusted rate	33/42.1 (78.5%)	41/44.7 (91.8%)	42/47.5 (88.4%)
Terminal rate	20/27 (74.1%)	29/32 (90.6%)	31/36 (86.1%)
First incidence (days)	515	513	447
Poly-3 test	P=0.251	P=0.133	P=0.317

(T) Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals with tissue examined microscopically
[b] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] P values are two sided. Beneath the control incidence (0% ethanol) is the P value associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and that exposed group. The Poly-3 test accounts for the differential mortality in animals that do not reach terminal sacrifice.
[e] Not applicable; no neoplasms in animal group
[f] Value of statistic cannot be computed.

Table A2c
Statistical Analysis of Primary Neoplasms in Male Mice Exposed to Ethanol and 10 ppm Urethane in Drinking Water for 2 Years

	0% Ethanol	2.5% Ethanol	5% Ethanol
Adrenal Cortex: Adenoma			
Overall rate[a]	2/44 (4.5%)	1/45 (2.2%)	3/47 (6.4%)
Adjusted rate[b]	2/33.6 (6.0%)	1/38.5 (2.6%)	3/38.6 (7.8%)
Terminal rate[c]	1/23 (4.3%)	1/28 (3.6%)	3/29 (10.3%)
First incidence (days)	665	765 (T)	765 (T)
Poly-3 test[d]	P=0.897	P=0.905	P=1.000
Adrenal Medulla: Benign Pheochromocytoma			
Overall rate	0/43 (0.0%)	2/42 (4.8%)	6/46 (13.0%)
Adjusted rate	0/32.7 (0.0%)	2/35.5 (5.6%)	6/37.7 (15.9%)
Terminal rate	0/23 (0.0%)	2/25 (8.0%)	5/28 (17.9%)
First incidence (days)	—[e]	765 (T)	739
Poly-3 test	P=0.020	P=0.510	P=0.045
Harderian Gland: Adenoma			
Overall rate	11/47 (23.4%)	14/48 (29.2%)	12/48 (25.0%)
Adjusted rate	11/36.5 (30.1%)	14/41.4 (33.8%)	12/40.0 (30.0%)
Terminal rate	7/26 (26.9%)	12/30 (40.0%)	10/29 (34.5%)
First incidence (days)	691	628	517
Poly-3 test	P=1.000	P=0.912	P=1.000
Harderian Gland: Adenoma or Carcinoma			
Overall rate	12/47 (25.5%)	14/48 (29.2%)	14/48 (29.2%)
Adjusted rate	12/36.5 (32.8%)	14/41.4 (33.8%)	14/40.1 (34.9%)
Terminal rate	8/26 (30.8%)	12/30 (40.0%)	11/29 (37.9%)
First incidence (days)	691	628	517
Poly-3 test	P=0.946	P=1.000	P=1.000
Liver: Hemangiosarcoma			
Overall rate	2/47 (4.3%)	4/48 (8.3%)	2/46 (4.3%)
Adjusted rate	2/35.6 (5.6%)	4/41.0 (9.8%)	2/38.4 (5.2%)
Terminal rate	1/26 (3.8%)	3/30 (10.0%)	1/29 (3.4%)
First incidence (days)	754	681	620
Poly-3 test	P=1.000	P=0.808	P=1.000
Liver: Hemangioma or Hemangiosarcoma			
Overall rate	2/47 (4.3%)	4/48 (8.3%)	4/46 (8.7%)
Adjusted rate	2/35.6 (5.6%)	4/41.0 (9.8%)	4/38.4 (10.4%)
Terminal rate	1/26 (3.8%)	3/30 (10.0%)	3/29 (10.3%)
First incidence (days)	754	681	620
Poly-3 test	P=0.625	P=0.808	P=0.743
Liver: Histiocytic Sarcoma			
Overall rate	2/47 (4.3%)	4/48 (8.3%)	0/46 (0.0%)
Adjusted rate	2/36.1 (5.5%)	4/41.4 (9.7%)	0/37.9 (0.0%)
Terminal rate	0/26 (0.0%)	1/30 (3.3%)	0/29 (0.0%)
First incidence (days)	614	638	—
Poly-3 test	P=0.393	P=0.804	P=0.451
Liver: Hepatocellular Adenoma			
Overall rate	13/47 (27.7%)	15/48 (31.3%)	9/46 (19.6%)
Adjusted rate	13/36.1 (36.0%)	15/41.6 (36.1%)	9/38.1 (23.7%)
Terminal rate	11/26 (42.3%)	13/30 (43.3%)	7/29 (24.1%)
First incidence (days)	662	620	747
Poly-3 test	P=0.301	P=1.000	P=0.359

Table A2c
Statistical Analysis of Primary Neoplasms in Male Mice Exposed to Ethanol and 10 ppm Urethane in Drinking Water for 2 Years

	0% Ethanol	2.5% Ethanol	5% Ethanol
Liver: Hepatocellular Carcinoma			
Overall rate	6/47 (12.8%)	5/48 (10.4%)	9/46 (19.6%)
Adjusted rate	6/36.0 (16.7%)	5/41.4 (12.1%)	9/39.2 (23.0%)
Terminal rate	3/26 (11.5%)	4/30 (13.3%)	6/29 (20.7%)
First incidence (days)	665	523	542
Poly-3 test	P=0.535	P=0.804	P=0.693
Liver: Hepatocellular Adenoma or Carcinoma			
Overall rate	18/47 (38.3%)[f]	19/48 (39.6%)	16/46 (34.8%)
Adjusted rate	18/36.6 (49.2%)	19/42.2 (45.0%)	16/39.2 (40.8%)
Terminal rate	13/26 (50.0%)	16/30 (53.3%)	12/29 (41.4%)
First incidence (days)	662	523	542
Poly-3 test	P=0.538	P=0.881	P=0.608
Lung: Alveolar/bronchiolar Adenoma			
Overall rate	17/48 (35.4%)	16/48 (33.3%)	8/48 (16.7%)
Adjusted rate	17/38.4 (44.3%)	16/41.4 (38.6%)	8/38.7 (20.7%)
Terminal rate	11/26 (42.3%)	13/30 (43.3%)	8/29 (27.6%)
First incidence (days)	511	617	765 (T)
Poly-3 test	P=0.037	P=0.773	P=0.042
Lung: Alveolar/bronchiolar Carcinoma			
Overall rate	1/48 (2.1%)	3/48 (6.3%)	4/48 (8.3%)
Adjusted rate	1/36.3 (2.8%)	3/41.3 (7.3%)	4/38.7 (10.3%)
Terminal rate	1/26 (3.8%)	1/30 (3.3%)	4/29 (13.8%)
First incidence (days)	765 (T)	620	765 (T)
Poly-3 test	P=0.301	P=0.705	P=0.394
Lung: Alveolar/bronchiolar Adenoma or Carcinoma			
Overall rate	18/48 (37.5%)	19/48 (39.6%)	11/48 (22.9%)
Adjusted rate	18/38.4 (46.9%)	19/42.0 (45.3%)	11/38.7 (28.4%)
Terminal rate	12/26 (46.2%)	14/30 (46.7%)	11/29 (37.9%)
First incidence (days)	511	617	765 (T)
Poly-3 test	P=0.121	P=1.000	P=0.141
Lymph Node (Mesenteric): Histiocytic Sarcoma			
Overall rate	2/47 (4.3%)	4/48 (8.3%)	0/44 (0.0%)
Adjusted rate	2/36.8 (5.4%)	4/41.4 (9.7%)	0/36.6 (0.0%)
Terminal rate	0/26 (0.0%)	1/30 (3.3%)	0/28 (0.0%)
First incidence (days)	614	638	—
Poly-3 test	P=0.425	P=0.785	P=0.475
Skin: Sarcoma			
Overall rate	9/48 (18.8%)	10/48 (20.8%)	10/47 (21.3%)
Adjusted rate	9/37.8 (23.8%)	10/42.3 (23.6%)	10/40.8 (24.5%)
Terminal rate	5/26 (19.2%)	5/30 (16.7%)	2/29 (6.9%)
First incidence (days)	520	617	517
Poly-3 test	P=1.000	P=1.000	P=1.000
Skin: Fibroma or Sarcoma			
Overall rate	11/48 (22.9%)	13/48 (27.1%)	12/47 (25.5%)
Adjusted rate	11/37.8 (29.1%)	13/42.3 (30.7%)	12/40.8 (29.4%)
Terminal rate	7/26 (26.9%)	8/30 (26.7%)	4/29 (13.8%)
First incidence (days)	520	617	517
Poly-3 test	P=1.000	P=1.000	P=1.000

Table A2c
Statistical Analysis of Primary Neoplasms in Male Mice Exposed to Ethanol and 10 ppm Urethane in Drinking Water for 2 Years

	0% Ethanol	2.5% Ethanol	5% Ethanol
Spleen: Histiocytic Sarcoma			
Overall rate	3/46 (6.5%)	3/46 (6.5%)	0/46 (0.0%)
Adjusted rate	3/36.7 (8.2%)	3/40.9 (7.3%)	0/37.9 (0.0%)
Terminal rate	1/26 (3.8%)	1/30 (3.3%)	0/29 (0.0%)
First incidence (days)	614	638	—
Poly-3 test	P=0.186	P=1.000	P=0.224
Stomach (Forestomach): Squamous Cell Papilloma			
Overall rate	1/47 (2.1%)	4/47 (8.5%)	2/47 (4.3%)
Adjusted rate	1/36.5 (2.7%)	4/41.4 (9.7%)	2/38.0 (5.3%)
Terminal rate	0/26 (0.0%)	2/30 (6.7%)	2/29 (6.9%)
First incidence (days)	691	523	765 (T)
Poly-3 test	P=0.861	P=0.437	P=1.000
Stomach (Forestomach): Squamous Cell Papilloma or Squamous Cell Carcinoma			
Overall rate	2/47 (4.3%)	4/47 (8.5%)	2/47 (4.3%)
Adjusted rate	2/37.2 (5.4%)	4/41.4 (9.7%)	2/38.0 (5.3%)
Terminal rate	0/26 (0.0%)	2/30 (6.7%)	2/29 (6.9%)
First incidence (days)	537	523	765 (T)
Poly-3 test	P=1.000	P=0.776	P=1.000
All Organs: Hemangioma			
Overall rate	2/48 (4.2%)	0/48 (0.0%)	3/48 (6.3%)
Adjusted rate	2/36.3 (5.5%)	0/40.7 (0.0%)	3/38.7 (7.8%)
Terminal rate	1/26 (3.8%)	0/30 (0.0%)	3/29 (10.3%)
First incidence (days)	754	—	765 (T)
Poly-3 test	P=0.804	P=0.424	P=1.000
All Organs: Hemangiosarcoma			
Overall rate	4/48 (8.3%)	5/48 (10.4%)	3/48 (6.3%)
Adjusted rate	4/36.6 (10.9%)	5/41.0 (12.2%)	3/39.1 (7.7%)
Terminal rate	2/26 (7.7%)	4/30 (13.3%)	2/29 (6.9%)
First incidence (days)	691	681	620
Poly-3 test	P=0.774	P=1.000	P=0.926
All Organs: Hemangioma or Hemangiosarcoma			
Overall rate	5/48 (10.4%)	5/48 (10.4%)	6/48 (12.5%)
Adjusted rate	5/36.6 (13.7%)	5/41.0 (12.2%)	6/39.1 (15.3%)
Terminal rate	3/26 (11.5%)	4/30 (13.3%)	5/29 (17.2%)
First incidence (days)	691	681	620
Poly-3 test	P=0.960	P=1.000	P=1.000
All Organs: Histiocytic Sarcoma			
Overall rate	3/48 (6.3%)	4/48 (8.3%)	0/48 (0.0%)
Adjusted rate	3/36.8 (8.1%)	4/41.4 (9.7%)	0/38.7 (0.0%)
Terminal rate	1/26 (3.8%)	1/30 (3.3%)	0/29 (0.0%)
First incidence (days)	614	638	—
Poly-3 test	P=0.205	P=1.000	P=0.218
All Organs: Malignant Lymphoma			
Overall rate	7/48 (14.6%)	6/48 (12.5%)	10/48 (20.8%)
Adjusted rate	7/36.7 (19.1%)	6/41.2 (14.6%)	10/38.9 (25.7%)
Terminal rate	6/26 (23.1%)	5/30 (16.7%)	9/29 (31.0%)
First incidence (days)	642	622	701
Poly-3 test	P=0.545	P=0.821	P=0.679

Table A2c
Statistical Analysis of Primary Neoplasms in Male Mice Exposed to Ethanol and 10 ppm Urethane in Drinking Water for 2 Years

	0% Ethanol	2.5% Ethanol	5% Ethanol
All Organs: Benign Neoplasms			
Overall rate	29/48 (60.4%)	33/48 (68.8%)	29/48 (60.4%)
Adjusted rate	29/39.0 (74.4%)	33/43.7 (75.4%)	29/40.6 (71.4%)
Terminal rate	19/26 (73.1%)	24/30 (80.0%)	23/29 (79.3%)
First incidence (days)	511	523	517
Poly-3 test	P=0.850	P=1.000	P=0.958
All Organs: Malignant Neoplasms			
Overall rate	30/48 (62.5%)	32/48 (66.7%)	30/48 (62.5%)
Adjusted rate	30/40.4 (74.2%)	32/45.9 (69.7%)	30/42.9 (70.0%)
Terminal rate	17/26 (65.4%)	18/30 (60.0%)	18/29 (62.1%)
First incidence (days)	520	382	421
Poly-3 test	P=0.771	P=0.822	P=0.849
All Organs: Benign or Malignant Neoplasms			
Overall rate	39/48 (81.3%)	45/48 (93.8%)	41/48 (85.4%)
Adjusted rate	39/41.3 (94.3%)	45/46.3 (97.2%)	41/43.2 (94.8%)
Terminal rate	24/26 (92.3%)	29/30 (96.7%)	28/29 (96.6%)
First incidence (days)	511	382	421
Poly-3 test	P=1.000	P=0.885	P=1.000

(T) Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals with tissue examined microscopically
[b] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] P values are two sided. Beneath the control incidence (0% ethanol) is the P value associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and that exposed group. The Poly-3 test accounts for the differential mortality in animals that do not reach terminal sacrifice.
[e] Not applicable; no neoplasms in animal group
[f] A single incidence of hepatoblastoma occurred in an animal that also had a carcinoma.

Table A2d
Statistical Analysis of Primary Neoplasms in Male Mice Exposed to Ethanol and 30 ppm Urethane in Drinking Water for 2 Years

	0% Ethanol	2.5% Ethanol	5% Ethanol
Adrenal Medulla: Benign Pheochromocytoma			
Overall rate[a]	2/42 (4.8%)	2/45 (4.4%)	3/46 (6.5%)
Adjusted rate[b]	2/36.1 (5.5%)	2/34.1 (5.9%)	3/36.6 (8.2%)
Terminal rate[c]	0/23 (0.0%)	1/24 (4.2%)	1/24 (4.2%)
First incidence (days)	432	734	507
Poly-3 test[d]	P=0.833	P=1.000	P=1.000
Harderian Gland: Adenoma			
Overall rate	25/47 (53.2%)	21/47 (44.7%)	15/48 (31.3%)
Adjusted rate	25/41.2 (60.7%)	21/37.2 (56.4%)	15/39.1 (38.4%)
Terminal rate	17/26 (65.4%)	17/25 (68.0%)	10/25 (40.0%)
First incidence (days)	456	426	507
Poly-3 test	P=0.050	P=0.875	P=0.064
Harderian Gland: Carcinoma			
Overall rate	7/47 (14.9%)	1/47 (2.1%)	2/48 (4.2%)
Adjusted rate	7/41.2 (17.0%)	1/35.5 (2.8%)	2/37.7 (5.3%)
Terminal rate	2/26 (7.7%)	1/25 (4.0%)	1/25 (4.0%)
First incidence (days)	510	765 (T)	539
Poly-3 test	P=0.080	P=0.095	P=0.199
Harderian Gland: Adenoma or Carcinoma			
Overall rate	30/47 (63.8%)	21/47 (44.7%)	17/48 (35.4%)
Adjusted rate	30/43.3 (69.2%)	21/37.2 (56.4%)	17/39.7 (42.8%)
Terminal rate	17/26 (65.4%)	17/25 (68.0%)	11/25 (44.0%)
First incidence (days)	456	426	507
Poly-3 test	P=0.014	P=0.323	P=0.020
Liver: Hemangiosarcoma			
Overall rate	5/46 (10.9%)	3/46 (6.5%)	4/48 (8.3%)
Adjusted rate	5/39.6 (12.6%)	3/35.2 (8.5%)	4/37.4 (10.7%)
Terminal rate	3/26 (11.5%)	2/25 (8.0%)	3/25 (12.0%)
First incidence (days)	510	684	660
Poly-3 test	P=0.919	P=0.844	P=1.000
Liver: Hemangioma or Hemangiosarcoma			
Overall rate	5/46 (10.9%)	3/46 (6.5%)	6/48 (12.5%)
Adjusted rate	5/39.6 (12.6%)	3/35.2 (8.5%)	6/37.4 (16.0%)
Terminal rate	3/26 (11.5%)	2/25 (8.0%)	5/25 (20.0%)
First incidence (days)	510	684	660
Poly-3 test	P=0.811	P=0.844	P=0.918
Liver: Histiocytic Sarcoma			
Overall rate	5/46 (10.9%)	3/46 (6.5%)	4/48 (8.3%)
Adjusted rate	5/39.3 (12.7%)	3/36.2 (8.3%)	4/37.8 (10.6%)
Terminal rate	2/26 (7.7%)	0/25 (0.0%)	1/25 (4.0%)
First incidence (days)	668	514	625
Poly-3 test	P=0.894	P=0.802	P=1.000
Liver: Hepatocellular Adenoma			
Overall rate	17/46 (37.0%)	16/46 (34.8%)	16/48 (33.3%)
Adjusted rate	17/41.3 (41.2%)	16/36.3 (44.0%)	16/38.2 (41.9%)
Terminal rate	9/26 (34.6%)	10/25 (40.0%)	12/25 (48.0%)
First incidence (days)	456	528	570
Poly-3 test	P=1.000	P=0.981	P=1.000

Table A2d
Statistical Analysis of Primary Neoplasms in Male Mice Exposed to Ethanol and 30 ppm Urethane in Drinking Water for 2 Years

	0% Ethanol	2.5% Ethanol	5% Ethanol
Liver: Hepatocellular Carcinoma			
Overall rate	9/46 (19.6%)	5/46 (10.9%)	2/48 (4.2%)
Adjusted rate	9/40.3 (22.3%)	5/35.4 (14.1%)	2/37.9 (5.3%)
Terminal rate	5/26 (19.2%)	2/25 (8.0%)	0/25 (0.0%)
First incidence (days)	542	711	570
Poly-3 test	P=0.041	P=0.537	P=0.060
Liver: Hepatocellular Adenoma or Carcinoma			
Overall rate	24/46 (52.2%)	17/46 (37.0%)	17/48 (35.4%)
Adjusted rate	24/42.5 (56.5%)	17/36.3 (46.8%)	17/38.4 (44.3%)
Terminal rate	13/26 (50.0%)	11/25 (44.0%)	12/25 (48.0%)
First incidence (days)	456	528	570
Poly-3 test	P=0.299	P=0.519	P=0.372
Lung: Histiocytic Sarcoma			
Overall rate	2/47 (4.3%)	3/47 (6.4%)	3/48 (6.3%)
Adjusted rate	2/39.1 (5.1%)	3/36.8 (8.2%)	3/37.8 (7.9%)
Terminal rate	0/26 (0.0%)	0/25 (0.0%)	0/25 (0.0%)
First incidence (days)	752	514	625
Poly-3 test	P=0.794	P=0.944	P=0.970
Lung: Alveolar/bronchiolar Adenoma			
Overall rate	22/47 (46.8%)	19/47 (40.4%)	9/48 (18.8%)
Adjusted rate	22/41.2 (53.4%)	19/36.7 (51.8%)	9/38.1 (23.6%)
Terminal rate	16/26 (61.5%)	15/25 (60.0%)	6/25 (24.0%)
First incidence (days)	456	593	507
Poly-3 test	P=0.008	P=1.000	P=0.009
Lung: Alveolar/bronchiolar Carcinoma			
Overall rate	9/47 (19.1%)	8/47 (17.0%)	5/48 (10.4%)
Adjusted rate	9/40.5 (22.2%)	8/36.4 (22.0%)	5/37.6 (13.3%)
Terminal rate	5/26 (19.2%)	5/25 (20.0%)	3/25 (12.0%)
First incidence (days)	542	640	671
Poly-3 test	P=0.403	P=1.000	P=0.463
Lung: Alveolar/bronchiolar Adenoma or Carcinoma			
Overall rate	29/47 (61.7%)	24/47 (51.1%)	14/48 (29.2%)
Adjusted rate	29/42.2 (68.8%)	24/37.3 (64.4%)	14/38.6 (36.2%)
Terminal rate	20/26 (76.9%)	18/25 (72.0%)	9/25 (36.0%)
First incidence (days)	456	593	507
Poly-3 test	P=0.003	P=0.852	P=0.004
Lymph Node (Mesenteric): Histiocytic Sarcoma			
Overall rate	2/43 (4.7%)	4/45 (8.9%)	3/42 (7.1%)
Adjusted rate	2/36.8 (5.4%)	4/36.3 (11.0%)	3/34.8 (8.6%)
Terminal rate	0/25 (0.0%)	0/25 (0.0%)	1/25 (4.0%)
First incidence (days)	668	514	678
Poly-3 test	P=0.772	P=0.660	P=0.948
Skin: Sarcoma			
Overall rate	5/47 (10.6%)	10/46 (21.7%)	15/48 (31.3%)
Adjusted rate	5/39.9 (12.5%)	10/37.7 (26.5%)	15/42.4 (35.4%)
Terminal rate	3/26 (11.5%)	5/24 (20.8%)	3/25 (12.0%)
First incidence (days)	432	362	368
Poly-3 test	P=0.020	P=0.197	P=0.026

Table A2d
Statistical Analysis of Primary Neoplasms in Male Mice Exposed to Ethanol and 30 ppm Urethane in Drinking Water for 2 Years

	0% Ethanol	2.5% Ethanol	5% Ethanol
Skin: Fibroma or Sarcoma			
Overall rate	8/47 (17.0%)	11/46 (23.9%)	16/48 (33.3%)
Adjusted rate	8/39.9 (20.0%)	11/37.7 (29.2%)	16/42.4 (37.7%)
Terminal rate	6/26 (23.1%)	6/24 (25.0%)	4/25 (16.0%)
First incidence (days)	432	362	368
Poly-3 test	P=0.093	P=0.498	P=0.121
Skin: Hemangiosarcoma			
Overall rate	0/47 (0.0%)	4/46 (8.7%)	0/48 (0.0%)
Adjusted rate	0/39.0 (0.0%)	4/34.9 (11.5%)	0/37.1 (0.0%)
Terminal rate	0/26 (0.0%)	2/24 (8.3%)	0/25 (0.0%)
First incidence (days)	—[e]	710	—
Poly-3 test	P=1.000	P=0.092	—[f]
Skin: Squamous Cell Papilloma or Squamous Cell Carcinoma			
Overall rate	3/47 (6.4%)	4/46 (8.7%)	0/48 (0.0%)
Adjusted rate	3/39.1 (7.7%)	4/35.0 (11.4%)	0/37.1 (0.0%)
Terminal rate	2/26 (7.7%)	3/24 (12.5%)	0/25 (0.0%)
First incidence (days)	762	642	—
Poly-3 test	P=0.272	P=0.878	P=0.254
Skin: Squamous Cell Papilloma, Basal Cell Adenoma, or Squamous Cell Carcinoma			
Overall rate	5/47 (10.6%)	4/46 (8.7%)	0/48 (0.0%)
Adjusted rate	5/39.1 (12.8%)	4/35.0 (11.4%)	0/37.1 (0.0%)
Terminal rate	3/26 (11.5%)	3/24 (12.5%)	0/25 (0.0%)
First incidence (days)	746	642	—
Poly-3 test	P=0.067	P=1.000	P=0.068
Spleen: Hemangioma or Hemangiosarcoma			
Overall rate	3/45 (6.7%)	2/46 (4.3%)	0/46 (0.0%)
Adjusted rate	3/38.1 (7.9%)	2/35.1 (5.7%)	0/36.4 (0.0%)
Terminal rate	2/26 (7.7%)	1/25 (4.0%)	0/25 (0.0%)
First incidence (days)	724	733	—
Poly-3 test	P=0.179	P=1.000	P=0.252
Spleen: Histiocytic Sarcoma			
Overall rate	3/45 (6.7%)	2/46 (4.3%)	3/46 (6.5%)
Adjusted rate	3/38.7 (7.8%)	2/36.0 (5.6%)	3/37.1 (8.1%)
Terminal rate	0/26 (0.0%)	0/25 (0.0%)	0/25 (0.0%)
First incidence (days)	643	514	625
Poly-3 test	P=1.000	P=1.000	P=1.000
Stomach (Forestomach): Squamous Cell Papilloma			
Overall rate	3/44 (6.8%)	1/46 (2.2%)	3/45 (6.7%)
Adjusted rate	3/37.7 (7.9%)	1/35.0 (2.9%)	3/36.6 (8.2%)
Terminal rate	3/26 (11.5%)	1/25 (4.0%)	2/25 (8.0%)
First incidence (days)	765 (T)	765 (T)	614
Poly-3 test	P=1.000	P=0.665	P=1.000
Stomach (Forestomach): Squamous Cell Papilloma or Squamous Cell Carcinoma			
Overall rate	3/44 (6.8%)	1/46 (2.2%)	4/45 (8.9%)
Adjusted rate	3/37.7 (7.9%)	1/35.0 (2.9%)	4/36.6 (10.9%)
Terminal rate	3/26 (11.5%)	1/25 (4.0%)	2/25 (8.0%)
First incidence (days)	765 (T)	765 (T)	614
Poly-3 test	P=0.809	P=0.665	P=0.966

Table A2d
Statistical Analysis of Primary Neoplasms in Male Mice Exposed to Ethanol and 30 ppm Urethane in Drinking Water for 2 Years

	0% Ethanol	2.5% Ethanol	5% Ethanol
All Organs: Hemangioma			
Overall rate	2/47 (4.3%)	3/47 (6.4%)	2/48 (4.2%)
Adjusted rate	2/39.2 (5.1%)	3/35.9 (8.3%)	2/37.1 (5.4%)
Terminal rate	1/26 (3.8%)	1/25 (4.0%)	2/25 (8.0%)
First incidence (days)	724	710	765 (T)
Poly-3 test	P=1.000	P=0.921	P=1.000
All Organs: Hemangiosarcoma			
Overall rate	7/47 (14.9%)	9/47 (19.1%)	5/48 (10.4%)
Adjusted rate	7/39.9 (17.5%)	9/36.2 (24.8%)	5/37.4 (13.4%)
Terminal rate	4/26 (15.4%)	5/25 (20.0%)	4/25 (16.0%)
First incidence (days)	510	684	660
Poly-3 test	P=0.784	P=0.616	P=0.848
All Organs: Hemangioma or Hemangiosarcoma			
Overall rate	9/47 (19.1%)	11/47 (23.4%)	7/48 (14.6%)
Adjusted rate	9/40.1 (22.4%)	11/36.4 (30.2%)	7/37.4 (18.7%)
Terminal rate	5/26 (19.2%)	6/25 (24.0%)	6/25 (24.0%)
First incidence (days)	510	684	660
Poly-3 test	P=0.840	P=0.609	P=0.900
All Organs: Histiocytic Sarcoma			
Overall rate	6/47 (12.8%)	5/47 (10.6%)	4/48 (8.3%)
Adjusted rate	6/39.9 (15.1%)	5/37.1 (13.5%)	4/37.8 (10.6%)
Terminal rate	2/26 (7.7%)	1/25 (4.0%)	1/25 (4.0%)
First incidence (days)	643	514	625
Poly-3 test	P=0.682	P=1.000	P=0.802
All Organs: Malignant Lymphoma			
Overall rate	6/47 (12.8%)	10/47 (21.3%)	8/48 (16.7%)
Adjusted rate	6/40.3 (14.9%)	10/36.2 (27.6%)	8/37.1 (21.6%)
Terminal rate	3/26 (11.5%)	8/25 (32.0%)	8/25 (32.0%)
First incidence (days)	410	655	765 (T)
Poly-3 test	P=0.520	P=0.274	P=0.639
All Organs: Benign Neoplasms			
Overall rate	41/47 (87.2%)	37/47 (78.7%)	32/48 (66.7%)
Adjusted rate	41/44.1 (92.9%)	37/39.5 (93.7%)	32/41.2 (77.7%)
Terminal rate	25/26 (96.2%)	25/25 (100.0%)	21/25 (84.0%)
First incidence (days)	432	426	368
Poly-3 test	P=0.022	P=1.000	P=0.056
All Organs: Malignant Neoplasms			
Overall rate	37/47 (78.7%)	33/47 (70.2%)	37/48 (77.1%)
Adjusted rate	37/45.3 (81.7%)	33/42.2 (78.1%)	37/44.8 (82.6%)
Terminal rate	19/26 (73.1%)	16/25 (64.0%)	18/25 (72.0%)
First incidence (days)	410	362	368
Poly-3 test	P=1.000	P=0.881	P=1.000

Table A2d
Statistical Analysis of Primary Neoplasms in Male Mice Exposed to Ethanol and 30 ppm Urethane in Drinking Water for 2 Years

	0% Ethanol	2.5% Ethanol	5% Ethanol
All Organs: Benign or Malignant Neoplasms			
Overall rate	46/47 (97.9%)	42/47 (89.4%)	44/48 (91.7%)
Adjusted rate	46/46.1 (99.7%)	42/42.2 (99.4%)	44/45.2 (97.4%)
Terminal rate	26/26 (100.0%)	25/25 (100.0%)	24/25 (96.0%)
First incidence (days)	410	362	368
Poly-3 test	P=0.522	P=1.000	P=0.951

(T) Terminal sacrifice
a Number of neoplasm-bearing animals/number of animals with tissue examined microscopically
b Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
c Observed incidence at terminal kill
d P values are two sided. Beneath the control incidence (0% ethanol) is the P value associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and that exposed group. The Poly-3 test accounts for the differential mortality in animals that do not reach terminal sacrifice.
e Not applicable; no neoplasms in animal group
f Value of statistic cannot be computed.

Table A2e
Statistical Analysis of Primary Neoplasms in Male Mice Exposed to Ethanol and 90 ppm Urethane in Drinking Water for 2 Years

	0% Ethanol	2.5% Ethanol	5% Ethanol
Adrenal Medulla: Benign Pheochromocytoma			
Overall rate[a]	6/43 (14.0%)	4/46 (8.7%)	2/45 (4.4%)
Adjusted rate[b]	6/29.4 (20.4%)	4/35.2 (11.4%)	2/31.6 (6.3%)
Terminal rate[c]	0/8 (0.0%)	2/16 (12.5%)	1/12 (8.3%)
First incidence (days)	453	524	753
Poly-3 test[d]	P=0.149	P=0.512	P=0.205
Adrenal Medulla: Benign or Malignant Pheochromocytoma			
Overall rate	6/43 (14.0%)	4/46 (8.7%)	3/45 (6.7%)
Adjusted rate	6/29.4 (20.4%)	4/35.2 (11.4%)	3/31.8 (9.4%)
Terminal rate	0/8 (0.0%)	2/16 (12.5%)	1/12 (8.3%)
First incidence (days)	453	524	691
Poly-3 test	P=0.299	P=0.512	P=0.390
Harderian Gland: Adenoma			
Overall rate	28/47 (59.6%)	27/48 (56.3%)	26/45 (57.8%)
Adjusted rate	28/36.0 (77.8%)	27/41.2 (65.6%)	26/38.3 (67.9%)
Terminal rate	8/8 (100.0%)	10/16 (62.5%)	6/12 (50.0%)
First incidence (days)	466	395	444
Poly-3 test	P=0.415	P=0.301	P=0.439
Harderian Gland: Carcinoma			
Overall rate	16/47 (34.0%)	16/48 (33.3%)	10/45 (22.2%)
Adjusted rate	16/35.7 (44.9%)	16/41.6 (38.4%)	10/33.8 (29.6%)
Terminal rate	3/8 (37.5%)	2/16 (12.5%)	4/12 (33.3%)
First incidence (days)	453	395	478
Poly-3 test	P=0.233	P=0.729	P=0.266
Harderian Gland: Adenoma or Carcinoma			
Overall rate	38/47 (80.9%)	38/48 (79.2%)	35/45 (77.8%)
Adjusted rate	38/42.0 (90.6%)	38/45.2 (84.1%)	35/39.8 (87.9%)
Terminal rate	8/8 (100.0%)	12/16 (75.0%)	10/12 (83.3%)
First incidence (days)	453	395	444
Poly-3 test	P=0.816	P=0.530	P=0.969
Heart: Hemangiosarcoma			
Overall rate	5/48 (10.4%)	4/48 (8.3%)	4/48 (8.3%)
Adjusted rate	5/31.0 (16.1%)	4/37.0 (10.8%)	4/33.9 (11.8%)
Terminal rate	1/8 (12.5%)	1/16 (6.3%)	2/12 (16.7%)
First incidence (days)	453	552	670
Poly-3 test	P=0.770	P=0.777	P=0.886
Kidney: Hemangiosarcoma			
Overall rate	1/45 (2.2%)	2/47 (4.3%)	3/48 (6.3%)
Adjusted rate	1/28.4 (3.5%)	2/35.9 (5.6%)	3/34.0 (8.8%)
Terminal rate	0/8 (0.0%)	0/16 (0.0%)	1/12 (8.3%)
First incidence (days)	761	569	643
Poly-3 test	P=0.559	P=1.000	P=0.741
Liver: Hemangiosarcoma			
Overall rate	13/44 (29.5%)	11/48 (22.9%)	13/48 (27.1%)
Adjusted rate	13/31.1 (41.8%)	11/38.3 (28.7%)	13/35.2 (36.9%)
Terminal rate	2/8 (25.0%)	4/16 (25.0%)	5/12 (41.7%)
First incidence (days)	493	488	507
Poly-3 test	P=0.818	P=0.363	P=0.872

Table A2e
Statistical Analysis of Primary Neoplasms in Male Mice Exposed to Ethanol and 90 ppm Urethane in Drinking Water for 2 Years

	0% Ethanol	2.5% Ethanol	5% Ethanol
Liver: Histiocytic Sarcoma			
Overall rate	2/44 (4.5%)	6/48 (12.5%)	5/48 (10.4%)
Adjusted rate	2/28.4 (7.1%)	6/37.1 (16.2%)	5/35.2 (14.2%)
Terminal rate	0/8 (0.0%)	2/16 (12.5%)	1/12 (8.3%)
First incidence (days)	680	536	577
Poly-3 test	P=0.585	P=0.465	P=0.616
Liver: Hepatocellular Adenoma			
Overall rate	17/44 (38.6%)	24/48 (50.0%)	12/48 (25.0%)
Adjusted rate	17/33.8 (50.3%)	24/38.8 (61.9%)	12/35.1 (34.2%)
Terminal rate	4/8 (50.0%)	13/16 (81.3%)	6/12 (50.0%)
First incidence (days)	453	395	570
Poly-3 test	P=0.197	P=0.420	P=0.241
Liver: Hepatocellular Carcinoma			
Overall rate	9/44 (20.5%)	4/48 (8.3%)	9/48 (18.8%)
Adjusted rate	9/30.0 (30.0%)	4/35.6 (11.2%)	9/36.5 (24.7%)
Terminal rate	2/8 (25.0%)	4/16 (25.0%)	1/12 (8.3%)
First incidence (days)	580	765 (T)	553
Poly-3 test	P=0.843	P=0.104	P=0.835
Liver: Hepatocellular Adenoma or Carcinoma			
Overall rate	23/44 (52.3%)	24/48 (50.0%)	18/48 (37.5%)
Adjusted rate	23/35.2 (65.3%)	24/38.8 (61.9%)	18/37.1 (48.6%)
Terminal rate	5/8 (62.5%)	13/16 (81.3%)	7/12 (58.3%)
First incidence (days)	453	395	553
Poly-3 test	P=0.156	P=0.944	P=0.198
Liver: Hepatocellular Carcinoma or Hepatoblastoma			
Overall rate	9/44 (20.5%)	4/48 (8.3%)	10/48 (20.8%)
Adjusted rate	9/30.0 (30.0%)	4/35.6 (11.2%)	10/36.5 (27.4%)
Terminal rate	2/8 (25.0%)	4/16 (25.0%)	2/12 (16.7%)
First incidence (days)	580	765 (T)	553
Poly-3 test	P=1.000	P=0.104	P=1.000
Lung: Histiocytic Sarcoma			
Overall rate	1/48 (2.1%)	4/48 (8.3%)	3/48 (6.3%)
Adjusted rate	1/29.4 (3.4%)	4/37.1 (10.8%)	3/34.4 (8.7%)
Terminal rate	0/8 (0.0%)	0/16 (0.0%)	1/12 (8.3%)
First incidence (days)	729	536	593
Poly-3 test	P=0.666	P=0.512	P=0.723
Lung: Alveolar/bronchiolar Adenoma			
Overall rate	34/48 (70.8%)	35/48 (72.9%)	33/48 (68.8%)
Adjusted rate	34/39.5 (86.2%)	35/43.3 (80.9%)	33/42.2 (78.2%)
Terminal rate	8/8 (100.0%)	14/16 (87.5%)	9/12 (75.0%)
First incidence (days)	293	395	355
Poly-3 test	P=0.389	P=0.690	P=0.460
Lung: Alveolar/bronchiolar Carcinoma			
Overall rate	9/48 (18.8%)	24/48 (50.0%)	17/48 (35.4%)
Adjusted rate	9/30.8 (29.2%)	24/39.6 (60.7%)	17/37.1 (45.9%)
Terminal rate	3/8 (37.5%)	9/16 (56.3%)	5/12 (41.7%)
First incidence (days)	521	569	478
Poly-3 test	P=0.320	P=0.010	P=0.228

Table A2e
Statistical Analysis of Primary Neoplasms in Male Mice Exposed to Ethanol and 90 ppm Urethane in Drinking Water for 2 Years

	0% Ethanol	2.5% Ethanol	5% Ethanol
Lung: Alveolar/bronchiolar Adenoma or Carcinoma			
Overall rate	37/48 (77.1%)	43/48 (89.6%)	40/48 (83.3%)
Adjusted rate	37/40.4 (91.7%)	43/45.1 (95.3%)	40/44.5 (89.9%)
Terminal rate	8/8 (100.0%)	15/16 (93.8%)	11/12 (91.7%)
First incidence (days)	293	395	355
Poly-3 test	P=0.871	P=0.746	P=1.000
Lymph Node (Mesenteric): Hemangiosarcoma			
Overall rate	1/38 (2.6%)	3/44 (6.8%)	1/43 (2.3%)
Adjusted rate	1/25.4 (3.9%)	3/33.2 (9.0%)	1/30.7 (3.3%)
Terminal rate	0/8 (0.0%)	1/15 (6.7%)	0/12 (0.0%)
First incidence (days)	761	569	691
Poly-3 test	P=1.000	P=0.809	P=1.000
Lymph Node (Mesenteric): Histiocytic Sarcoma			
Overall rate	1/38 (2.6%)	4/44 (9.1%)	4/43 (9.3%)
Adjusted rate	1/25.5 (3.9%)	4/33.7 (11.9%)	4/31.8 (12.6%)
Terminal rate	0/8 (0.0%)	1/15 (6.7%)	1/12 (8.3%)
First incidence (days)	729	536	577
Poly-3 test	P=0.430	P=0.541	P=0.496
Preputial Gland: Hemangioma			
Overall rate	0/43 (0.0%)	3/46 (6.5%)	0/44 (0.0%)
Adjusted rate	0/26.6 (0.0%)	3/34.4 (8.7%)	0/31.3 (0.0%)
Terminal rate	0/7 (0.0%)	2/15 (13.3%)	0/12 (0.0%)
First incidence (days)	—[e]	620	—
Poly-3 test	P=1.000	P=0.337	—[f]
Preputial Gland: Hemangioma or Hemangiosarcoma			
Overall rate	0/43 (0.0%)	4/46 (8.7%)	0/44 (0.0%)
Adjusted rate	0/26.6 (0.0%)	4/34.4 (11.6%)	0/31.3 (0.0%)
Terminal rate	0/7 (0.0%)	2/15 (13.3%)	0/12 (0.0%)
First incidence (days)	—	620	—
Poly-3 test	P=1.000	P=0.194	—
Skin: Sarcoma			
Overall rate	14/48 (29.2%)	8/47 (17.0%)	12/45 (26.7%)
Adjusted rate	14/34.7 (40.3%)	8/36.8 (21.7%)	12/34.4 (34.9%)
Terminal rate	1/8 (12.5%)	2/16 (12.5%)	4/12 (33.3%)
First incidence (days)	453	395	467
Poly-3 test	P=0.737	P=0.133	P=0.822
Skin: Fibroma or Sarcoma			
Overall rate	15/48 (31.3%)	8/47 (17.0%)	13/45 (28.9%)
Adjusted rate	15/35.0 (42.9%)	8/36.8 (21.7%)	13/34.4 (37.8%)
Terminal rate	1/8 (12.5%)	2/16 (12.5%)	4/12 (33.3%)
First incidence (days)	453	395	467
Poly-3 test	P=0.758	P=0.083	P=0.846
Skin: Hemangioma or Hemangiosarcoma			
Overall rate	3/48 (6.3%)	1/47 (2.1%)	1/45 (2.2%)
Adjusted rate	3/30.3 (9.9%)	1/34.9 (2.9%)	1/32.4 (3.1%)
Terminal rate	1/8 (12.5%)	1/16 (6.3%)	0/12 (0.0%)
First incidence (days)	576	765 (T)	623
Poly-3 test	P=0.394	P=0.507	P=0.558

Table A2e
Statistical Analysis of Primary Neoplasms in Male Mice Exposed to Ethanol and 90 ppm Urethane in Drinking Water for 2 Years

	0% Ethanol	2.5% Ethanol	5% Ethanol
Skin: Squamous Cell Papilloma			
Overall rate	5/48 (10.4%)	3/47 (6.4%)	6/45 (13.3%)
Adjusted rate	5/30.4 (16.4%)	3/35.7 (8.4%)	6/32.4 (18.5%)
Terminal rate	2/8 (25.0%)	2/16 (12.5%)	2/12 (16.7%)
First incidence (days)	453	453	710
Poly-3 test	P=0.906	P=0.534	P=1.000
Skin: Squamous Cell Papilloma or Squamous Cell Carcinoma			
Overall rate	6/48 (12.5%)	7/47 (14.9%)	7/45 (15.6%)
Adjusted rate	6/31.0 (19.4%)	7/37.6 (18.6%)	7/32.4 (21.6%)
Terminal rate	2/8 (25.0%)	2/16 (12.5%)	2/12 (16.7%)
First incidence (days)	453	453	710
Poly-3 test	P=0.949	P=1.000	P=1.000
Skin: Basal Cell Carcinoma or Squamous Cell Carcinoma			
Overall rate	2/48 (4.2%)	4/47 (8.5%)	1/45 (2.2%)
Adjusted rate	2/30.5 (6.6%)	4/36.8 (10.9%)	1/32.0 (3.1%)
Terminal rate	0/8 (0.0%)	0/16 (0.0%)	0/12 (0.0%)
First incidence (days)	530	524	753
Poly-3 test	P=0.749	P=0.854	P=0.966
Skin: Squamous Cell Papilloma, Basal Cell Adenoma, Basal Cell Carcinoma, or Squamous Cell Carcinoma			
Overall rate	8/48 (16.7%)	7/47 (14.9%)	10/45 (22.2%)
Adjusted rate	8/31.8 (25.2%)	7/37.6 (18.6%)	10/32.9 (30.4%)
Terminal rate	2/8 (25.0%)	2/16 (12.5%)	3/12 (25.0%)
First incidence (days)	453	453	691
Poly-3 test	P=0.706	P=0.711	P=0.847
Spleen: Hemangiosarcoma			
Overall rate	5/42 (11.9%)	3/46 (6.5%)	1/45 (2.2%)
Adjusted rate	5/28.1 (17.8%)	3/35.2 (8.5%)	1/32.4 (3.1%)
Terminal rate	1/8 (12.5%)	1/16 (6.3%)	0/12 (0.0%)
First incidence (days)	548	552	753
Poly-3 test	P=0.091	P=0.472	P=0.134
Spleen: Hemangioma or Hemangiosarcoma			
Overall rate	6/42 (14.3%)	3/46 (6.5%)	1/45 (2.2%)
Adjusted rate	6/28.9 (20.8%)	3/35.2 (8.5%)	1/32.4 (3.1%)
Terminal rate	1/8 (12.5%)	1/16 (6.3%)	0/12 (0.0%)
First incidence (days)	483	552	753
Poly-3 test	P=0.042	P=0.294	P=0.069
Spleen: Histiocytic Sarcoma			
Overall rate	2/42 (4.8%)	3/46 (6.5%)	3/45 (6.7%)
Adjusted rate	2/27.5 (7.3%)	3/35.6 (8.4%)	3/33.1 (9.1%)
Terminal rate	0/8 (0.0%)	0/16 (0.0%)	1/12 (8.3%)
First incidence (days)	680	536	593
Poly-3 test	P=1.000	P=1.000	P=1.000
Stomach (Forestomach): Squamous Cell Papilloma			
Overall rate	3/45 (6.7%)	2/46 (4.3%)	5/48 (10.4%)
Adjusted rate	3/29.3 (10.2%)	2/34.5 (5.8%)	5/33.8 (14.8%)
Terminal rate	0/8 (0.0%)	2/16 (12.5%)	2/12 (16.7%)
First incidence (days)	646	765 (T)	697
Poly-3 test	P=0.658	P=0.850	P=0.873

Table A2e
Statistical Analysis of Primary Neoplasms in Male Mice Exposed to Ethanol and 90 ppm Urethane in Drinking Water for 2 Years

	0% Ethanol	2.5% Ethanol	5% Ethanol
Stomach (Forestomach): Squamous Cell Papilloma or Squamous Cell Carcinoma			
Overall rate	5/45 (11.1%)	3/46 (6.5%)	5/48 (10.4%)
Adjusted rate	5/29.6 (16.9%)	3/34.5 (8.7%)	5/33.8 (14.8%)
Terminal rate	1/8 (12.5%)	3/16 (18.8%)	2/12 (16.7%)
First incidence (days)	646	765 (T)	697
Poly-3 test	P=1.000	P=0.541	P=1.000
All Organs: Hemangioma			
Overall rate	3/48 (6.3%)	4/48 (8.3%)	2/48 (4.2%)
Adjusted rate	3/30.1 (10.0%)	4/36.0 (11.1%)	2/33.6 (6.0%)
Terminal rate	1/8 (12.5%)	3/16 (18.8%)	1/12 (8.3%)
First incidence (days)	483	620	748
Poly-3 test	P=0.722	P=1.000	P=0.898
All Organs: Hemangiosarcoma			
Overall rate	19/48 (39.6%)	21/48 (43.8%)	18/48 (37.5%)
Adjusted rate	19/34.5 (55.2%)	21/39.5 (53.1%)	18/36.2 (49.7%)
Terminal rate	3/8 (37.5%)	8/16 (50.0%)	7/12 (58.3%)
First incidence (days)	453	488	507
Poly-3 test	P=0.726	P=1.000	P=0.815
All Organs: Hemangioma or Hemangiosarcoma			
Overall rate	21/48 (43.8%)	22/48 (45.8%)	19/48 (39.6%)
Adjusted rate	21/35.2 (59.7%)	22/39.5 (55.6%)	19/36.3 (52.4%)
Terminal rate	4/8 (50.0%)	9/16 (56.3%)	7/12 (58.3%)
First incidence (days)	453	488	507
Poly-3 test	P=0.601	P=0.900	P=0.681
All Organs: Histiocytic Sarcoma			
Overall rate	2/48 (4.2%)	7/48 (14.6%)	5/48 (10.4%)
Adjusted rate	2/29.7 (6.7%)	7/37.1 (18.8%)	5/35.2 (14.2%)
Terminal rate	0/8 (0.0%)	3/16 (18.8%)	1/12 (8.3%)
First incidence (days)	680	536	577
Poly-3 test	P=0.595	P=0.279	P=0.574
All Organs: Malignant Lymphoma			
Overall rate	4/48 (8.3%)	7/48 (14.6%)	14/48 (29.2%)
Adjusted rate	4/29.8 (13.4%)	7/36.6 (19.1%)	14/37.1 (37.7%)
Terminal rate	2/8 (25.0%)	5/16 (31.3%)	4/12 (33.3%)
First incidence (days)	600	588	296
Poly-3 test	P=0.022	P=0.772	P=0.043
All Organs: Benign Neoplasms			
Overall rate	45/48 (93.8%)	46/48 (95.8%)	40/48 (83.3%)
Adjusted rate	45/45.8 (98.3%)	46/46.3 (99.2%)	40/42.8 (93.5%)
Terminal rate	8/8 (100.0%)	16/16 (100.0%)	12/12 (100.0%)
First incidence (days)	293	395	355
Poly-3 test	P=0.156	P=1.000	P=0.385
All Organs: Malignant Neoplasms			
Overall rate	43/48 (89.6%)	45/48 (93.8%)	45/48 (93.8%)
Adjusted rate	43/44.0 (97.8%)	45/46.2 (97.4%)	45/45.5 (98.9%)
Terminal rate	8/8 (100.0%)	15/16 (93.8%)	12/12 (100.0%)
First incidence (days)	453	395	296
Poly-3 test	P=0.998	P=1.000	P=1.000

Table A2e
Statistical Analysis of Primary Neoplasms in Male Mice Exposed to Ethanol and 90 ppm Urethane in Drinking Water for 2 Years

	0% Ethanol	2.5% Ethanol	5% Ethanol
All Organs: Benign or Malignant Neoplasms			
Overall rate	47/48 (97.9%)	47/48 (97.9%)	46/48 (95.8%)
Adjusted rate	47/47.1 (99.8%)	47/47.0 (100.0%)	46/46.3 (99.4%)
Terminal rate	8/8 (100.0%)	16/16 (100.0%)	12/12 (100.0%)
First incidence (days)	293	395	296
Poly-3 test	P=1.000	P=1.000	P=1.000

(T) Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals with tissue examined microscopically
[b] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] P values are two sided. Beneath the control incidence (0% ethanol) is the P value associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and that exposed group. The Poly-3 test accounts for the differential mortality in animals that do not reach terminal sacrifice.
[e] Not applicable; no neoplasms in animal group
[f] Value of statistic cannot be computed.

TABLE A3a
Historical Incidence of Hemangiosarcoma (All Sites) in Control Male B6C3F$_1$/Nctr BR Mice[a]

Study	Incidence in Controls
Chloral hydrate	2/48
Chloral hydrate	1/48
Doxylamine	0/48
Fumonisin B$_1$	0/48
Pyrilamine	0/47
Sulfamethazine	3/187
Triprolidine	1/48
Total (%)	7/474 (1.5%)
Range	0%-4%

[a] Data as of January 2002. Studies were conducted at the National Center for Toxicological Research in animals given NIH-31 feed.

TABLE A3b
Historical Incidence of Hepatocellular Neoplasms in Control Male B6C3F$_1$/Nctr BR Mice[a]

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Chloral hydrate	18/48	10/48	24/48
Chloral hydrate	12/48	4/48	16/48
Doxylamine	6/48	4/48	9/48
Fumonisin B$_1$	9/47	4/47	12/47
Pyrilamine	10/46	3/46	13/46
Sulfamethazine	25/185	20/185	42/185
Triprolidine	9/48	5/48	13/48
Total (%)	89/470 (18.9%)	50/470 (10.6%)	129/470 (27.4%)
Range	13%-38%	7%-21%	19%-50%

[a] Data as of January 2002. Studies were conducted at the National Center for Toxicological Research in animals given NIH-31 feed.

TABLE A3c
Historical Incidence of Alveolar/bronchiolar Neoplasms in Control Male B6C3F$_1$/Nctr BR Mice[a]

Study	Incidence in Controls Adenoma	Carcinoma	Adenoma or Carcinoma
Chloral hydrate	4/48	4/48	8/48
Chloral hydrate	13/48	2/48	15/48
Doxylamine	9/48	0/48	9/48
Fumonisin B$_1$	6/48	0/48	6/48
Pyrilamine	5/47	0/47	5/47
Sulfamethazine	25/186	3/186	28/186
Triprolidine	9/48	2/48	11/48
Total (%)	71/473 (15.0%)	11/473 (2.3%)	82/473 (17.3%)
Range	8%-27%	0%-8%	11%-31%

[a] Data as of January 2002. Studies were conducted at the National Center for Toxicological Research in animals given NIH-31 feed.

TABLE A3d
Historical Incidence of Harderian Gland Neoplasms in Control Male B6C3F$_1$/Nctr BR Mice[a]

Study	Incidence in Controls Adenoma	Carcinoma	Adenoma or Carcinoma
Chloral hydrate	4/48	0/48	4/48
Chloral hydrate	5/47	0/47	5/47
Fumonisin B$_1$	1/46	0/46	1/46
Sulfamethazine	15/184	0/184	15/184
Total (%)	25/325 (7.7%)	0/325	25/325 (7.7%)
Range	2%-11%		2%-11%

[a] Data as of January 2002. Studies were conducted at the National Center for Toxicological Research in animals given NIH-31 feed.

Table A3e
Historical Incidence of Squamous Cell Papilloma or Carcinoma (Combined) of the Skin in Control Male B6C3F$_1$/Nctr BR Mice[a]

Study	Incidence in Controls
Chloral hydrate	0/47
Chloral hydrate	0/48
Doxylamine	0/47
Fumonisin B$_1$	0/47
Pyrilamine	0/47
Sulfamethazine	0/183
Triprolidine	0/48
Total	0/468

[a] Data as of January 2002. Studies were conducted at the National Center for Toxicological Research in animals given NIH-31 feed.

Table A4
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Drinking Water Study of Urethane and 0% Ethanol[a]

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
Disposition Summary				
Animals initially in study	48	48	48	48
Early deaths				
Moribund	2	8	4	11
Natural deaths	19	14	18	29
Survivors				
Terminal sacrifice	27	26	26	8
Animals examined microscopically	48	48	47	48
Alimentary System				
Gallbladder	(35)	(38)	(36)	(23)
Concretion	1 (3%)			
Cytoplasmic alteration, moderate, epithelium			1 (3%)	
Infiltration cellular, lymphocytic, mild	2 (6%)			
Inflammation, acute, mild		1 (3%)	1 (3%)	
Inflammation, acute, minimal		1 (3%)		
Inflammation, acute, moderate			1 (3%)	
Intestine large, rectum	(45)	(47)	(45)	(44)
Cyst, minimal	1 (2%)			
Erosion, moderate		1 (2%)		
Infiltration cellular, lymphocytic, marked, serosa	1 (2%)			
Inflammation, chronic active, moderate		3 (6%)		
Necrosis, marked	1 (2%)			
Intestine small, duodenum	(35)	(38)	(36)	(26)
Inflammation, chronic active, mild				1 (4%)
Intestine small, ileum	(37)	(37)	(35)	(26)
Inflammation, chronic active, minimal				1 (4%)
Intestine small, jejunum	(39)	(39)	(37)	(24)
Inflammation, chronic active, minimal				1 (4%)
Liver	(46)	(47)	(46)	(44)
Amyloid deposition, minimal		1 (2%)		
Angiectasis		4 (9%)	6 (13%)	17 (39%)
Basophilic focus	1 (2%)	1 (2%)	2 (4%)	1 (2%)
Clear cell focus	3 (7%)		5 (11%)	2 (5%)
Cyst, marked, bile duct	1 (2%)			
Cyst, mild, bile duct			1 (2%)	
Cyst, minimal, bile duct			1 (2%)	
Eosinophilic focus	6 (13%)	6 (13%)	19 (41%)	28 (64%)
Eosinophilic focus, multiple		1 (2%)		
Hematopoietic cell proliferation, marked			1 (2%)	
Hematopoietic cell proliferation, mild	1 (2%)	1 (2%)	3 (7%)	2 (5%)
Hematopoietic cell proliferation, minimal		2 (4%)	4 (9%)	7 (16%)
Hematopoietic cell proliferation, moderate		2 (4%)	1 (2%)	2 (5%)
Hyperplasia, marked, Kupffer cell		1 (2%)		2 (5%)
Hyperplasia, mild, Kupffer cell	2 (4%)	3 (6%)	5 (11%)	4 (9%)
Hyperplasia, minimal, bile duct			1 (2%)	
Hyperplasia, minimal, Kupffer cell	2 (4%)	3 (6%)	2 (4%)	1 (2%)
Hyperplasia, minimal, oval cell		1 (2%)		
Hyperplasia, moderate, Kupffer cell	1 (2%)	3 (6%)	3 (7%)	5 (11%)
Hypertrophy, hepatocyte	1 (2%)			

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

Table A4
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Drinking Water Study of Urethane and 0% Ethanol

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
Alimentary System (continued)				
Liver (continued)	(46)	(47)	(46)	(44)
Infiltration cellular, lymphocytic, marked		1 (2%)		
Infiltration cellular, lymphocytic, minimal	1 (2%)			
Infiltration cellular, lymphocytic, moderate		1 (2%)		
Infiltration cellular, mixed cell, mild		1 (2%)	2 (4%)	1 (2%)
Infiltration cellular, mixed cell, minimal	1 (2%)	2 (4%)	2 (4%)	1 (2%)
Inflammation, subacute, moderate		1 (2%)		
Mixed cell focus	1 (2%)	1 (2%)	3 (7%)	
Necrosis, marked	1 (2%)			2 (5%)
Necrosis, marked, hepatocyte		1 (2%)		
Necrosis, mild	1 (2%)			2 (5%)
Necrosis, mild, hepatocyte			2 (4%)	2 (5%)
Necrosis, minimal		1 (2%)	1 (2%)	
Necrosis, minimal, hepatocyte	3 (7%)	3 (6%)	2 (4%)	
Necrosis, moderate	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Necrosis, moderate, hepatocyte		1 (2%)	1 (2%)	1 (2%)
Nuclear alteration, mild, hepatocyte	2 (4%)			
Nuclear alteration, minimal, hepatocyte	1 (2%)			
Regeneration		1 (2%)	2 (4%)	1 (2%)
Syncytial alteration, mild, hepatocyte	3 (7%)	3 (6%)	2 (4%)	
Syncytial alteration, minimal, hepatocyte	5 (11%)	3 (6%)	6 (13%)	1 (2%)
Tension lipidosis	1 (2%)			
Vacuolization cytoplasmic, mild, hepatocyte		2 (4%)	1 (2%)	
Vacuolization cytoplasmic, minimal, hepatocyte	2 (4%)	1 (2%)		
Mesentery	(1)	(1)	(1)	(1)
Cyst, moderate			1 (100%)	
Necrosis, fat	1 (100%)	1 (100%)		
Pancreas	(45)	(44)	(44)	(42)
Atrophy, marked, acinar cell	1 (2%)			
Atrophy, moderate, acinar cell				1 (2%)
Basophilic focus				1 (2%)
Infiltration cellular, lymphocytic, minimal	4 (9%)	3 (7%)	5 (11%)	2 (5%)
Necrosis, mild				1 (2%)
Vacuolization cytoplasmic, mild, acinar cell		1 (2%)		
Salivary glands	(47)	(48)	(46)	(46)
Atrophy, mild	2 (4%)	1 (2%)	1 (2%)	2 (4%)
Atrophy, minimal		1 (2%)	1 (2%)	2 (4%)
Atrophy, moderate		2 (4%)		
Hyperplasia, lymphoid, moderate	1 (2%)			
Infiltration cellular, lymphocytic, mild	18 (38%)	19 (40%)	22 (48%)	7 (15%)
Infiltration cellular, lymphocytic, minimal	12 (26%)	17 (35%)	16 (35%)	19 (41%)
Infiltration cellular, lymphocytic, moderate	2 (4%)	1 (2%)	1 (2%)	
Stomach, forestomach	(46)	(47)	(44)	(45)
Cyst, marked			1 (2%)	
Cytoplasmic alteration, minimal, epithelium				1 (2%)
Diverticulum				1 (2%)
Hyperplasia, marked, epithelium			2 (5%)	
Hyperplasia, mild, epithelium			1 (2%)	1 (2%)
Hyperplasia, minimal, epithelium	1 (2%)		1 (2%)	

Table A4
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Drinking Water Study of Urethane and 0% Ethanol

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
Alimentary System (continued)				
Stomach, glandular	(43)	(43)	(44)	(42)
Cyst, minimal	1 (2%)	2 (5%)	3 (7%)	1 (2%)
Cyst, moderate		1 (2%)		
Ectopic tissue		1 (2%)		
Erosion, mild			1 (2%)	1 (2%)
Erosion, minimal	1 (2%)			
Hyperplasia, mild, epithelium		1 (2%)		
Infiltration cellular, lymphocytic, minimal	1 (2%)	1 (2%)		
Inflammation, acute, mild	1 (2%)			
Inflammation, acute, minimal	1 (2%)			
Inflammation, chronic, minimal		1 (2%)		
Inflammation, subacute, mild	1 (2%)			
Inflammation, subacute, minimal				1 (2%)
Mineralization, minimal		1 (2%)		
Tongue	(47)	(48)	(47)	(48)
Infiltration cellular, lymphocytic, mild	1 (2%)			
Necrosis, minimal	1 (2%)			
Cardiovascular System				
Heart	(48)	(48)	(47)	(48)
Angiectasis, mild			1 (2%)	3 (6%)
Angiectasis, minimal		1 (2%)	1 (2%)	8 (17%)
Bacterium			1 (2%)	
Cardiomyopathy, minimal		1 (2%)		
Hyperplasia, mild, endothelium			2 (4%)	3 (6%)
Hyperplasia, minimal, endothelium			2 (4%)	5 (10%)
Hyperplasia, moderate, endothelium				1 (2%)
Hypertrophy, minimal, parenchymal cell		2 (4%)		1 (2%)
Infiltration cellular, lymphocytic, minimal, atrium	1 (2%)			
Inflammation, acute, mild, myocardium	1 (2%)		1 (2%)	
Inflammation, acute, mild, valve			1 (2%)	1 (2%)
Inflammation, acute, minimal, myocardium	1 (2%)			
Inflammation, chronic, mild, myocardium			1 (2%)	
Inflammation, chronic, mild, valve			1 (2%)	
Inflammation, chronic, minimal, epicardium			1 (2%)	
Inflammation, chronic, minimal, myocardium		2 (4%)	1 (2%)	1 (2%)
Inflammation, chronic, minimal, valve			1 (2%)	
Mineralization, mild		1 (2%)	1 (2%)	
Mineralization, minimal		1 (2%)		
Mineralization, moderate			1 (2%)	
Necrosis, mild			1 (2%)	
Necrosis, minimal		1 (2%)		
Thrombosis, marked, atrium				1 (2%)

Table A4
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Drinking Water Study of Urethane and 0% Ethanol

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
Endocrine System				
Adrenal gland, cortex	(44)	(44)	(44)	(44)
Angiectasis, moderate			1 (2%)	
Cyst, mild	1 (2%)			
Degeneration, minimal			1 (2%)	
Hyperplasia, focal, mild		1 (2%)		1 (2%)
Hyperplasia, focal, moderate	1 (2%)		4 (9%)	1 (2%)
Hyperplasia, marked, subcapsular	1 (2%)	1 (2%)	2 (5%)	
Hyperplasia, mild, subcapsular	12 (27%)	7 (16%)	9 (20%)	12 (27%)
Hyperplasia, minimal, subcapsular	23 (52%)	25 (57%)	22 (50%)	23 (52%)
Hyperplasia, moderate, subcapsular	2 (5%)	2 (5%)		1 (2%)
Hypertrophy, mild	4 (9%)	5 (11%)	1 (2%)	1 (2%)
Hypertrophy, minimal	3 (7%)	2 (5%)	2 (5%)	1 (2%)
Hypertrophy, moderate	1 (2%)			
Adrenal gland, medulla	(44)	(43)	(42)	(43)
Amyloid deposition, mild			1 (2%)	
Fibrosis, mild				1 (2%)
Hyperplasia, mild			1 (2%)	
Hyperplasia, minimal			1 (2%)	
Hyperplasia, moderate			1 (2%)	1 (2%)
Pigmentation, mild			1 (2%)	
Islets, pancreatic	(45)	(44)	(44)	(42)
Hyperplasia, marked			1 (2%)	1 (2%)
Hyperplasia, mild	1 (2%)		1 (2%)	1 (2%)
Hyperplasia, minimal	3 (7%)	2 (5%)		
Parathyroid gland	(42)	(33)	(30)	(28)
Cyst, mild		1 (3%)		
Cyst, minimal	1 (2%)			
Infiltration cellular, lymphocytic, mild		1 (3%)		
Infiltration cellular, lymphocytic, minimal				1 (4%)
Inflammation, acute, mild	1 (2%)			
Pituitary gland	(35)	(42)	(39)	(38)
Cyst, mild, pars distalis		1 (2%)		
Cyst, minimal, pars distalis				1 (3%)
Hyperplasia, focal, minimal, pars distalis				1 (3%)
Thyroid gland	(46)	(46)	(46)	(45)
Crystals	1 (2%)	1 (2%)		
Cyst, mild, follicle		1 (2%)		2 (4%)
Cyst, minimal, follicle				1 (2%)
Hyperplasia, focal, minimal, follicular cell				1 (2%)
Infiltration cellular, lymphocytic, minimal		1 (2%)		
Inflammation, chronic, minimal	1 (2%)			
Ultimobranchial cyst	8 (17%)	10 (22%)	12 (26%)	9 (20%)

General Body System
None

Table A4
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Drinking Water Study of Urethane and 0% Ethanol

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
Genital System				
Coagulating gland	(46)	(48)	(46)	(46)
Atrophy, marked			1 (2%)	
Atrophy, mild	1 (2%)	1 (2%)	2 (4%)	5 (11%)
Atrophy, minimal		1 (2%)	2 (4%)	
Dilatation, mild		3 (6%)		
Dilatation, minimal			1 (2%)	
Dilatation, moderate	1 (2%)			
Infiltration cellular, lymphocytic, mild		1 (2%)		
Infiltration cellular, lymphocytic, minimal	9 (20%)	4 (8%)	3 (7%)	
Inflammation, acute, moderate	2 (4%)			
Epididymis	(47)	(48)	(46)	(44)
Infiltration cellular, lymphocytic, mild		1 (2%)	2 (4%)	1 (2%)
Infiltration cellular, lymphocytic, minimal	5 (11%)	3 (6%)	10 (22%)	3 (7%)
Infiltration cellular, mixed cell, mild		1 (2%)		
Inflammation, chronic, mild	2 (4%)	3 (6%)		
Inflammation, chronic, minimal	1 (2%)			1 (2%)
Inflammation, subacute, minimal	1 (2%)			1 (2%)
Mineralization, minimal	1 (2%)			1 (2%)
Necrosis, minimal	1 (2%)			
Penis		(1)	(1)	(2)
Cyst, minimal			1 (100%)	
Hyperplasia, mild				1 (50%)
Inflammation, chronic active, mild				1 (50%)
Inflammation, chronic active, moderate		1 (100%)		
Inflammation, chronic, mild			1 (100%)	
Preputial gland	(45)	(44)	(43)	(43)
Angiectasis, marked	1 (2%)			
Angiectasis, minimal		1 (2%)		
Atrophy, marked	3 (7%)	4 (9%)	5 (12%)	11 (26%)
Atrophy, mild	5 (11%)	3 (7%)	4 (9%)	7 (16%)
Atrophy, minimal	2 (4%)	4 (9%)	2 (5%)	1 (2%)
Atrophy, moderate	8 (18%)	3 (7%)	3 (7%)	9 (21%)
Cyst, moderate		1 (2%)		
Dilatation, marked		1 (2%)	2 (5%)	
Dilatation, mild	4 (9%)	12 (27%)	7 (16%)	4 (9%)
Dilatation, minimal	1 (2%)	5 (11%)	1 (2%)	1 (2%)
Dilatation, moderate	2 (4%)	2 (5%)	6 (14%)	5 (12%)
Inflammation, acute, marked	1 (2%)			
Inflammation, acute, mild	1 (2%)	2 (5%)		
Inflammation, acute, minimal		1 (2%)		
Inflammation, acute, moderate	1 (2%)			
Inflammation, chronic active, marked	3 (7%)	2 (5%)	1 (2%)	
Inflammation, chronic active, mild	2 (4%)	4 (9%)	3 (7%)	6 (14%)
Inflammation, chronic active, moderate	5 (11%)	6 (14%)	5 (12%)	4 (9%)
Inflammation, chronic, marked				1 (2%)
Inflammation, chronic, mild	1 (2%)	1 (2%)	7 (16%)	2 (5%)
Inflammation, chronic, minimal	6 (13%)	5 (11%)	2 (5%)	6 (14%)
Inflammation, subacute, mild				1 (2%)
Inflammation, subacute, minimal			1 (2%)	

Table A4
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Drinking Water Study of Urethane and 0% Ethanol

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
Genital System (continued)				
Prostate	(46)	(45)	(45)	(45)
Atrophy, mild	1 (2%)			2 (4%)
Atrophy, minimal		1 (2%)	1 (2%)	2 (4%)
Atrophy, moderate				1 (2%)
Dilatation, mild		1 (2%)		
Hyperplasia, marked, epithelium			1 (2%)	
Infiltration cellular, lymphocytic, mild	1 (2%)			
Infiltration cellular, lymphocytic, minimal		2 (4%)	1 (2%)	1 (2%)
Infiltration cellular, lymphocytic, moderate	1 (2%)			
Inflammation, acute, marked	1 (2%)			
Inflammation, acute, mild	1 (2%)	1 (2%)		2 (4%)
Inflammation, acute, moderate	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Inflammation, chronic, moderate, artery	1 (2%)			
Inflammation, subacute, mild	2 (4%)			1 (2%)
Inflammation, subacute, minimal	13 (28%)	16 (36%)	13 (29%)	4 (9%)
Seminal vesicle	(46)	(48)	(46)	(46)
Atrophy, mild	2 (4%)	3 (6%)	2 (4%)	2 (4%)
Atrophy, minimal			2 (4%)	3 (7%)
Dilatation, mild	3 (7%)	1 (2%)	3 (7%)	
Dilatation, minimal	1 (2%)		1 (2%)	
Dilatation, moderate	1 (2%)	1 (2%)		
Infiltration cellular, lymphocytic, minimal			1 (2%)	1 (2%)
Inflammation, acute, marked		1 (2%)		
Inflammation, acute, mild		1 (2%)		1 (2%)
Inflammation, acute, minimal	1 (2%)			
Inflammation, chronic, mild			1 (2%)	
Testes	(47)	(48)	(46)	(46)
Atrophy, mild, germinal epithelium	1 (2%)	2 (4%)	1 (2%)	2 (4%)
Atrophy, minimal, germinal epithelium	1 (2%)			
Atrophy, moderate, germinal epithelium		2 (4%)	2 (4%)	
Degeneration, mild, germinal epithelium		3 (6%)		
Degeneration, minimal, germinal epithelium	3 (6%)	1 (2%)	3 (7%)	1 (2%)
Developmental malformation			1 (2%)	
Hemorrhage, mild				1 (2%)
Mineralization, minimal	1 (2%)	1 (2%)		2 (4%)
Ovotestis			1 (2%)	
Hematopoietic System				
Bone marrow	(46)	(47)	(45)	(45)
Angiectasis, moderate			2 (4%)	
Hyperplasia, mild	3 (7%)	5 (11%)	4 (9%)	4 (9%)
Hyperplasia, minimal	3 (7%)	1 (2%)	2 (4%)	5 (11%)
Hyperplasia, moderate				1 (2%)
Necrosis, marked	1 (2%)			
Thrombosis			1 (2%)	
Lymph node	(47)	(47)	(46)	(46)
Autolysis, renal			1 (2%)	
Degeneration, cystic, inguinal		1 (2%)		
Hemorrhage, moderate, inguinal				1 (2%)

Table A4
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Drinking Water Study of Urethane and 0% Ethanol

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
Hematopoietic System (continued)				
Lymph node (continued)	(47)	(47)	(46)	(46)
Hyperplasia, lymphoid, marked, renal			1 (2%)	
Hyperplasia, lymphoid, mild, axillary				1 (2%)
Hyperplasia, lymphoid, mild, inguinal				1 (2%)
Hyperplasia, lymphoid, mild, lumbar	1 (2%)			
Hyperplasia, lymphoid, mild, renal				1 (2%)
Hyperplasia, lymphoid, moderate, inguinal		1 (2%)		1 (2%)
Hyperplasia, lymphoid, moderate, renal			1 (2%)	1 (2%)
Lymph node, mandibular	(46)	(46)	(46)	(45)
Angiectasis, marked			1 (2%)	
Hemorrhage, minimal		1 (2%)		1 (2%)
Hyperplasia, lymphoid, marked	1 (2%)	2 (4%)		1 (2%)
Hyperplasia, lymphoid, mild	5 (11%)	2 (4%)	6 (13%)	6 (13%)
Hyperplasia, lymphoid, minimal	4 (9%)	4 (9%)	9 (20%)	3 (7%)
Hyperplasia, lymphoid, moderate	2 (4%)	1 (2%)	2 (4%)	1 (2%)
Infiltration cellular, histiocytic, mild	2 (4%)	1 (2%)		1 (2%)
Infiltration cellular, histiocytic, minimal	2 (4%)	2 (4%)	2 (4%)	3 (7%)
Mineralization, minimal	1 (2%)			
Pigmentation, mild			1 (2%)	
Pigmentation, minimal	1 (2%)			
Lymph node, mesenteric	(43)	(47)	(43)	(38)
Angiectasis	1 (2%)			
Angiectasis, marked	1 (2%)	2 (4%)		3 (8%)
Angiectasis, mild	11 (26%)	11 (23%)	11 (26%)	10 (26%)
Angiectasis, minimal	3 (7%)	6 (13%)	9 (21%)	2 (5%)
Angiectasis, moderate	6 (14%)	2 (4%)	5 (12%)	2 (5%)
Hematopoietic cell proliferation, minimal				1 (3%)
Hemorrhage, mild		1 (2%)		
Hemorrhage, minimal				1 (3%)
Hemorrhage, moderate				1 (3%)
Hyperplasia, lymphoid, marked		1 (2%)	1 (2%)	
Hyperplasia, lymphoid, mild	2 (5%)	7 (15%)	5 (12%)	1 (3%)
Hyperplasia, lymphoid, minimal	4 (9%)	5 (11%)	3 (7%)	4 (11%)
Hyperplasia, lymphoid, moderate			2 (5%)	
Infiltration cellular, histiocytic, mild	1 (2%)			
Infiltration cellular, histiocytic, minimal	1 (2%)			2 (5%)
Infiltration cellular, lymphocytic, moderate		1 (2%)		
Necrosis, mild		1 (2%)		
Spleen	(44)	(46)	(45)	(42)
Angiectasis, mild			1 (2%)	
Angiectasis, moderate			1 (2%)	
Atrophy, mild, lymphoid follicle	1 (2%)	1 (2%)		1 (2%)
Atrophy, minimal, lymphoid follicle		1 (2%)		
Atrophy, moderate, lymphoid follicle	2 (5%)	1 (2%)		
Hematopoietic cell proliferation, marked	5 (11%)	6 (13%)	5 (11%)	9 (21%)
Hematopoietic cell proliferation, mild	6 (14%)	7 (15%)	4 (9%)	6 (14%)
Hematopoietic cell proliferation, minimal			5 (11%)	3 (7%)
Hematopoietic cell proliferation, moderate	8 (18%)	9 (20%)	3 (7%)	14 (33%)
Hyperplasia, marked, lymphoid follicle	5 (11%)	3 (7%)	6 (13%)	1 (2%)
Hyperplasia, mild, lymphoid follicle	3 (7%)	8 (17%)	7 (16%)	1 (2%)
Hyperplasia, minimal, lymphoid follicle	2 (5%)	3 (7%)	3 (7%)	
Hyperplasia, moderate, lymphoid follicle		2 (4%)	4 (9%)	

Table A4
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Drinking Water Study of Urethane and 0% Ethanol

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
Hematopoietic System (continued)				
Spleen (continued)	(44)	(46)	(45)	(42)
Infiltration cellular, lymphocytic, moderate		1 (2%)		
Inflammation, chronic active, mild				1 (2%)
Necrosis, moderate				1 (2%)
Pigmentation, mild			1 (2%)	
Thymus	(32)	(29)	(35)	(27)
Atrophy, marked	6 (19%)	6 (21%)	4 (11%)	7 (26%)
Atrophy, mild	4 (13%)	1 (3%)	4 (11%)	3 (11%)
Atrophy, minimal	1 (3%)	2 (7%)	4 (11%)	3 (11%)
Atrophy, moderate	4 (13%)	2 (7%)	2 (6%)	5 (19%)
Cyst, mild			1 (3%)	
Cyst, minimal	3 (9%)		1 (3%)	1 (4%)
Hyperplasia, mild, medulla		1 (3%)		
Hyperplasia, minimal, cortex			1 (3%)	
Hyperplasia, minimal, epithelial cell			1 (3%)	
Hyperplasia, minimal, medulla	1 (3%)			
Integumentary System				
Mammary gland		(2)	(5)	(1)
Cyst, mild			1 (20%)	
Skin	(47)	(48)	(47)	(48)
Edema, mild			2 (4%)	1 (2%)
Erosion, marked				1 (2%)
Erosion, minimal	1 (2%)			
Hyperplasia, marked, epithelium	1 (2%)			
Hyperplasia, mild, epithelium	1 (2%)	2 (4%)		
Hyperplasia, moderate, sebaceous gland				1 (2%)
Inflammation, acute, minimal	1 (2%)			
Inflammation, chronic active, marked		1 (2%)		
Inflammation, chronic active, mild		1 (2%)		1 (2%)
Inflammation, chronic active, minimal		1 (2%)		
Inflammation, chronic active, moderate	1 (2%)			
Inflammation, chronic, mild	4 (9%)	2 (4%)		1 (2%)
Inflammation, chronic, minimal		2 (4%)		
Inflammation, chronic, moderate				2 (4%)
Metaplasia, osseous, mild	1 (2%)	1 (2%)		
Metaplasia, osseous, moderate		1 (2%)		
Ulcer, marked	1 (2%)	1 (2%)		
Ulcer, mild		1 (2%)		
Ulcer, moderate	2 (4%)	1 (2%)		
Musculoskeletal System				
Bone	(48)	(48)	(47)	(48)
Hyperostosis, mild, sternum	1 (2%)			
Hyperostosis, minimal, sternum	1 (2%)			1 (2%)
Osteomalacia, mild, sternum				1 (2%)

Table A4
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Drinking Water Study of Urethane and 0% Ethanol

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
Musculoskeletal System (continued)				
Bone, femur	(48)	(48)	(47)	(48)
Degeneration, marked, joint, cartilage		1 (2%)		
Degeneration, mild, joint, cartilage	2 (4%)	3 (6%)	1 (2%)	1 (2%)
Degeneration, minimal, joint, cartilage	1 (2%)	6 (13%)	8 (17%)	
Degeneration, moderate, joint, cartilage		2 (4%)	1 (2%)	2 (4%)
Hyperostosis, mild				1 (2%)
Hyperostosis, moderate, joint				1 (2%)
Osteomalacia, mild	1 (2%)			
Skeletal muscle	(48)	(48)	(47)	(48)
Infiltration cellular, lymphocytic, mild		1 (2%)		1 (2%)
Infiltration cellular, lymphocytic, minimal	2 (4%)	2 (4%)	4 (9%)	1 (2%)
Inflammation, subacute, minimal			1 (2%)	
Mineralization, minimal			1 (2%)	
Necrosis, minimal	1 (2%)			
Nervous System				
Brain, cerebellum	(48)	(47)	(44)	(46)
Inflammation, acute, mild, meninges			1 (2%)	
Brain, cerebrum	(48)	(48)	(47)	(47)
Cyst epithelial inclusion		1 (2%)		
Inflammation, acute, mild			1 (2%)	
Mineralization, mild, thalamus	2 (4%)	1 (2%)	1 (2%)	2 (4%)
Mineralization, minimal, thalamus	23 (48%)	23 (48%)	22 (47%)	15 (32%)
Necrosis, mild				1 (2%)
Peripheral nerve	(47)	(48)	(47)	(48)
Degeneration, mild				1 (2%)
Degeneration, minimal	6 (13%)	7 (15%)	5 (11%)	1 (2%)
Respiratory System				
Larynx	(45)	(45)	(46)	(45)
Inflammation, acute, minimal				1 (2%)
Inflammation, chronic, minimal		1 (2%)		
Lung	(48)	(48)	(47)	(48)
Hemorrhage, minimal				1 (2%)
Hyperplasia, marked, alveolar epithelium		1 (2%)		4 (8%)
Hyperplasia, mild, alveolar epithelium	1 (2%)		3 (6%)	4 (8%)
Hyperplasia, minimal, alveolar epithelium	1 (2%)		3 (6%)	1 (2%)
Hyperplasia, moderate, alveolar epithelium				2 (4%)
Infiltration cellular, histiocytic, minimal			1 (2%)	2 (4%)
Infiltration cellular, histiocytic, moderate				1 (2%)
Infiltration cellular, lymphocytic, mild	3 (6%)	1 (2%)	2 (4%)	
Infiltration cellular, lymphocytic, mild, pleura	1 (2%)			
Infiltration cellular, lymphocytic, minimal	3 (6%)	5 (10%)	4 (9%)	
Infiltration cellular, lymphocytic, moderate		1 (2%)		
Inflammation, chronic active, minimal	1 (2%)			
Inflammation, chronic active, moderate		1 (2%)		
Inflammation, chronic, minimal	2 (4%)	1 (2%)		1 (2%)
Inflammation, subacute, mild, vein			1 (2%)	
Parasite protozoan		1 (2%)		
Pigmentation, mild			1 (2%)	1 (2%)

Table A4
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Drinking Water Study of Urethane and 0% Ethanol

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
Respiratory System (continued)				
Nose	(47)	(48)	(47)	(47)
Cyst, minimal, mucosa	1 (2%)			
Cytoplasmic alteration, mild, olfactory epithelium	10 (21%)	12 (25%)	12 (26%)	8 (17%)
Cytoplasmic alteration, mild, respiratory epithelium	18 (38%)	15 (31%)	14 (30%)	9 (19%)
Cytoplasmic alteration, minimal, olfactory epithelium	11 (23%)	14 (29%)	9 (19%)	8 (17%)
Cytoplasmic alteration, minimal, respiratory epithelium	8 (17%)	9 (19%)	6 (13%)	8 (17%)
Cytoplasmic alteration, moderate, olfactory epithelium		1 (2%)		
Cytoplasmic alteration, moderate, respiratory epithelium		1 (2%)	2 (4%)	
Inflammation, mild				1 (2%)
Inflammation, minimal			2 (4%)	
Special Senses System				
Eye	(47)	(47)	(47)	(47)
Atrophy, marked				1 (2%)
Cataract, mild, lens			2 (4%)	
Cataract, minimal, lens		1 (2%)	1 (2%)	
Degeneration, mild, cornea				1 (2%)
Hyperplasia, mild, cornea			1 (2%)	
Inflammation, acute, mild, cornea	1 (2%)			1 (2%)
Inflammation, acute, mild, iris				1 (2%)
Inflammation, chronic active, mild, cornea				1 (2%)
Inflammation, chronic active, minimal, lids			1 (2%)	
Inflammation, chronic active, moderate, cornea		1 (2%)		1 (2%)
Inflammation, chronic, marked, cornea				1 (2%)
Inflammation, chronic, mild, cornea			4 (9%)	2 (4%)
Inflammation, chronic, minimal, cornea			1 (2%)	
Inflammation, chronic, moderate, cornea			1 (2%)	3 (6%)
Harderian gland	(47)	(47)	(47)	(47)
Hyperplasia, focal, marked			1 (2%)	
Hyperplasia, focal, mild		1 (2%)	1 (2%)	
Hyperplasia, focal, moderate			2 (4%)	2 (4%)
Infiltration cellular, lymphocytic, mild	2 (4%)	1 (2%)	2 (4%)	
Infiltration cellular, lymphocytic, minimal	16 (34%)	17 (36%)	9 (19%)	5 (11%)
Inflammation, chronic, mild				1 (2%)
Inflammation, chronic, minimal		1 (2%)		
Lacrimal gland	(47)	(47)	(44)	(47)
Atrophy, focal, mild				1 (2%)
Atrophy, marked	1 (2%)			
Atrophy, mild	2 (4%)	5 (11%)	1 (2%)	4 (9%)
Atrophy, minimal	4 (9%)	5 (11%)	4 (9%)	1 (2%)
Atrophy, moderate				3 (6%)
Hyperplasia, focal, minimal			1 (2%)	
Infiltration cellular, lymphocytic, mild	3 (6%)	4 (9%)	4 (9%)	2 (4%)
Infiltration cellular, lymphocytic, minimal	17 (36%)	10 (21%)	7 (16%)	9 (19%)
Infiltration cellular, lymphocytic, moderate		1 (2%)		
Mineralization, minimal				1 (2%)
Zymbal's gland	(45)	(45)	(45)	(45)
Dilatation, mild				1 (2%)
Dilatation, moderate			1 (2%)	
Hyperplasia, mild			2 (4%)	

Table A4
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Drinking Water Study of Urethane and 0% Ethanol

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
Urinary System				
Kidney	(46)	(47)	(46)	(45)
Accumulation, hyaline droplet, moderate, renal tubule			1 (2%)	
Amyloid deposition, mild		1 (2%)		
Amyloid deposition, minimal		4 (9%)		
Cyst, mild	1 (2%)		2 (4%)	
Cyst, minimal	3 (7%)	2 (4%)	3 (7%)	3 (7%)
Degeneration, marked, renal tubule		1 (2%)		
Degeneration, mild, renal tubule	4 (9%)	2 (4%)	1 (2%)	2 (4%)
Degeneration, minimal, renal tubule	14 (30%)	18 (38%)	9 (20%)	4 (9%)
Degeneration, moderate, renal tubule				1 (2%)
Dilatation, minimal, pelvis		1 (2%)		
Glomerulosclerosis, mild	7 (15%)	12 (26%)	10 (22%)	9 (20%)
Glomerulosclerosis, minimal	22 (48%)	23 (49%)	23 (50%)	16 (36%)
Glomerulosclerosis, moderate	1 (2%)		2 (4%)	2 (4%)
Hematopoietic cell proliferation, mild			1 (2%)	
Hyperplasia, focal, mild, renal tubule				1 (2%)
Hyperplasia, focal, minimal, renal tubule	1 (2%)	2 (4%)		
Hypoplasia, focal, mild			1 (2%)	
Infiltration cellular, lymphocytic, mild	3 (7%)	2 (4%)	6 (13%)	1 (2%)
Infiltration cellular, lymphocytic, minimal	11 (24%)	15 (32%)	15 (33%)	17 (38%)
Infiltration cellular, lymphocytic, moderate	1 (2%)			
Inflammation, acute, marked, pelvis	1 (2%)			
Inflammation, acute, mild, pelvis	3 (7%)	1 (2%)		
Inflammation, chronic, minimal				1 (2%)
Inflammation, chronic, minimal, pelvis		1 (2%)	2 (4%)	
Inflammation, chronic, moderate	1 (2%)			
Inflammation, subacute, mild, pelvis		1 (2%)		
Mineralization, mild	1 (2%)	1 (2%)		
Mineralization, minimal	7 (15%)	7 (15%)	7 (15%)	3 (7%)
Necrosis, mild, papilla		1 (2%)		
Nephropathy, minimal		1 (2%)		
Pigmentation, mild	1 (2%)			
Pigmentation, moderate				1 (2%)
Thrombosis, mild, glomerulus				1 (2%)
Thrombosis, mild, vein				1 (2%)
Urethra		(1)		(1)
Congestion, marked, bulbourethral gland		1 (100%)		
Urinary bladder	(46)	(46)	(46)	(40)
Dilatation, marked	1 (2%)			
Dilatation, mild		1 (2%)		
Dilatation, moderate				2 (5%)
Edema, mild			1 (2%)	1 (3%)
Edema, minimal	1 (2%)			
Edema, moderate		1 (2%)		
Infiltration cellular, lymphocytic, mild	3 (7%)	3 (7%)	3 (7%)	3 (8%)
Infiltration cellular, lymphocytic, minimal	16 (35%)	18 (39%)	17 (37%)	6 (15%)
Inflammation, acute, marked		1 (2%)		
Inflammation, acute, mild	2 (4%)			3 (8%)
Inflammation, acute, minimal	1 (2%)		1 (2%)	1 (3%)
Inflammation, acute, moderate	1 (2%)	1 (2%)		
Inflammation, chronic active, moderate	2 (4%)			

APPENDIX B
SUMMARY OF LESIONS IN MALE MICE IN THE 2-YEAR DRINKING WATER STUDY OF URETHANE AND 2.5% ETHANOL

Table B1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Drinking Water Study of Urethane and 2.5% Ethanol[a]

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
Disposition Summary				
Animals initially in study	48	48	48	48
Early deaths				
Moribund	10	5	7	9
Natural deaths	6	13	16	23
Survivors				
Terminal sacrifice	32	30	25	16
Animals examined microscopically	48	48	47	48
Alimentary System				
Gallbladder	(39)	(41)	(40)	(39)
Lymphoma malignant			1 (3%)	1 (3%)
Sarcoma, metastatic, skin				1 (3%)
Intestine large, cecum	(46)	(40)	(42)	(43)
Lymphoma malignant			1 (2%)	
Intestine small, duodenum	(43)	(42)	(40)	(42)
Lymphoma malignant			2 (5%)	
Polyp adenomatous				1 (2%)
Intestine small, ileum	(42)	(42)	(41)	(41)
Histiocytic sarcoma			1 (2%)	
Lymphoma malignant		1 (2%)	2 (5%)	1 (2%)
Intestine small, jejunum	(42)	(41)	(41)	(37)
Histiocytic sarcoma		1 (2%)		
Lymphoma malignant		1 (2%)	1 (2%)	1 (3%)
Liver	(47)	(48)	(46)	(48)
Alveolar/bronchiolar carcinoma, metastatic, lung				1 (2%)
Hemangiosarcoma	3 (6%)	4 (8%)	3 (7%)	11 (23%)
Hepatocellular adenoma	10 (21%)	13 (27%)	12 (26%)	13 (27%)
Hepatocellular adenoma, multiple	2 (4%)	2 (4%)	4 (9%)	11 (23%)
Hepatocellular carcinoma	5 (11%)	3 (6%)	5 (11%)	4 (8%)
Hepatocellular carcinoma, multiple	1 (2%)	2 (4%)		
Histiocytic sarcoma	1 (2%)	4 (8%)	3 (7%)	6 (13%)
Lymphoma malignant	1 (2%)	2 (4%)	2 (4%)	3 (6%)
Mesothelioma malignant, metastatic, pancreas	1 (2%)			
Sarcoma, metastatic, skin	1 (2%)			3 (6%)
Mesentery		(3)	(2)	(3)
Alveolar/bronchiolar carcinoma, metastatic, lung		1 (33%)		
Histiocytic sarcoma			1 (50%)	1 (33%)
Lymphoma malignant				1 (33%)
Mesothelioma NOS		1 (33%)		
Sarcoma			1 (50%)	
Pancreas	(47)	(45)	(46)	(46)
Alveolar/bronchiolar carcinoma, metastatic, lung		1 (2%)		
Hemangiosarcoma		1 (2%)		
Histiocytic sarcoma				1 (2%)
Lymphoma malignant	1 (2%)		1 (2%)	2 (4%)
Mesothelioma malignant	1 (2%)			
Mesothelioma NOS, metastatic, mesentery		1 (2%)		
Sarcoma, metastatic, skin				1 (2%)
Salivary glands	(48)	(48)	(46)	(48)
Lymphoma malignant	1 (2%)		2 (4%)	2 (4%)
Sarcoma, metastatic, skin	1 (2%)			

Table B1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Drinking Water Study of Urethane and 2.5% Ethanol

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
Alimentary System (continued)				
Stomach, forestomach	(47)	(47)	(46)	(46)
Lymphoma malignant	1 (2%)			1 (2%)
Sarcoma, metastatic, skin				1 (2%)
Squamous cell carcinoma	1 (2%)			2 (4%)
Squamous cell papilloma		4 (9%)	1 (2%)	2 (4%)
Stomach, glandular	(47)	(45)	(45)	(46)
Adenoma				1 (2%)
Lymphoma malignant	1 (2%)			1 (2%)
Tongue	(47)	(48)	(46)	(48)
Lymphoma malignant				1 (2%)
Cardiovascular System				
Heart	(48)	(48)	(47)	(48)
Alveolar/bronchiolar carcinoma, metastatic, lung		1 (2%)		1 (2%)
Hemangiosarcoma			2 (4%)	4 (8%)
Lymphoma malignant				1 (2%)
Mesothelioma NOS, metastatic, mesentery		1 (2%)		
Sarcoma, metastatic, skin				1 (2%)
Endocrine System				
Adrenal gland, cortex	(46)	(45)	(46)	(46)
Adenoma	2 (4%)	1 (2%)		
Adenoma, subcapsular	1 (2%)		1 (2%)	
Histiocytic sarcoma			1 (2%)	
Lymphoma malignant				1 (2%)
Mesothelioma malignant, metastatic, pancreas	1 (2%)			
Sarcoma, metastatic, skin				1 (2%)
Adrenal gland, medulla	(44)	(42)	(45)	(46)
Histiocytic sarcoma			1 (2%)	
Pheochromocytoma benign	2 (5%)	2 (5%)	2 (4%)	3 (7%)
Pheochromocytoma benign, bilateral				1 (2%)
Sarcoma, metastatic, skin				1 (2%)
Islets, pancreatic	(47)	(45)	(46)	(46)
Adenoma				2 (4%)
Lymphoma malignant				1 (2%)
Pituitary gland	(46)	(42)	(41)	(42)
Adenoma, pars distalis	1 (2%)			
Thyroid gland	(46)	(48)	(46)	(47)
Adenoma, follicular cell	1 (2%)	2 (4%)	1 (2%)	2 (4%)
Lymphoma malignant				1 (2%)
General Body System				
Tissue NOS	(1)			
Mesothelioma malignant, metastatic, pancreas	1 (100%)			

Table B1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Drinking Water Study of Urethane and 2.5% Ethanol

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
Genital System				
Coagulating gland	(46)	(48)	(45)	(46)
Lymphoma malignant			1 (2%)	2 (4%)
Mesothelioma NOS, metastatic, mesentery		1 (2%)		
Epididymis	(48)	(48)	(46)	(48)
Hemangioma			1 (2%)	1 (2%)
Histiocytic sarcoma			1 (2%)	1 (2%)
Lymphoma malignant			1 (2%)	3 (6%)
Mesothelioma malignant			1 (2%)	
Mesothelioma malignant, metastatic, pancreas	1 (2%)			
Mesothelioma NOS, metastatic, mesentery		1 (2%)		
Preputial gland	(46)	(45)	(45)	(46)
Adenoma		1 (2%)		
Hemangioma			1 (2%)	3 (7%)
Hemangiosarcoma			1 (2%)	1 (2%)
Lymphoma malignant			1 (2%)	1 (2%)
Sarcoma, metastatic, skin	1 (2%)			
Prostate	(46)	(47)	(43)	(48)
Histiocytic sarcoma				1 (2%)
Lymphoma malignant		2 (4%)	1 (2%)	2 (4%)
Seminal vesicle	(47)	(48)	(46)	(47)
Hemangiosarcoma				1 (2%)
Histiocytic sarcoma				1 (2%)
Lymphoma malignant			2 (4%)	2 (4%)
Mesothelioma NOS, metastatic, mesentery		1 (2%)		
Sarcoma, metastatic, mesentery			1 (2%)	
Testes	(48)	(48)	(47)	(47)
Histiocytic sarcoma				1 (2%)
Lipoma, bilateral			1 (2%)	
Hematopoietic System				
Bone marrow	(48)	(48)	(47)	(46)
Histiocytic sarcoma		1 (2%)	2 (4%)	
Lymphoma malignant			1 (2%)	2 (4%)
Lymph node	(48)	(48)	(47)	(47)
Hemangiosarcoma, inguinal				1 (2%)
Lymphoma malignant, axillary			1 (2%)	
Lymphoma malignant, inguinal			2 (4%)	2 (4%)
Lymphoma malignant, lumbar	1 (2%)		1 (2%)	1 (2%)
Lymphoma malignant, renal	1 (2%)	2 (4%)	2 (4%)	3 (6%)
Lymphoma malignant, thoracic		1 (2%)		
Mesothelioma malignant, metastatic, renal, pancreas	1 (2%)			
Sarcoma, metastatic, axillary, skin				1 (2%)
Sarcoma, metastatic, mediastinal, skin		1 (2%)		
Squamous cell carcinoma, metastatic, skin			1 (2%)	
Lymph node, mandibular	(48)	(48)	(45)	(47)
Carcinoma, metastatic, harderian gland				1 (2%)
Hemangiosarcoma				1 (2%)
Histiocytic sarcoma		2 (4%)	1 (2%)	2 (4%)
Lymphoma malignant	2 (4%)	2 (4%)	4 (9%)	3 (6%)
Sarcoma, metastatic, skin	1 (2%)			

Table B1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Drinking Water Study of Urethane and 2.5% Ethanol

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
Hematopoietic System (continued)				
Lymph node, mesenteric	(48)	(48)	(45)	(44)
Carcinoma, metastatic, harderian gland				1 (2%)
Hemangiosarcoma				3 (7%)
Histiocytic sarcoma		4 (8%)	4 (9%)	4 (9%)
Lymphoma malignant	9 (19%)	4 (8%)	6 (13%)	6 (14%)
Mesothelioma malignant, metastatic, pancreas	1 (2%)			
Mesothelioma NOS, metastatic, mesentery		1 (2%)		
Sarcoma, metastatic, skin				1 (2%)
Spleen	(46)	(46)	(46)	(46)
Hemangioma			1 (2%)	
Hemangiosarcoma			1 (2%)	3 (7%)
Histiocytic sarcoma		3 (7%)	2 (4%)	3 (7%)
Lymphoma malignant	7 (15%)	4 (9%)	5 (11%)	5 (11%)
Mesothelioma malignant, metastatic, pancreas	1 (2%)			
Thymus	(35)	(32)	(28)	(32)
Alveolar/bronchiolar carcinoma, metastatic, lung		1 (3%)		2 (6%)
Lymphoma malignant	1 (3%)	1 (3%)	3 (11%)	3 (9%)
Sarcoma, metastatic, skin				1 (3%)
Integumentary System				
Skin	(48)	(48)	(46)	(47)
Basal cell adenoma		1 (2%)		
Fibroma	2 (4%)	3 (6%)		
Fibroma, multiple			1 (2%)	
Fibroma, prepuce		1 (2%)		
Fibroma, tail		1 (2%)		
Hemangiosarcoma			4 (9%)	1 (2%)
Lymphoma malignant	1 (2%)			1 (2%)
Rhabdomyosarcoma, metastatic, skeletal muscle	1 (2%)			
Sarcoma	16 (33%)	9 (19%)	9 (20%)	7 (15%)
Sarcoma, multiple		1 (2%)	1 (2%)	1 (2%)
Squamous cell carcinoma		1 (2%)	2 (4%)	4 (9%)
Squamous cell papilloma			2 (4%)	3 (6%)
Musculoskeletal System				
Bone	(48)	(48)	(47)	(48)
Alveolar/bronchiolar carcinoma, metastatic, lung				1 (2%)
Alveolar/bronchiolar carcinoma, metastatic, vertebra, lung				1 (2%)
Skeletal muscle	(48)	(48)	(47)	(48)
Alveolar/bronchiolar carcinoma, metastatic				1 (2%)
Alveolar/bronchiolar carcinoma, metastatic, diaphragm, lung				1 (2%)
Alveolar/bronchiolar carcinoma, metastatic, lung		1 (2%)		
Fibrosarcoma	1 (2%)			
Histiocytic sarcoma				1 (2%)
Lymphoma malignant			1 (2%)	
Rhabdomyosarcoma	1 (2%)			
Sarcoma, metastatic, skin	1 (2%)			1 (2%)

Table B1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Drinking Water Study of Urethane and 2.5% Ethanol

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
Nervous System				
Brain, cerebellum	(47)	(48)	(47)	(48)
Lymphoma malignant				1 (2%)
Brain, cerebrum	(48)	(48)	(47)	(48)
Lymphoma malignant				1 (2%)
Oligodendroglioma malignant		1 (2%)		
Spinal cord, thoracic	(48)	(48)	(47)	(48)
Lymphoma malignant				1 (2%)
Respiratory System				
Larynx	(44)	(47)	(46)	(47)
Lymphoma malignant				1 (2%)
Lung	(48)	(48)	(47)	(48)
Alveolar/bronchiolar adenoma	9 (19%)	14 (29%)	11 (23%)	11 (23%)
Alveolar/bronchiolar adenoma, multiple	1 (2%)	2 (4%)	8 (17%)	24 (50%)
Alveolar/bronchiolar carcinoma	2 (4%)	3 (6%)	7 (15%)	20 (42%)
Alveolar/bronchiolar carcinoma, multiple			1 (2%)	4 (8%)
Carcinoma, metastatic, harderian gland				1 (2%)
Hepatocellular carcinoma, metastatic, liver	2 (4%)	1 (2%)	2 (4%)	3 (6%)
Histiocytic sarcoma		2 (4%)	3 (6%)	4 (8%)
Lymphoma malignant	1 (2%)		2 (4%)	2 (4%)
Mesothelioma malignant, metastatic, pancreas	1 (2%)			
Mesothelioma NOS, metastatic, mesentery		1 (2%)		
Sarcoma, metastatic, skin	1 (2%)			3 (6%)
Nose	(48)	(48)	(47)	(48)
Lymphoma malignant			1 (2%)	1 (2%)
Special Senses System				
Eye	(47)	(47)	(47)	(46)
Alveolar/bronchiolar carcinoma, metastatic, lung		1 (2%)		
Lymphoma malignant				1 (2%)
Harderian gland	(48)	(48)	(47)	(48)
Adenoma	6 (13%)	13 (27%)	17 (36%)	19 (40%)
Adenoma, bilateral		1 (2%)	4 (9%)	8 (17%)
Carcinoma			1 (2%)	13 (27%)
Carcinoma, bilateral				3 (6%)
Lymphoma malignant			1 (2%)	1 (2%)
Lacrimal gland	(48)	(47)	(45)	(46)
Lymphoma malignant	1 (2%)		1 (2%)	1 (2%)
Zymbal's gland	(47)	(45)	(46)	(43)
Lymphoma malignant				1 (2%)
Sarcoma, metastatic, skin			1 (2%)	
Urinary System				
Kidney	(48)	(48)	(47)	(47)
Adenoma, multiple, renal tubule				1 (2%)
Alveolar/bronchiolar carcinoma, metastatic, lung		1 (2%)		
Hemangiosarcoma				2 (4%)
Histiocytic sarcoma		1 (2%)	2 (4%)	1 (2%)
Lymphoma malignant	1 (2%)	1 (2%)	2 (4%)	3 (6%)
Mesothelioma malignant, metastatic, pancreas	1 (2%)			
Sarcoma, metastatic, skin				1 (2%)

Table B1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Drinking Water Study of Urethane and 2.5% Ethanol

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
Urinary System (continued)				
Urinary bladder	(47)	(46)	(45)	(46)
Histiocytic sarcoma		1 (2%)		
Lymphoma malignant			1 (2%)	1 (2%)
Neoplasm Summary				
Total animals with primary neoplasms[b]	41	45	42	47
Total primary neoplasms	99	127	181	289
Total animals with benign neoplasms	27	33	37	46
Total benign neoplasms	37	61	68	106
Total animals with malignant neoplasms	31	32	33	45
Total malignant neoplasms	62	65	113	183
Total animals with metastatic neoplasms	10	4	5	11
Total metastatic neoplasms	18	16	5	30
Total animals with uncertain neoplasms-benign or malignant		1		
Total uncertain neoplasms		1		

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

Table B2
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Drinking Water Study of Urethane and 2.5% Ethanol

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
Adrenal Cortex: Adenoma				
Overall rate[a]	3/46 (6.5%)	1/45 (2.2%)	1/46 (2.2%)	0/46 (0.0%)
Adjusted rate[b]	3/38.9 (7.7%)	1/38.5 (2.6%)	1/35.0 (2.9%)	0/34.5 (0.0%)
Terminal rate[c]	3/31 (9.7%)	1/28 (3.6%)	1/25 (4.0%)	0/16 (0.0%)
First incidence (days)	765 (T)	765 (T)	765 (T)	—[e]
Poly-3 test[d]	P=0.130N	P=0.308N	P=0.344N	P=0.141N
Adrenal Cortex: Adenoma or Carcinoma				
Overall rate	3/46 (6.5%)	1/45 (2.2%)	1/46 (2.2%)	0/46 (0.0%)
Adjusted rate	3/38.9 (7.7%)	1/38.5 (2.6%)	1/35.0 (2.9%)	0/34.5 (0.0%)
Terminal rate	3/31 (9.7%)	1/28 (3.6%)	1/25 (4.0%)	0/16 (0.0%)
First incidence (days)	765 (T)	765 (T)	765 (T)	—
Poly-3 test	P=0.130N	P=0.308N	P=0.344N	P=0.141N
Adrenal Medulla: Benign Pheochromocytoma				
Overall rate	2/44 (4.5%)	2/42 (4.8%)	2/45 (4.4%)	4/46 (8.7%)
Adjusted rate	2/36.9 (5.4%)	2/35.5 (5.6%)	2/34.1 (5.9%)	4/35.2 (11.4%)
Terminal rate	2/29 (6.9%)	2/25 (8.0%)	1/24 (4.2%)	2/16 (12.5%)
First incidence (days)	765 (T)	765 (T)	734	524
Poly-3 test	P=0.204	P=0.681	P=0.666	P=0.314
Harderian Gland: Adenoma				
Overall rate	6/48 (12.5%)	14/48 (29.2%)	21/47 (44.7%)	27/48 (56.3%)
Adjusted rate	6/41.1 (14.6%)	14/41.4 (33.8%)	21/37.2 (56.4%)	27/41.2 (65.6%)
Terminal rate	4/32 (12.5%)	12/30 (40.0%)	17/25 (68.0%)	10/16 (62.5%)
First incidence (days)	582	628	426	395
Poly-3 test	P=0.001	P=0.034	P=0.001	P=0.001
Harderian Gland: Carcinoma				
Overall rate	0/48 (0.0%)	0/48 (0.0%)	1/47 (2.1%)	16/48 (33.3%)
Adjusted rate	0/40.1 (0.0%)	0/40.7 (0.0%)	1/35.5 (2.8%)	16/41.6 (38.4%)
Terminal rate	0/32 (0.0%)	0/30 (0.0%)	1/25 (4.0%)	2/16 (12.5%)
First incidence (days)	—	—	765 (T)	395
Poly-3 test	P=0.001	—[f]	P=0.476	P=0.001
Harderian Gland: Adenoma or Carcinoma				
Overall rate	6/48 (12.5%)	14/48 (29.2%)	21/47 (44.7%)	38/48 (79.2%)
Adjusted rate	6/41.1 (14.6%)	14/41.4 (33.8%)	21/37.2 (56.4%)	38/45.2 (84.1%)
Terminal rate	4/32 (12.5%)	12/30 (40.0%)	17/25 (68.0%)	12/16 (75.0%)
First incidence (days)	582	628	426	395
Poly-3 test	P=0.001	P=0.034	P=0.001	P=0.001
Heart: Hemangiosarcoma				
Overall rate	0/48 (0.0%)	0/48 (0.0%)	2/47 (4.3%)	4/48 (8.3%)
Adjusted rate	0/40.1 (0.0%)	0/40.7 (0.0%)	2/35.6 (5.6%)	4/37.0 (10.8%)
Terminal rate	0/32 (0.0%)	0/30 (0.0%)	1/25 (4.0%)	1/16 (6.3%)
First incidence (days)	—	—	743	552
Poly-3 test	P=0.007	—	P=0.211	P=0.049
Liver: Hemangiosarcoma				
Overall rate	3/47 (6.4%)	4/48 (8.3%)	3/46 (6.5%)	11/48 (22.9%)
Adjusted rate	3/40.0 (7.5%)	4/41.0 (9.8%)	3/35.2 (8.5%)	11/38.3 (28.7%)
Terminal rate	2/32 (6.3%)	3/30 (10.0%)	2/25 (8.0%)	4/16 (25.0%)
First incidence (days)	719	681	684	488
Poly-3 test	P=0.002	P=0.514	P=0.604	P=0.013

Table B2
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Drinking Water Study of Urethane and 2.5% Ethanol

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
Liver: Histiocytic Sarcoma				
Overall rate	1/47 (2.1%)	4/48 (8.3%)	3/46 (6.5%)	6/48 (12.5%)
Adjusted rate	1/39.8 (2.5%)	4/41.4 (9.7%)	3/36.2 (8.3%)	6/37.1 (16.2%)
Terminal rate	1/32 (3.1%)	1/30 (3.3%)	0/25 (0.0%)	2/16 (12.5%)
First incidence (days)	765 (T)	638	514	536
Poly-3 test	P=0.053	P=0.190	P=0.271	P=0.044
Liver: Hepatocellular Adenoma				
Overall rate	12/47 (25.5%)	15/48 (31.3%)	16/46 (34.8%)	24/48 (50.0%)
Adjusted rate	12/41.1 (29.2%)	15/41.6 (36.1%)	16/36.3 (44.0%)	24/38.8 (61.9%)
Terminal rate	9/32 (28.1%)	13/30 (43.3%)	10/25 (40.0%)	13/16 (81.3%)
First incidence (days)	582	620	528	395
Poly-3 test	P=0.001	P=0.332	P=0.129	P=0.002
Liver: Hepatocellular Carcinoma				
Overall rate	6/47 (12.8%)	5/48 (10.4%)	5/46 (10.9%)	4/48 (8.3%)
Adjusted rate	6/40.9 (14.7%)	5/41.4 (12.1%)	5/35.4 (14.1%)	4/35.6 (11.2%)
Terminal rate	3/32 (9.4%)	4/30 (13.3%)	2/25 (8.0%)	4/16 (25.0%)
First incidence (days)	607	523	711	765 (T)
Poly-3 test	P=0.443N	P=0.492N	P=0.603N	P=0.460N
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rate	16/47 (34.0%)	19/48 (39.6%)	17/46 (37.0%)	24/48 (50.0%)
Adjusted rate	16/41.9 (38.2%)	19/42.2 (45.0%)	17/36.3 (46.8%)	24/38.8 (61.9%)
Terminal rate	11/32 (34.4%)	16/30 (53.3%)	11/25 (44.0%)	13/16 (81.3%)
First incidence (days)	582	523	528	395
Poly-3 test	P=0.019	P=0.339	P=0.294	P=0.023
Lung: Histiocytic Sarcoma				
Overall rate	0/48 (0.0%)	2/48 (4.2%)	3/47 (6.4%)	4/48 (8.3%)
Adjusted rate	0/40.1 (0.0%)	2/41.0 (4.9%)	3/36.8 (8.2%)	4/37.1 (10.8%)
Terminal rate	0/32 (0.0%)	0/30 (0.0%)	0/25 (0.0%)	0/16 (0.0%)
First incidence (days)	—	713	514	536
Poly-3 test	P=0.057	P=0.242	P=0.103	P=0.050
Lung: Alveolar/bronchiolar Adenoma				
Overall rate	10/48 (20.8%)	16/48 (33.3%)	19/47 (40.4%)	35/48 (72.9%)
Adjusted rate	10/40.8 (24.5%)	16/41.4 (38.6%)	19/36.7 (51.8%)	35/43.3 (80.9%)
Terminal rate	8/32 (25.0%)	13/30 (43.3%)	15/25 (60.0%)	14/16 (87.5%)
First incidence (days)	614	617	593	395
Poly-3 test	P=0.001	P=0.124	P=0.010	P=0.001
Lung: Alveolar/bronchiolar Carcinoma				
Overall rate	2/48 (4.2%)	3/48 (6.3%)	8/47 (17.0%)	24/48 (50.0%)
Adjusted rate	2/40.1 (5.0%)	3/41.3 (7.3%)	8/36.4 (22.0%)	24/39.6 (60.7%)
Terminal rate	2/32 (6.3%)	1/30 (3.3%)	5/25 (20.0%)	9/16 (56.3%)
First incidence (days)	765 (T)	620	640	569
Poly-3 test	P=0.001	P=0.513	P=0.029	P=0.001
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rate	11/48 (22.9%)	19/48 (39.6%)	24/47 (51.1%)	43/48 (89.6%)
Adjusted rate	11/40.8 (27.0%)	19/42.0 (45.3%)	24/37.3 (64.4%)	43/45.1 (95.3%)
Terminal rate	9/32 (28.1%)	14/30 (46.7%)	18/25 (72.0%)	15/16 (93.8%)
First incidence (days)	614	617	593	395
Poly-3 test	P=0.001	P=0.062	P=0.001	P=0.001

Table B2
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Drinking Water Study of Urethane and 2.5% Ethanol

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
Lymph Node (Mesenteric): Hemangiosarcoma				
Overall rate	0/48 (0.0%)	0/48 (0.0%)	0/45 (0.0%)	3/44 (6.8%)
Adjusted rate	0/40.1 (0.0%)	0/40.7 (0.0%)	0/34.8 (0.0%)	3/33.2 (9.0%)
Terminal rate	0/32 (0.0%)	0/30 (0.0%)	0/25 (0.0%)	1/15 (6.7%)
First incidence (days)	—	—	—	569
Poly-3 test	P=0.005	—	—	P=0.086
Lymph Node (Mesenteric): Histiocytic Sarcoma				
Overall rate	0/48 (0.0%)	4/48 (8.3%)	4/45 (8.9%)	4/44 (9.1%)
Adjusted rate	0/40.1 (0.0%)	4/41.4 (9.7%)	4/36.3 (11.0%)	4/33.7 (11.9%)
Terminal rate	0/32 (0.0%)	1/30 (3.3%)	0/25 (0.0%)	1/15 (6.7%)
First incidence (days)	—	638	514	536
Poly-3 test	P=0.121	P=0.064	P=0.047	P=0.040
Skin: Sarcoma				
Overall rate	16/48 (33.3%)	10/48 (20.8%)	10/46 (21.7%)	8/47 (17.0%)
Adjusted rate	16/43.1 (37.1%)	10/42.3 (23.6%)	10/37.7 (26.5%)	8/36.8 (21.7%)
Terminal rate	9/32 (28.1%)	5/30 (16.7%)	5/24 (20.8%)	2/16 (12.5%)
First incidence (days)	582	617	362	395
Poly-3 test	P=0.159N	P=0.129N	P=0.218N	P=0.102N
Skin: Fibroma or Sarcoma				
Overall rate	18/48 (37.5%)	13/48 (27.1%)	11/46 (23.9%)	8/47 (17.0%)
Adjusted rate	18/43.1 (41.8%)	13/42.3 (30.7%)	11/37.7 (29.2%)	8/36.8 (21.7%)
Terminal rate	11/32 (34.4%)	8/30 (26.7%)	6/24 (25.0%)	2/16 (12.5%)
First incidence (days)	582	617	362	395
Poly-3 test	P=0.058N	P=0.200N	P=0.172N	P=0.044N
Skin: Hemangiosarcoma				
Overall rate	0/48 (0.0%)	0/48 (0.0%)	4/46 (8.7%)	1/47 (2.1%)
Adjusted rate	0/40.1 (0.0%)	0/40.7 (0.0%)	4/34.9 (11.5%)	1/34.9 (2.9%)
Terminal rate	0/32 (0.0%)	0/30 (0.0%)	2/24 (8.3%)	1/16 (6.3%)
First incidence (days)	—	—	710	765 (T)
Poly-3 test	P=0.324	—	P=0.043	P=0.473
Skin: Squamous Cell Papilloma				
Overall rate	0/48 (0.0%)	0/48 (0.0%)	2/46 (4.3%)	3/47 (6.4%)
Adjusted rate	0/40.1 (0.0%)	0/40.7 (0.0%)	2/34.5 (5.8%)	3/35.7 (8.4%)
Terminal rate	0/32 (0.0%)	0/30 (0.0%)	2/24 (8.3%)	2/16 (12.5%)
First incidence (days)	—	—	765 (T)	453
Poly-3 test	P=0.026	—	P=0.205	P=0.098
Skin: Squamous Cell Carcinoma				
Overall rate	0/48 (0.0%)	1/48 (2.1%)	2/46 (4.3%)	4/47 (8.5%)
Adjusted rate	0/40.1 (0.0%)	1/40.7 (2.5%)	2/35.0 (5.7%)	4/36.8 (10.9%)
Terminal rate	0/32 (0.0%)	1/30 (3.3%)	1/24 (4.2%)	0/16 (0.0%)
First incidence (days)	—	765 (T)	642	524
Poly-3 test	P=0.021	P=0.503	P=0.207	P=0.049
Skin: Squamous Cell Papilloma or Squamous Cell Carcinoma				
Overall rate	0/48 (0.0%)	1/48 (2.1%)	4/46 (8.7%)	7/47 (14.9%)
Adjusted rate	0/40.1 (0.0%)	1/40.7 (2.5%)	4/35.0 (11.4%)	7/37.6 (18.6%)
Terminal rate	0/32 (0.0%)	1/30 (3.3%)	3/24 (12.5%)	2/16 (12.5%)
First incidence (days)	—	765 (T)	642	453
Poly-3 test	P=0.001	P=0.503	P=0.043	P=0.005

Table B2
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Drinking Water Study of Urethane and 2.5% Ethanol

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
Skin: Basal Cell Adenoma, Squamous Cell Papilloma, or Squamous Cell Carcinoma				
Overall rate	0/48 (0.0%)	2/48 (4.2%)	4/46 (8.7%)	7/47 (14.9%)
Adjusted rate	0/40.1 (0.0%)	2/40.7 (4.9%)	4/35.0 (11.4%)	7/37.6 (18.6%)
Terminal rate	0/32 (0.0%)	2/30 (6.7%)	3/24 (12.5%)	2/16 (12.5%)
First incidence (days)	—	765 (T)	642	453
Poly-3 test	P=0.003	P=0.240	P=0.043	P=0.005
Spleen: Hemangiosarcoma				
Overall rate	0/46 (0.0%)	0/46 (0.0%)	1/46 (2.2%)	3/46 (6.5%)
Adjusted rate	0/39.2 (0.0%)	0/40.4 (0.0%)	1/35.1 (2.9%)	3/35.2 (8.5%)
Terminal rate	0/32 (0.0%)	0/30 (0.0%)	0/25 (0.0%)	1/16 (6.3%)
First incidence (days)	—	—	733	552
Poly-3 test	P=0.015	—	P=0.478	P=0.099
Spleen: Hemangioma or Hemangiosarcoma				
Overall rate	0/46 (0.0%)	0/46 (0.0%)	2/46 (4.3%)	3/46 (6.5%)
Adjusted rate	0/39.2 (0.0%)	0/40.4 (0.0%)	2/35.1 (5.7%)	3/35.2 (8.5%)
Terminal rate	0/32 (0.0%)	0/30 (0.0%)	1/25 (4.0%)	1/16 (6.3%)
First incidence (days)	—	—	733	552
Poly-3 test	P=0.026	—	P=0.213	P=0.099
Spleen: Histiocytic Sarcoma				
Overall rate	0/46 (0.0%)	3/46 (6.5%)	2/46 (4.3%)	3/46 (6.5%)
Adjusted rate	0/39.2 (0.0%)	3/40.9 (7.3%)	2/36.0 (5.6%)	3/35.6 (8.4%)
Terminal rate	0/32 (0.0%)	1/30 (3.3%)	0/25 (0.0%)	0/16 (0.0%)
First incidence (days)	—	638	514	536
Poly-3 test	P=0.194	P=0.126	P=0.218	P=0.101
Stomach (Forestomach): Squamous Cell Papilloma				
Overall rate	0/47 (0.0%)	4/47 (8.5%)	1/46 (2.2%)	2/46 (4.3%)
Adjusted rate	0/39.8 (0.0%)	4/41.4 (9.7%)	1/35.0 (2.9%)	2/34.5 (5.8%)
Terminal rate	0/32 (0.0%)	2/30 (6.7%)	1/25 (4.0%)	2/16 (12.5%)
First incidence (days)	—	523	765 (T)	765 (T)
Poly-3 test	P=0.466	P=0.065	P=0.474	P=0.206
Stomach (Forestomach): Squamous Cell Papilloma or Squamous Cell Carcinoma				
Overall rate	1/47 (2.1%)	4/47 (8.5%)	1/46 (2.2%)	3/46 (6.5%)
Adjusted rate	1/40.0 (2.5%)	4/41.4 (9.7%)	1/35.0 (2.9%)	3/34.5 (8.7%)
Terminal rate	0/32 (0.0%)	2/30 (6.7%)	1/25 (4.0%)	3/16 (18.8%)
First incidence (days)	719	523	765 (T)	765 (T)
Poly-3 test	P=0.360	P=0.189	P=0.730	P=0.253
Preputial Gland: Hemangioma				
Overall rate	0/46 (0.0%)	0/45 (0.0%)	1/45 (2.2%)	3/46 (6.5%)
Adjusted rate	0/38.9 (0.0%)	0/38.2 (0.0%)	1/33.9 (2.9%)	3/34.4 (8.7%)
Terminal rate	0/32 (0.0%)	0/28 (0.0%)	0/24 (0.0%)	2/15 (13.3%)
First incidence (days)	—	—	710	620
Poly-3 test	P=0.016	—	P=0.473	P=0.097
Preputial Gland: Hemangioma or Hemangiosarcoma				
Overall rate	0/46 (0.0%)	0/45 (0.0%)	2/45 (4.4%)	4/46 (8.7%)
Adjusted rate	0/38.9 (0.0%)	0/38.2 (0.0%)	2/33.9 (5.9%)	4/34.4 (11.6%)
Terminal rate	0/32 (0.0%)	0/28 (0.0%)	1/24 (4.2%)	2/15 (13.3%)
First incidence (days)	—	—	710	620
Poly-3 test	P=0.006	—	P=0.207	P=0.045

Table B2
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Drinking Water Study of Urethane and 2.5% Ethanol

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
All Organs: Hemangioma				
Overall rate	0/48 (0.0%)	0/48 (0.0%)	3/47 (6.4%)	4/48 (8.3%)
Adjusted rate	0/40.1 (0.0%)	0/40.7 (0.0%)	3/35.9 (8.3%)	4/36.0 (11.1%)
Terminal rate	0/32 (0.0%)	0/30 (0.0%)	1/25 (4.0%)	3/16 (18.8%)
First incidence (days)	—	—	710	620
Poly-3 test	P=0.010	—	P=0.099	P=0.047
All Organs: Hemangiosarcoma				
Overall rate	3/48 (6.3%)	5/48 (10.4%)	9/47 (19.1%)	21/48 (43.8%)
Adjusted rate	3/40.3 (7.4%)	5/41.0 (12.2%)	9/36.2 (24.8%)	21/39.5 (53.1%)
Terminal rate	2/32 (6.3%)	4/30 (13.3%)	5/25 (20.0%)	8/16 (50.0%)
First incidence (days)	719	681	684	488
Poly-3 test	P=0.001	P=0.365	P=0.035	P=0.001
All Organs: Hemangioma or Hemangiosarcoma				
Overall rate	3/48 (6.3%)	5/48 (10.4%)	11/47 (23.4%)	22/48 (45.8%)
Adjusted rate	3/40.3 (7.4%)	5/41.0 (12.2%)	11/36.4 (30.2%)	22/39.5 (55.6%)
Terminal rate	2/32 (6.3%)	4/30 (13.3%)	6/25 (24.0%)	9/16 (56.3%)
First incidence (days)	719	681	684	488
Poly-3 test	P=0.001	P=0.365	P=0.009	P=0.001
All Organs: Histiocytic Sarcoma				
Overall rate	1/48 (2.1%)	4/48 (8.3%)	5/47 (10.6%)	7/48 (14.6%)
Adjusted rate	1/40.1 (2.5%)	4/41.4 (9.7%)	5/37.1 (13.5%)	7/37.1 (18.8%)
Terminal rate	1/32 (3.1%)	1/30 (3.3%)	1/25 (4.0%)	3/16 (18.8%)
First incidence (days)	765 (T)	638	514	536
Poly-3 test	P=0.027	P=0.187	P=0.083	P=0.021
All Organs: Malignant Lymphoma				
Overall rate	11/48 (22.9%)	6/48 (12.5%)	10/47 (21.3%)	7/48 (14.6%)
Adjusted rate	11/41.0 (26.8%)	6/41.2 (14.6%)	10/36.2 (27.6%)	7/36.6 (19.1%)
Terminal rate	9/32 (28.1%)	5/30 (16.7%)	8/25 (32.0%)	5/16 (31.3%)
First incidence (days)	614	622	655	588
Poly-3 test	P=0.435N	P=0.134N	P=0.570	P=0.297N
All Organs: Benign Neoplasms				
Overall rate	27/48 (56.3%)	33/48 (68.8%)	37/47 (78.7%)	46/48 (95.8%)
Adjusted rate	27/42.4 (63.6%)	33/43.7 (75.4%)	37/39.5 (93.7%)	46/46.3 (99.2%)
Terminal rate	21/32 (65.6%)	24/30 (80.0%)	25/25 (100.0%)	16/16 (100.0%)
First incidence (days)	582	523	426	395
Poly-3 test	P=0.001	P=0.159	P=0.001	P=0.001
All Organs: Malignant Neoplasms				
Overall rate	31/48 (64.6%)	32/48 (66.7%)	33/47 (70.2%)	45/48 (93.8%)
Adjusted rate	31/44.7 (69.4%)	32/45.9 (69.7%)	33/42.2 (78.1%)	45/46.2 (97.4%)
Terminal rate	19/32 (59.4%)	18/30 (60.0%)	16/25 (64.0%)	15/16 (93.8%)
First incidence (days)	513	382	362	395
Poly-3 test	P=0.001	P=0.577	P=0.246	P=0.001

Table B2
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Drinking Water Study of Urethane and 2.5% Ethanol

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
All Organs: Benign or Malignant Neoplasms				
Overall rate	41/48 (85.4%)	45/48 (93.8%)	42/47 (89.4%)	47/48 (97.9%)
Adjusted rate	41/44.7 (91.8%)	45/46.3 (97.2%)	42/42.2 (99.4%)	47/47.0 (100.0%)
Terminal rate	29/32 (90.6%)	29/30 (96.7%)	25/25 (100.0%)	16/16 (100.0%)
First incidence (days)	513	382	362	395
Poly-3 test	P=0.045	P=0.231	P=0.090	P=0.054

(T) Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals with tissue examined microscopically
[b] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the control incidence (0 ppm urethane) is the P value associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and that exposed group. The Poly-3 test accounts for the differential mortality in animals that do not reach terminal sacrifice. A negative trend or a lower incidence in an exposed group is indicated by **N**.
[e] Not applicable; no neoplasms in animal group
[f] Value of statistic cannot be computed.

TABLE B3
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Drinking Water Study of Urethane and 2.5% Ethanol[a]

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
Disposition Summary				
Animals initially in study	48	48	48	48
Early deaths				
Moribund	10	5	7	9
Natural deaths	6	13	16	23
Survivors				
Terminal sacrifice	32	30	25	16
Animals examined microscopically	48	48	47	48
Alimentary System				
Gallbladder	(39)	(41)	(40)	(39)
Cyst, minimal		1 (2%)		
Inflammation, acute, minimal		1 (2%)		
Pigmentation, moderate			1 (3%)	
Intestine large, cecum	(46)	(40)	(42)	(43)
Hemorrhage, marked				1 (2%)
Intestine large, colon	(47)	(43)	(44)	(46)
Hyperplasia, minimal, lymphoid tissue		1 (2%)		
Intestine large, rectum	(47)	(47)	(47)	(47)
Erosion, focal, mild, anus			1 (2%)	
Inflammation, acute, moderate, serosa	1 (2%)			
Inflammation, chronic active, marked, serosa			1 (2%)	
Inflammation, chronic active, moderate	1 (2%)			
Ulcer, mild	1 (2%)			
Intestine small, ileum	(42)	(42)	(41)	(41)
Hyperplasia, mild, lymphoid tissue		1 (2%)		
Inflammation, chronic active, mild	1 (2%)			
Liver	(47)	(48)	(46)	(48)
Amyloid deposition, moderate			1 (2%)	
Angiectasis			7 (15%)	16 (33%)
Basophilic focus	2 (4%)	1 (2%)	1 (2%)	2 (4%)
Clear cell focus		3 (6%)	5 (11%)	
Cyst, moderate, bile duct	1 (2%)			
Eosinophilic focus	6 (13%)	3 (6%)	17 (37%)	22 (46%)
Hematopoietic cell proliferation, marked	1 (2%)		1 (2%)	1 (2%)
Hematopoietic cell proliferation, mild	1 (2%)	1 (2%)		6 (13%)
Hematopoietic cell proliferation, minimal	2 (4%)		3 (7%)	1 (2%)
Hematopoietic cell proliferation, moderate	2 (4%)		1 (2%)	3 (6%)
Hyperplasia, mild, Kupffer cell	2 (4%)	6 (13%)	5 (11%)	6 (13%)
Hyperplasia, mild, oval cell		1 (2%)		
Hyperplasia, minimal, Kupffer cell	4 (9%)	6 (13%)	2 (4%)	
Hyperplasia, moderate, Kupffer cell	1 (2%)		2 (4%)	7 (15%)
Infiltration cellular, lymphocytic, minimal		2 (4%)		
Infiltration cellular, mixed cell, mild	1 (2%)	2 (4%)		
Infiltration cellular, mixed cell, minimal	4 (9%)	1 (2%)	5 (11%)	
Inflammation, chronic active, moderate			1 (2%)	
Mixed cell focus		3 (6%)	4 (9%)	1 (2%)
Necrosis, marked	1 (2%)		1 (2%)	
Necrosis, mild		1 (2%)	1 (2%)	
Necrosis, mild, hepatocyte		2 (4%)	2 (4%)	2 (4%)
Necrosis, minimal	1 (2%)	2 (4%)	1 (2%)	

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

Table B3
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Drinking Water Study of Urethane and 2.5% Ethanol

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
Alimentary System (continued)				
Liver (continued)	(47)	(48)	(46)	(48)
Necrosis, minimal, hepatocyte	3 (6%)	3 (6%)	2 (4%)	1 (2%)
Necrosis, moderate	1 (2%)	1 (2%)	1 (2%)	4 (8%)
Necrosis, moderate, hepatocyte	1 (2%)	1 (2%)	1 (2%)	
Nuclear alteration, mild, hepatocyte		2 (4%)		
Nuclear alteration, minimal, hepatocyte	1 (2%)		1 (2%)	
Pigmentation, mild	1 (2%)			
Regeneration		1 (2%)	1 (2%)	9 (19%)
Syncytial alteration, mild, hepatocyte	2 (4%)	3 (6%)	1 (2%)	1 (2%)
Syncytial alteration, minimal, hepatocyte	6 (13%)	3 (6%)	4 (9%)	3 (6%)
Syncytial alteration, moderate, hepatocyte	1 (2%)			
Vacuolization cytoplasmic, mild, hepatocyte	1 (2%)	2 (4%)	1 (2%)	
Vacuolization cytoplasmic, minimal, hepatocyte	3 (6%)	2 (4%)	1 (2%)	
Vacuolization cytoplasmic, moderate, hepatocyte	1 (2%)			1 (2%)
Mesentery		(3)	(2)	(3)
Necrosis, fat		1 (33%)	1 (50%)	1 (33%)
Pancreas	(47)	(45)	(46)	(46)
Amyloid deposition, minimal		1 (2%)		
Atrophy, minimal, acinar cell		1 (2%)		
Basophilic focus			1 (2%)	
Degeneration, mild, acinar cell			1 (2%)	
Eosinophilic focus		1 (2%)		
Hyperplasia, focal, mild, acinar cell		1 (2%)		
Infiltration cellular, lymphocytic, mild		1 (2%)		
Infiltration cellular, lymphocytic, minimal	2 (4%)	4 (9%)	2 (4%)	1 (2%)
Inflammation, chronic, minimal			1 (2%)	
Vacuolization cytoplasmic, mild, acinar cell	1 (2%)			
Vacuolization cytoplasmic, minimal, acinar cell	2 (4%)	1 (2%)		1 (2%)
Salivary glands	(48)	(48)	(46)	(48)
Atrophy, mild				1 (2%)
Atrophy, minimal	1 (2%)	1 (2%)		1 (2%)
Atrophy, moderate	1 (2%)		2 (4%)	1 (2%)
Atrophy, moderate, parotid gland		1 (2%)		
Infiltration cellular, lymphocytic, mild	18 (38%)	18 (38%)	10 (22%)	12 (25%)
Infiltration cellular, lymphocytic, minimal	11 (23%)	18 (38%)	17 (37%)	17 (35%)
Infiltration cellular, lymphocytic, moderate	4 (8%)	1 (2%)	1 (2%)	
Infiltration cellular, mixed cell, moderate	1 (2%)			
Inflammation, chronic active, moderate			1 (2%)	
Mineralization, minimal			1 (2%)	
Stomach, forestomach	(47)	(47)	(46)	(46)
Cyst, minimal		2 (4%)	1 (2%)	
Erosion, minimal		1 (2%)		
Hyperplasia, marked, epithelium		1 (2%)		
Hyperplasia, mild, epithelium	1 (2%)	2 (4%)		3 (7%)
Hyperplasia, minimal, epithelium				2 (4%)
Inflammation, mild			1 (2%)	
Stomach, glandular	(47)	(45)	(45)	(46)
Angiectasis, minimal, mucosa				1 (2%)
Angiectasis, moderate, serosa				1 (2%)
Cyst, minimal	1 (2%)	2 (4%)		
Erosion, mild			1 (2%)	1 (2%)
Hyperplasia, marked, epithelium		1 (2%)		
Hyperplasia, mild, epithelium			2 (4%)	
Hyperplasia, minimal, epithelium			1 (2%)	

Table B3
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Drinking Water Study of Urethane and 2.5% Ethanol

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
Alimentary System (continued)				
Stomach, glandular (continued)	(47)	(45)	(45)	(46)
Infiltration cellular, lymphocytic, minimal	1 (2%)	2 (4%)		
Inflammation, acute, minimal	1 (2%)			
Inflammation, chronic, minimal	1 (2%)			
Tongue	(47)	(48)	(46)	(48)
Foreign body			1 (2%)	
Hyperplasia, focal, marked, epithelium			1 (2%)	
Infiltration cellular, lymphocytic, minimal		1 (2%)		
Inflammation, chronic active, minimal				1 (2%)
Inflammation, chronic, minimal		1 (2%)	2 (4%)	
Cardiovascular System				
Blood vessel	(48)	(48)	(45)	(48)
Mineralization, mild			1 (2%)	
Heart	(48)	(48)	(47)	(48)
Angiectasis, marked				2 (4%)
Angiectasis, mild			1 (2%)	4 (8%)
Angiectasis, minimal			3 (6%)	5 (10%)
Angiectasis, moderate			3 (6%)	2 (4%)
Bacterium, valve				1 (2%)
Cardiomyopathy, minimal				2 (4%)
Hyperplasia, mild, endothelium			2 (4%)	4 (8%)
Hyperplasia, minimal, endothelium		1 (2%)	1 (2%)	5 (10%)
Hyperplasia, moderate, endothelium			1 (2%)	
Hypertrophy, minimal, parenchymal cell	4 (8%)		1 (2%)	
Inflammation, acute, mild, epicardium		1 (2%)		
Inflammation, acute, moderate, valve			1 (2%)	
Inflammation, chronic active, marked, valve				1 (2%)
Inflammation, chronic, mild, artery	2 (4%)			
Inflammation, chronic, mild, epicardium			1 (2%)	
Inflammation, chronic, mild, myocardium				2 (4%)
Inflammation, chronic, mild, valve	1 (2%)			
Inflammation, chronic, minimal, artery		1 (2%)		
Inflammation, chronic, minimal, myocardium			1 (2%)	1 (2%)
Inflammation, subacute, minimal, epicardium			1 (2%)	
Mineralization, mild		1 (2%)		
Mineralization, minimal			1 (2%)	
Necrosis, minimal	1 (2%)			1 (2%)
Endocrine System				
Adrenal gland, cortex	(46)	(45)	(46)	(46)
Cyst, minimal			1 (2%)	
Hyperplasia, focal, marked	1 (2%)			
Hyperplasia, focal, mild		1 (2%)	1 (2%)	
Hyperplasia, focal, minimal		1 (2%)		1 (2%)
Hyperplasia, marked, subcapsular			1 (2%)	
Hyperplasia, mild, subcapsular	8 (17%)	7 (16%)	14 (30%)	10 (22%)
Hyperplasia, minimal, subcapsular	24 (52%)	26 (58%)	22 (48%)	32 (70%)
Hyperplasia, moderate, subcapsular	3 (7%)	5 (11%)	1 (2%)	
Hypertrophy, marked				2 (4%)
Hypertrophy, mild	4 (9%)	2 (4%)	4 (9%)	5 (11%)

Table B3
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Drinking Water Study of Urethane and 2.5% Ethanol

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
Endocrine System (continued)				
Adrenal gland, cortex (continued)	(46)	(45)	(46)	(46)
Hypertrophy, minimal	2 (4%)	3 (7%)	2 (4%)	4 (9%)
Hypertrophy, moderate			1 (2%)	
Vacuolization cytoplasmic, focal, mild				1 (2%)
Adrenal gland, medulla	(44)	(42)	(45)	(46)
Hyperplasia, mild	1 (2%)			
Hyperplasia, minimal	1 (2%)	1 (2%)		
Hyperplasia, moderate	1 (2%)			1 (2%)
Islets, pancreatic	(47)	(45)	(46)	(46)
Hyperplasia, mild	2 (4%)	2 (4%)	2 (4%)	1 (2%)
Hyperplasia, minimal		1 (2%)	1 (2%)	
Hyperplasia, moderate				1 (2%)
Infiltration cellular, lymphocytic, minimal				1 (2%)
Parathyroid gland	(37)	(40)	(43)	(38)
Cyst, mild	1 (3%)	1 (3%)	1 (2%)	1 (3%)
Cyst, minimal	1 (3%)			
Infiltration cellular, lymphocytic, mild			1 (2%)	
Pituitary gland	(46)	(42)	(41)	(42)
Cyst, mild, pars distalis	1 (2%)		1 (2%)	1 (2%)
Cyst, minimal, pars distalis	1 (2%)	1 (2%)	1 (2%)	
Thyroid gland	(46)	(48)	(46)	(47)
Crystals	1 (2%)			
Cyst, mild, follicle		1 (2%)		
Infiltration cellular, lymphocytic, minimal	1 (2%)	1 (2%)	1 (2%)	
Inflammation, chronic, mild		1 (2%)		
Inflammation, chronic, minimal	1 (2%)			
Ultimobranchial cyst	11 (24%)	7 (15%)	13 (28%)	14 (30%)
General Body System				
None				
Genital System				
Coagulating gland	(46)	(48)	(45)	(46)
Atrophy, mild		4 (8%)	1 (2%)	3 (7%)
Atrophy, minimal	4 (9%)	2 (4%)	3 (7%)	5 (11%)
Dilatation, mild	1 (2%)			
Infiltration cellular, lymphocytic, mild	1 (2%)			
Infiltration cellular, lymphocytic, minimal	3 (7%)	6 (13%)	1 (2%)	2 (4%)
Infiltration cellular, mixed cell, mild	1 (2%)			
Inflammation, acute, moderate	1 (2%)			
Inflammation, chronic active, mild		1 (2%)		
Inflammation, chronic, mild			1 (2%)	
Inflammation, subacute, minimal		1 (2%)		
Epididymis	(48)	(48)	(46)	(48)
Fibrosis, mild				1 (2%)
Granuloma sperm, mild		1 (2%)		
Hyperplasia, focal, minimal, epithelium				1 (2%)
Infiltration cellular, lymphocytic, mild	1 (2%)			2 (4%)
Infiltration cellular, lymphocytic, minimal	8 (17%)	7 (15%)	2 (4%)	1 (2%)
Infiltration cellular, mixed cell, marked	1 (2%)			
Inflammation, chronic, mild		1 (2%)	1 (2%)	1 (2%)
Inflammation, chronic, minimal				1 (2%)

Table B3
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Drinking Water Study of Urethane and 2.5% Ethanol

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
Genital System (continued)				
Penis			(2)	(2)
Inflammation, acute, moderate				1 (50%)
Inflammation, chronic active, marked			1 (50%)	
Inflammation, chronic, mild				1 (50%)
Inflammation, chronic, minimal			1 (50%)	
Preputial gland	(46)	(45)	(45)	(46)
Atrophy, marked	1 (2%)	4 (9%)	6 (13%)	8 (17%)
Atrophy, mild	1 (2%)	3 (7%)	1 (2%)	5 (11%)
Atrophy, minimal	1 (2%)		2 (4%)	1 (2%)
Atrophy, moderate	11 (24%)	12 (27%)	11 (24%)	10 (22%)
Cyst, mild		2 (4%)	2 (4%)	
Cyst, minimal	1 (2%)			
Dilatation, marked	1 (2%)	2 (4%)	1 (2%)	1 (2%)
Dilatation, mild	8 (17%)	12 (27%)	10 (22%)	7 (15%)
Dilatation, minimal	4 (9%)		2 (4%)	2 (4%)
Dilatation, moderate	2 (4%)		2 (4%)	7 (15%)
Inflammation, acute, moderate	1 (2%)			1 (2%)
Inflammation, chronic active, marked	4 (9%)	1 (2%)	2 (4%)	
Inflammation, chronic active, mild	2 (4%)	1 (2%)	3 (7%)	2 (4%)
Inflammation, chronic active, moderate	3 (7%)	1 (2%)	3 (7%)	2 (4%)
Inflammation, chronic, mild	3 (7%)	4 (9%)	5 (11%)	6 (13%)
Inflammation, chronic, minimal	8 (17%)	4 (9%)	1 (2%)	5 (11%)
Inflammation, subacute, mild			1 (2%)	1 (2%)
Inflammation, subacute, minimal		1 (2%)		
Prostate	(46)	(47)	(43)	(48)
Atrophy, mild		2 (4%)		
Atrophy, minimal				2 (4%)
Hyperplasia, marked, epithelium		1 (2%)	1 (2%)	1 (2%)
Infiltration cellular, lymphocytic, minimal		1 (2%)		1 (2%)
Infiltration cellular, mixed cell, moderate	1 (2%)			
Inflammation, acute, mild			1 (2%)	
Inflammation, acute, minimal			1 (2%)	
Inflammation, acute, moderate	2 (4%)			
Inflammation, chronic active, minimal			1 (2%)	
Inflammation, subacute, mild	1 (2%)	1 (2%)		1 (2%)
Inflammation, subacute, minimal	13 (28%)	9 (19%)	7 (16%)	7 (15%)
Seminal vesicle	(47)	(48)	(46)	(47)
Atrophy, mild	3 (6%)	3 (6%)	2 (4%)	5 (11%)
Atrophy, minimal	3 (6%)	3 (6%)	4 (9%)	5 (11%)
Atrophy, moderate		1 (2%)		
Infiltration cellular, lymphocytic, minimal		1 (2%)		
Inflammation, acute, marked	1 (2%)			
Inflammation, acute, mild			1 (2%)	
Inflammation, chronic active, moderate		1 (2%)		
Inflammation, chronic, minimal		1 (2%)		
Inflammation, chronic, moderate		1 (2%)	1 (2%)	
Testes	(48)	(48)	(47)	(47)
Atrophy, marked, germinal epithelium	1 (2%)			
Atrophy, mild, germinal epithelium	1 (2%)	2 (4%)	1 (2%)	4 (9%)
Atrophy, moderate, germinal epithelium		1 (2%)		
Cyst, moderate				1 (2%)
Degeneration, mild, germinal epithelium	1 (2%)			3 (6%)
Degeneration, minimal, germinal epithelium	1 (2%)	2 (4%)	1 (2%)	2 (4%)
Degeneration, moderate, germinal epithelium		1 (2%)		1 (2%)

Table B3
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Drinking Water Study of Urethane and 2.5% Ethanol

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
Genital System (continued)				
Testes (continued)	(48)	(48)	(47)	(47)
Hemorrhage, mild		1 (2%)		
Mineralization, mild			2 (4%)	1 (2%)
Mineralization, minimal	2 (4%)	2 (4%)		3 (6%)
Mineralization, moderate	1 (2%)			
Hematopoietic System				
Bone marrow	(48)	(48)	(47)	(46)
Angiectasis, mild		2 (4%)		
Hemorrhage, marked			1 (2%)	
Hyperplasia, marked				1 (2%)
Hyperplasia, mild	9 (19%)	2 (4%)	5 (11%)	1 (2%)
Hyperplasia, minimal	3 (6%)	2 (4%)	1 (2%)	7 (15%)
Necrosis, mild		1 (2%)		
Lymph node	(48)	(48)	(47)	(47)
Hemorrhage, moderate, axillary				1 (2%)
Hyperplasia, lymphoid, mild, axillary	1 (2%)			
Hyperplasia, lymphoid, mild, inguinal	1 (2%)			
Hyperplasia, lymphoid, mild, thoracic			1 (2%)	
Hyperplasia, lymphoid, moderate, lumbar			1 (2%)	
Infiltration cellular, mixed cell, moderate, lumbar	1 (2%)			
Lymph node, mandibular	(48)	(48)	(45)	(47)
Angiectasis, mild				1 (2%)
Congestion, mild				1 (2%)
Depletion lymphoid, mild		1 (2%)		
Hemorrhage, mild				2 (4%)
Hyperplasia, lymphoid, marked		1 (2%)	1 (2%)	1 (2%)
Hyperplasia, lymphoid, mild	6 (13%)	3 (6%)	5 (11%)	6 (13%)
Hyperplasia, lymphoid, minimal	7 (15%)	4 (8%)	3 (7%)	3 (6%)
Hyperplasia, lymphoid, moderate		1 (2%)	2 (4%)	3 (6%)
Infiltration cellular, histiocytic, mild	2 (4%)	3 (6%)	2 (4%)	2 (4%)
Infiltration cellular, histiocytic, minimal		1 (2%)		2 (4%)
Infiltration cellular, histiocytic, moderate			1 (2%)	
Infiltration cellular, mixed cell, minimal	1 (2%)			
Pigmentation, minimal	2 (4%)			1 (2%)
Lymph node, mesenteric	(48)	(48)	(45)	(44)
Angiectasis, marked	1 (2%)		3 (7%)	1 (2%)
Angiectasis, mild	5 (10%)	9 (19%)	5 (11%)	11 (25%)
Angiectasis, minimal	10 (21%)	6 (13%)	7 (16%)	2 (5%)
Angiectasis, moderate	2 (4%)	5 (10%)	7 (16%)	4 (9%)
Hemorrhage, minimal				1 (2%)
Hemorrhage, moderate	1 (2%)			1 (2%)
Hyperplasia, lymphoid, marked	1 (2%)			
Hyperplasia, lymphoid, mild	3 (6%)	2 (4%)	4 (9%)	1 (2%)
Hyperplasia, lymphoid, minimal	7 (15%)	9 (19%)	2 (4%)	1 (2%)
Hyperplasia, lymphoid, moderate	2 (4%)	1 (2%)		1 (2%)
Infiltration cellular, histiocytic, minimal		2 (4%)		1 (2%)
Infiltration cellular, mixed cell, moderate	1 (2%)			
Inflammation, acute, mild	1 (2%)			
Inflammation, acute, moderate			1 (2%)	
Inflammation, chronic active, mild			1 (2%)	

Table B3
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Drinking Water Study of Urethane and 2.5% Ethanol

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
Hematopoietic System (continued)				
Spleen	(46)	(46)	(46)	(46)
Angiectasis, mild	1 (2%)			
Angiectasis, minimal		1 (2%)	1 (2%)	
Atrophy, mild, lymphoid follicle		1 (2%)		2 (4%)
Congestion, marked	1 (2%)			
Hematopoietic cell proliferation, marked	8 (17%)	5 (11%)	10 (22%)	12 (26%)
Hematopoietic cell proliferation, mild	2 (4%)	3 (7%)	4 (9%)	7 (15%)
Hematopoietic cell proliferation, minimal	2 (4%)	2 (4%)	2 (4%)	3 (7%)
Hematopoietic cell proliferation, moderate	8 (17%)	6 (13%)	6 (13%)	10 (22%)
Hyperplasia, marked, lymphoid follicle	6 (13%)	7 (15%)	6 (13%)	1 (2%)
Hyperplasia, mild, lymphoid follicle	3 (7%)	6 (13%)	9 (20%)	3 (7%)
Hyperplasia, minimal, lymphoid follicle	2 (4%)	3 (7%)	3 (7%)	3 (7%)
Hyperplasia, moderate, lymphoid follicle	8 (17%)	5 (11%)	3 (7%)	4 (9%)
Infiltration cellular, histiocytic, mild		1 (2%)		
Infiltration cellular, histiocytic, moderate			1 (2%)	
Pigmentation, mild		1 (2%)		
Thymus	(35)	(32)	(28)	(32)
Atrophy, marked	4 (11%)	5 (16%)	6 (21%)	8 (25%)
Atrophy, mild	1 (3%)	1 (3%)	1 (4%)	4 (13%)
Atrophy, minimal	2 (6%)	6 (19%)	1 (4%)	1 (3%)
Atrophy, moderate	5 (14%)	1 (3%)	5 (18%)	9 (28%)
Cyst, mild	1 (3%)			
Cyst, minimal	7 (20%)	4 (13%)	2 (7%)	1 (3%)
Infiltration cellular, mixed cell, moderate	1 (3%)			
Necrosis, mild		1 (3%)		
Integumentary System				
Skin	(48)	(48)	(46)	(47)
Edema, mild		1 (2%)		2 (4%)
Edema, minimal			1 (2%)	
Edema, moderate	1 (2%)			
Erosion, mild	1 (2%)	1 (2%)	1 (2%)	
Erosion, moderate			1 (2%)	1 (2%)
Hyperplasia, mild, epithelium		3 (6%)		1 (2%)
Hyperplasia, moderate, epithelium		1 (2%)		1 (2%)
Inflammation, acute, minimal			1 (2%)	
Inflammation, acute, minimal, prepuce		1 (2%)		
Inflammation, chronic active, marked	1 (2%)		1 (2%)	
Inflammation, chronic active, mild	1 (2%)			2 (4%)
Inflammation, chronic active, moderate			1 (2%)	3 (6%)
Inflammation, chronic, mild	1 (2%)	2 (4%)	1 (2%)	1 (2%)
Inflammation, chronic, minimal			1 (2%)	3 (6%)
Inflammation, chronic, moderate		3 (6%)		
Metaplasia, osseous, moderate	1 (2%)			
Ulcer, marked			1 (2%)	
Ulcer, mild	1 (2%)			3 (6%)
Ulcer, moderate			1 (2%)	2 (4%)
Musculoskeletal System				
Bone	(48)	(48)	(47)	(48)
Hyperostosis, mild, cranium				1 (2%)

Table B3
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Drinking Water Study of Urethane and 2.5% Ethanol

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
Musculoskeletal System (continued)				
Bone, femur	(48)	(48)	(47)	(48)
Degeneration, marked, joint, cartilage			1 (2%)	
Degeneration, mild, joint, cartilage	3 (6%)	6 (13%)	6 (13%)	6 (13%)
Degeneration, minimal, joint, cartilage	5 (10%)	3 (6%)	2 (4%)	3 (6%)
Degeneration, moderate, joint, cartilage	1 (2%)			
Inflammation, acute, mild, joint				1 (2%)
Inflammation, chronic active, moderate, joint		1 (2%)		
Skeletal muscle	(48)	(48)	(47)	(48)
Infiltration cellular, lymphocytic, mild	1 (2%)			
Infiltration cellular, lymphocytic, minimal	1 (2%)	2 (4%)	1 (2%)	1 (2%)
Mineralization, mild		1 (2%)		
Nervous System				
Brain, cerebellum	(47)	(48)	(47)	(48)
Hemorrhage, minimal				1 (2%)
Necrosis, marked			1 (2%)	
Brain, cerebrum	(48)	(48)	(47)	(48)
Mineralization, mild, thalamus	1 (2%)		1 (2%)	
Mineralization, minimal, thalamus	26 (54%)	25 (52%)	21 (45%)	23 (48%)
Necrosis, moderate			1 (2%)	
Peripheral nerve	(48)	(48)	(47)	(48)
Degeneration, mild				2 (4%)
Degeneration, minimal	3 (6%)	5 (10%)	6 (13%)	5 (10%)
Spinal cord, thoracic	(48)	(48)	(47)	(48)
Necrosis, mild		1 (2%)		
Necrosis, minimal				1 (2%)
Respiratory System				
Larynx	(44)	(47)	(46)	(47)
Cyst, mild				1 (2%)
Cyst, minimal		2 (4%)		
Inflammation, acute, minimal				1 (2%)
Inflammation, subacute, minimal		1 (2%)	1 (2%)	
Lung	(48)	(48)	(47)	(48)
Foreign body	1 (2%)	1 (2%)		
Hyperplasia, mild, alveolar epithelium		2 (4%)	3 (6%)	3 (6%)
Hyperplasia, minimal, alveolar epithelium				1 (2%)
Hyperplasia, moderate, alveolar epithelium		1 (2%)	1 (2%)	2 (4%)
Infiltration cellular, histiocytic, mild		1 (2%)		
Infiltration cellular, histiocytic, minimal		1 (2%)		1 (2%)
Infiltration cellular, lymphocytic, mild	1 (2%)		1 (2%)	1 (2%)
Infiltration cellular, lymphocytic, minimal	5 (10%)	4 (8%)	1 (2%)	1 (2%)
Infiltration cellular, lymphocytic, moderate			1 (2%)	
Infiltration cellular, mixed cell, moderate	1 (2%)			
Inflammation, acute, mild, vein				1 (2%)
Inflammation, chronic active, mild	1 (2%)			
Inflammation, chronic active, moderate		1 (2%)		
Inflammation, chronic, mild	1 (2%)		4 (9%)	
Inflammation, chronic, minimal	1 (2%)	1 (2%)		1 (2%)
Inflammation, chronic, moderate			1 (2%)	
Parasite protozoan			1 (2%)	

Table B3
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Drinking Water Study of Urethane and 2.5% Ethanol

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
Respiratory System (continued)				
Lung (continued)	(48)	(48)	(47)	(48)
Pigmentation, marked			1 (2%)	
Pigmentation, mild		1 (2%)		
Pigmentation, minimal				1 (2%)
Nose	(48)	(48)	(47)	(48)
Cyst, mild, mucosa	1 (2%)			
Cytoplasmic alteration, mild, olfactory epithelium	8 (17%)	7 (15%)	1 (2%)	3 (6%)
Cytoplasmic alteration, mild, respiratory epithelium	6 (13%)	4 (8%)	2 (4%)	
Cytoplasmic alteration, minimal, olfactory epithelium	5 (10%)	5 (10%)	3 (6%)	4 (8%)
Cytoplasmic alteration, minimal, respiratory epithelium	9 (19%)	5 (10%)	3 (6%)	3 (6%)
Foreign body		1 (2%)		
Hyperplasia, moderate, glands	1 (2%)			
Inflammation, minimal			1 (2%)	1 (2%)
Trachea	(47)	(48)	(45)	(48)
Inflammation, acute, minimal	1 (2%)			
Special Senses System				
Ear			(1)	
Inflammation, chronic active, moderate			1 (100%)	
Ulcer, moderate			1 (100%)	
Eye	(47)	(47)	(47)	(46)
Atrophy, marked			1 (2%)	
Cataract, marked, lens				1 (2%)
Cataract, mild, lens			3 (6%)	
Cataract, minimal, lens		1 (2%)		2 (4%)
Cataract, moderate, lens				3 (7%)
Inflammation, acute, mild, cornea				1 (2%)
Inflammation, acute, minimal, cornea				1 (2%)
Inflammation, acute, moderate, cornea				1 (2%)
Inflammation, chronic active, marked		1 (2%)		
Inflammation, chronic active, marked, cornea			1 (2%)	1 (2%)
Inflammation, chronic active, mild, cornea			2 (4%)	1 (2%)
Inflammation, chronic active, moderate, cornea			1 (2%)	1 (2%)
Inflammation, chronic, mild, cornea			1 (2%)	3 (7%)
Inflammation, chronic, minimal, cornea			1 (2%)	
Inflammation, chronic, moderate, cornea				2 (4%)
Mineralization, minimal			1 (2%)	
Harderian gland	(48)	(48)	(47)	(48)
Hyperplasia, focal, marked			1 (2%)	
Hyperplasia, focal, mild				1 (2%)
Infiltration cellular, lymphocytic, mild	3 (6%)	2 (4%)	1 (2%)	1 (2%)
Infiltration cellular, lymphocytic, minimal	13 (27%)	16 (33%)	7 (15%)	5 (10%)
Infiltration cellular, mixed cell, moderate	1 (2%)			
Inflammation, chronic active, mild			1 (2%)	
Inflammation, chronic, minimal				1 (2%)
Lacrimal gland	(48)	(47)	(45)	(46)
Atrophy, marked				1 (2%)
Atrophy, mild	3 (6%)	4 (9%)	3 (7%)	5 (11%)
Atrophy, minimal	4 (8%)	3 (6%)	7 (16%)	6 (13%)
Atrophy, moderate		1 (2%)		2 (4%)
Cyst, mild			1 (2%)	
Hyperplasia, moderate, duct		1 (2%)		

Table B3
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Drinking Water Study of Urethane and 2.5% Ethanol

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
Special Senses System (continued)				
Lacrimal gland (continued)	(48)	(47)	(45)	(46)
Infiltration cellular, lymphocytic, mild		2 (4%)	4 (9%)	2 (4%)
Infiltration cellular, lymphocytic, minimal	9 (19%)	10 (21%)	8 (18%)	13 (28%)
Infiltration cellular, mast cell, moderate				1 (2%)
Infiltration cellular, mixed cell, moderate	1 (2%)			
Inflammation, chronic active, mild			1 (2%)	
Zymbal's gland	(47)	(45)	(46)	(43)
Cyst, moderate	1 (2%)	1 (2%)		
Dilatation, mild				1 (2%)
Hyperplasia, minimal	1 (2%)			
Urinary System				
Kidney	(48)	(48)	(47)	(47)
Accumulation, hyaline droplet, minimal, renal tubule		1 (2%)		
Amyloid deposition, mild	1 (2%)	1 (2%)		1 (2%)
Amyloid deposition, minimal	3 (6%)	3 (6%)		1 (2%)
Atrophy, marked				1 (2%)
Atrophy, minimal	1 (2%)			
Bacterium	1 (2%)			1 (2%)
Cyst, mild	3 (6%)		1 (2%)	1 (2%)
Cyst, minimal	3 (6%)	5 (10%)	2 (4%)	2 (4%)
Degeneration, mild, renal tubule		2 (4%)	2 (4%)	
Degeneration, minimal, renal tubule	19 (40%)	11 (23%)	13 (28%)	6 (13%)
Degeneration, moderate, renal tubule	1 (2%)	1 (2%)	1 (2%)	
Dilatation, mild, pelvis	2 (4%)			1 (2%)
Dilatation, minimal, pelvis			2 (4%)	
Dilatation, moderate, pelvis		1 (2%)		1 (2%)
Glomerulosclerosis, marked		1 (2%)		
Glomerulosclerosis, mild	13 (27%)	5 (10%)	9 (19%)	11 (23%)
Glomerulosclerosis, minimal	22 (46%)	24 (50%)	23 (49%)	21 (45%)
Glomerulosclerosis, moderate		2 (4%)	2 (4%)	2 (4%)
Hyperplasia, focal, mild, renal tubule	2 (4%)		2 (4%)	2 (4%)
Hyperplasia, focal, minimal, renal tubule	1 (2%)			1 (2%)
Hyperplasia, focal, moderate, renal tubule		1 (2%)		
Hypoplasia, focal, minimal				1 (2%)
Infiltration cellular, lymphocytic, mild	4 (8%)	8 (17%)	1 (2%)	3 (6%)
Infiltration cellular, lymphocytic, minimal	23 (48%)	20 (42%)	18 (38%)	11 (23%)
Infiltration cellular, lymphocytic, moderate	2 (4%)			
Infiltration cellular, mixed cell, moderate	1 (2%)			
Inflammation, acute, mild, pelvis	1 (2%)			
Inflammation, acute, minimal	1 (2%)			
Inflammation, acute, minimal, pelvis		1 (2%)	1 (2%)	
Inflammation, chronic active, marked	1 (2%)			
Inflammation, chronic active, marked, pelvis				1 (2%)
Inflammation, chronic active, mild, pelvis		1 (2%)	1 (2%)	
Inflammation, chronic, minimal			1 (2%)	
Inflammation, chronic, moderate, pelvis				1 (2%)
Inflammation, mild, pelvis	1 (2%)			
Metaplasia, osseous, minimal	1 (2%)			
Mineralization, mild		1 (2%)	1 (2%)	1 (2%)
Mineralization, mild, pelvis		1 (2%)		
Mineralization, minimal	7 (15%)	6 (13%)	7 (15%)	2 (4%)
Mineralization, moderate				1 (2%)

Table B3
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Drinking Water Study of Urethane and 2.5% Ethanol

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
Urinary System (continued)				
Kidney (continued)	(48)	(48)	(47)	(47)
Necrosis, marked, renal tubule				1 (2%)
Necrosis, mild, papilla		1 (2%)		
Necrosis, moderate, papilla				1 (2%)
Nephropathy, minimal				1 (2%)
Urinary bladder	(47)	(46)	(45)	(46)
Dilatation, moderate		1 (2%)	1 (2%)	1 (2%)
Edema, mild			1 (2%)	2 (4%)
Edema, minimal				1 (2%)
Edema, moderate				1 (2%)
Hyperplasia, mild, transitional epithelium			1 (2%)	
Infiltration cellular, lymphocytic, mild	4 (9%)	2 (4%)	2 (4%)	1 (2%)
Infiltration cellular, lymphocytic, minimal	19 (40%)	21 (46%)	17 (38%)	16 (35%)
Infiltration cellular, lymphocytic, moderate	1 (2%)			
Infiltration cellular, mixed cell, moderate	1 (2%)			
Inflammation, acute, marked	1 (2%)			
Inflammation, acute, mild	1 (2%)			
Inflammation, acute, moderate				1 (2%)
Inflammation, chronic active, marked			1 (2%)	
Inflammation, chronic active, moderate				1 (2%)
Inflammation, chronic, mild				1 (2%)

APPENDIX C
SUMMARY OF LESIONS IN MALE MICE IN THE 2-YEAR DRINKING WATER STUDY OF URETHANE AND 5% ETHANOL

Table C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Drinking Water Study of Urethane and 5% Ethanol[a]

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
Disposition Summary				
Animals initially in study	48	48	48	48
Early deaths				
Moribund	5	6	6	15
Natural deaths	7	13	17	21
Survivors				
Terminal sacrifice	36	29	25	12
Animals examined microscopically	48	48	48	48
Alimentary System				
Esophagus	(47)	(46)	(48)	(48)
Lymphoma malignant				1 (2%)
Intestine large	(48)	(47)	(48)	(46)
Squamous cell carcinoma, anus				1 (2%)
Intestine large, cecum	(45)	(45)	(38)	(39)
Carcinoma	1 (2%)			
Histiocytic sarcoma				1 (3%)
Lymphoma malignant				1 (3%)
Intestine large, rectum	(47)	(46)	(48)	(46)
Carcinoma		1 (2%)		
Sarcoma, metastatic, skin			1 (2%)	
Intestine small, duodenum	(46)	(43)	(36)	(38)
Hemangioma				1 (3%)
Leukemia granulocytic		1 (2%)		
Lymphoma malignant		1 (2%)		1 (3%)
Polyp adenomatous	1 (2%)		1 (3%)	
Intestine small, ileum	(42)	(43)	(36)	(39)
Histiocytic sarcoma				1 (3%)
Lymphoma malignant	1 (2%)	1 (2%)	1 (3%)	4 (10%)
Intestine small, jejunum	(45)	(46)	(38)	(36)
Leukemia granulocytic		1 (2%)		
Lymphoma malignant	1 (2%)	1 (2%)	1 (3%)	1 (3%)
Liver	(48)	(46)	(48)	(48)
Hemangioma		2 (4%)	2 (4%)	
Hemangiosarcoma	2 (4%)	2 (4%)	4 (8%)	13 (27%)
Hepatoblastoma				1 (2%)
Hepatocellular adenoma	17 (35%)	6 (13%)	13 (27%)	9 (19%)
Hepatocellular adenoma, multiple	2 (4%)	3 (7%)	3 (6%)	3 (6%)
Hepatocellular carcinoma	7 (15%)	9 (20%)	2 (4%)	9 (19%)
Histiocytic sarcoma	2 (4%)		4 (8%)	5 (10%)
Ito cell tumor malignant			1 (2%)	
Leukemia granulocytic		1 (2%)		
Lymphoma malignant	1 (2%)	1 (2%)	3 (6%)	8 (17%)
Sarcoma, metastatic, skin	1 (2%)		1 (2%)	
Mesentery	(4)	(1)	(2)	
Hemangiosarcoma	1 (25%)		1 (50%)	
Pancreas	(48)	(46)	(45)	(44)
Hemangioma			1 (2%)	
Histiocytic sarcoma			1 (2%)	1 (2%)
Leukemia granulocytic		1 (2%)		
Lymphoma malignant	1 (2%)		3 (7%)	8 (18%)

Table C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Drinking Water Study of Urethane and 5% Ethanol

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
Alimentary System (continued)				
Salivary glands	(48)	(48)	(48)	(48)
Leukemia granulocytic		1 (2%)		
Lymphoma malignant			1 (2%)	1 (2%)
Rhabdomyosarcoma, metastatic, skeletal muscle				1 (2%)
Sarcoma, metastatic, skin	1 (2%)			
Stomach, forestomach	(48)	(47)	(45)	(48)
Hemangioma				1 (2%)
Histiocytic sarcoma				1 (2%)
Leukemia granulocytic		1 (2%)		
Squamous cell carcinoma		1 (2%)	1 (2%)	1 (2%)
Squamous cell papilloma	2 (4%)	2 (4%)	3 (7%)	5 (10%)
Stomach, glandular	(48)	(46)	(45)	(45)
Adenoma	1 (2%)			
Leukemia granulocytic		1 (2%)		
Lymphoma malignant	1 (2%)			2 (4%)
Tongue	(48)	(48)	(48)	(48)
Lymphoma malignant				1 (2%)
Squamous cell carcinoma		1 (2%)		1 (2%)
Cardiovascular System				
Blood vessel	(47)	(46)	(47)	(47)
Lymphoma malignant				1 (2%)
Heart	(47)	(48)	(48)	(48)
Alveolar/bronchiolar carcinoma, metastatic, lung				2 (4%)
Hemangiosarcoma			1 (2%)	4 (8%)
Histiocytic sarcoma	1 (2%)		1 (2%)	1 (2%)
Lymphoma malignant	1 (2%)			4 (8%)
Sarcoma, metastatic, thymus				1 (2%)
Endocrine System				
Adrenal gland	(46)	(47)	(47)	(45)
Rhabdomyosarcoma, metastatic, skeletal muscle				1 (2%)
Adrenal gland, cortex	(46)	(47)	(47)	(45)
Adenoma	2 (4%)	3 (6%)	1 (2%)	
Adenoma, subcapsular	1 (2%)			
Leukemia granulocytic		1 (2%)		
Lymphoma malignant			1 (2%)	
Adrenal gland, medulla	(46)	(46)	(46)	(45)
Leukemia granulocytic		1 (2%)		
Lymphoma malignant			1 (2%)	
Pheochromocytoma benign	2 (4%)	6 (13%)	3 (7%)	2 (4%)
Pheochromocytoma malignant				1 (2%)
Islets, pancreatic	(48)	(46)	(46)	(44)
Adenoma		1 (2%)		
Carcinoma			1 (2%)	
Leukemia granulocytic		1 (2%)		
Lymphoma malignant				1 (2%)
Pituitary gland	(39)	(39)	(42)	(42)
Lymphoma malignant				1 (2%)
Thyroid gland	(45)	(47)	(48)	(47)
Adenoma, follicular cell	1 (2%)			
Lymphoma malignant				3 (6%)

Table C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Drinking Water Study of Urethane and 5% Ethanol

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
General Body System				
Tissue NOS				(1)
Alveolar/bronchiolar carcinoma, metastatic, lung				1 (100%)
Genital System				
Coagulating gland	(47)	(47)	(48)	(44)
Lymphoma malignant				2 (5%)
Epididymis	(48)	(48)	(48)	(47)
Histiocytic sarcoma			1 (2%)	1 (2%)
Leukemia granulocytic		1 (2%)		
Lymphoma malignant				5 (11%)
Preputial gland	(45)	(46)	(45)	(44)
Hemangioma			1 (2%)	
Lymphoma malignant				1 (2%)
Prostate	(46)	(46)	(45)	(48)
Leukemia granulocytic		1 (2%)		
Lymphoma malignant	1 (2%)		2 (4%)	6 (13%)
Seminal vesicle	(47)	(47)	(48)	(45)
Adenoma			1 (2%)	
Histiocytic sarcoma				1 (2%)
Leukemia granulocytic		1 (2%)		
Lymphoma malignant				3 (7%)
Testes	(48)	(48)	(48)	(48)
Adenoma, interstitial cell		1 (2%)		
Hemangioma	1 (2%)			
Hematopoietic System				
Bone marrow	(48)	(46)	(46)	(46)
Hemangiosarcoma		1 (2%)		
Histiocytic sarcoma			1 (2%)	2 (4%)
Leukemia granulocytic		1 (2%)		
Lymphoma malignant				4 (9%)
Lymph node	(48)	(47)	(48)	(47)
Alveolar/bronchiolar carcinoma, metastatic, renal, lung				1 (2%)
Histiocytic sarcoma, axillary	1 (2%)			
Histiocytic sarcoma, lumbar			1 (2%)	1 (2%)
Lymphoma malignant, axillary			1 (2%)	2 (4%)
Lymphoma malignant, inguinal		1 (2%)	1 (2%)	4 (9%)
Lymphoma malignant, lumbar			2 (4%)	1 (2%)
Lymphoma malignant, pancreatic				1 (2%)
Lymphoma malignant, renal	1 (2%)	1 (2%)	3 (6%)	4 (9%)
Lymphoma malignant, thoracic			1 (2%)	
Lymph node, mandibular	(48)	(47)	(48)	(47)
Histiocytic sarcoma			1 (2%)	2 (4%)
Leukemia granulocytic		1 (2%)		
Lymphoma malignant	2 (4%)	5 (11%)	5 (10%)	8 (17%)
Sarcoma, metastatic, skin	2 (4%)	1 (2%)		
Lymph node, mesenteric	(46)	(44)	(42)	(43)
Hemangiosarcoma				1 (2%)
Histiocytic sarcoma			3 (7%)	4 (9%)
Leukemia granulocytic		1 (2%)		
Lymphoma malignant	6 (13%)	5 (11%)	7 (17%)	12 (28%)

Table C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Drinking Water Study of Urethane and 5% Ethanol

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
Hematopoietic System (continued)				
Spleen	(48)	(46)	(46)	(45)
Hemangiosarcoma		1 (2%)		1 (2%)
Histiocytic sarcoma	2 (4%)		3 (7%)	3 (7%)
Leukemia granulocytic		1 (2%)		
Lymphoma malignant	9 (19%)	9 (20%)	6 (13%)	10 (22%)
Sarcoma, metastatic, skin			1 (2%)	
Thymus	(34)	(33)	(32)	(35)
Alveolar/bronchiolar carcinoma, metastatic, lung				2 (6%)
Leukemia granulocytic		1 (3%)		
Lymphoma malignant		2 (6%)		10 (29%)
Sarcoma				1 (3%)
Thymoma benign			1 (3%)	1 (3%)
Integumentary System				
Skin	(48)	(47)	(48)	(45)
Adenoma, sebaceous gland				1 (2%)
Basal cell adenoma				2 (4%)
Fibroma	2 (4%)	2 (4%)	1 (2%)	1 (2%)
Fibroma, multiple			1 (2%)	
Hemangiosarcoma				1 (2%)
Lipoma				1 (2%)
Lymphoma malignant			1 (2%)	2 (4%)
Osteosarcoma			1 (2%)	
Sarcoma	10 (21%)	8 (17%)	12 (25%)	11 (24%)
Sarcoma, multiple	2 (4%)	2 (4%)	3 (6%)	1 (2%)
Squamous cell carcinoma				1 (2%)
Squamous cell papilloma		2 (4%)		6 (13%)
Musculoskeletal System				
Bone	(48)	(48)	(47)	(48)
Carcinoma, metastatic, sternum, harderian gland				1 (2%)
Skeletal muscle	(48)	(48)	(48)	(47)
Lymphoma malignant				1 (2%)
Rhabdomyosarcoma			1 (2%)	1 (2%)
Sarcoma		1 (2%)		
Sarcoma, metastatic, skin		1 (2%)		
Nervous System				
Brain, cerebrum	(48)	(48)	(48)	(48)
Leukemia granulocytic, meninges		1 (2%)		
Lymphoma malignant				2 (4%)
Peripheral nerve	(47)	(48)	(48)	(47)
Schwannoma malignant	1 (2%)			
Respiratory System				
Larynx	(46)	(47)	(45)	(47)
Leukemia granulocytic		1 (2%)		
Lymphoma malignant				3 (6%)

Table C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Drinking Water Study of Urethane and 5% Ethanol

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
Respiratory System (continued)				
Lung	(48)	(48)	(48)	(48)
Alveolar/bronchiolar adenoma	5 (10%)	7 (15%)	6 (13%)	19 (40%)
Alveolar/bronchiolar adenoma, multiple	1 (2%)	1 (2%)	3 (6%)	14 (29%)
Alveolar/bronchiolar carcinoma	5 (10%)	4 (8%)	5 (10%)	15 (31%)
Alveolar/bronchiolar carcinoma, multiple				2 (4%)
Carcinoma, metastatic, harderian gland				1 (2%)
Hemangiosarcoma				1 (2%)
Hepatocellular carcinoma, metastatic, liver		2 (4%)	1 (2%)	2 (4%)
Histiocytic sarcoma			3 (6%)	3 (6%)
Leukemia granulocytic		1 (2%)		
Lymphoma malignant	2 (4%)	1 (2%)	2 (4%)	4 (8%)
Rhabdomyosarcoma, metastatic, skeletal muscle				1 (2%)
Sarcoma, metastatic, skin	1 (2%)	4 (8%)	2 (4%)	
Sarcoma, metastatic, thymus				1 (2%)
Nose	(48)	(48)	(48)	(46)
Leukemia granulocytic		1 (2%)		
Lymphoma malignant				4 (9%)
Trachea	(47)	(48)	(48)	(48)
Leukemia granulocytic		1 (2%)		
Lymphoma malignant				2 (4%)
Special Senses System				
Eye	(48)	(48)	(48)	(46)
Leukemia granulocytic		1 (2%)		
Schwannoma malignant, metastatic, peripheral nerve	1 (2%)			
Harderian gland	(47)	(48)	(48)	(45)
Adenoma	5 (11%)	12 (25%)	12 (25%)	16 (36%)
Adenoma, bilateral			3 (6%)	10 (22%)
Carcinoma		2 (4%)	2 (4%)	7 (16%)
Carcinoma, bilateral				3 (7%)
Leukemia granulocytic		1 (2%)		
Lymphoma malignant				1 (2%)
Lacrimal gland	(47)	(47)	(48)	(47)
Leukemia granulocytic		1 (2%)		
Lymphoma malignant			1 (2%)	1 (2%)
Zymbal's gland	(46)	(45)	(47)	(42)
Carcinoma				1 (2%)
Leukemia granulocytic		1 (2%)		
Lymphoma malignant				1 (2%)
Urinary System				
Kidney	(48)	(47)	(48)	(48)
Alveolar/bronchiolar carcinoma, metastatic, lung				1 (2%)
Carcinoma, renal tubule				1 (2%)
Hemangiosarcoma				3 (6%)
Histiocytic sarcoma			1 (2%)	1 (2%)
Leukemia granulocytic		1 (2%)		
Lymphoma malignant			4 (8%)	7 (15%)
Sarcoma, metastatic, skin			2 (4%)	

Table C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Drinking Water Study of Urethane and 5% Ethanol

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
Urinary System (continued)				
Urinary bladder	(48)	(47)	(48)	(45)
Carcinoma				1 (2%)
Hemangioma	2 (4%)	1 (2%)		
Leukemia granulocytic		1 (2%)		
Lymphoma malignant	1 (2%)			3 (7%)
Neoplasm Summary				
Total animals with primary neoplasms[b]	42	40	44	46
Total primary neoplasms	108	138	158	345
Total animals with benign neoplasms	30	29	32	40
Total benign neoplasms	45	49	56	92
Total animals with malignant neoplasms	31	29	37	45
Total malignant neoplasms	63	89	102	253
Total animals with metastatic neoplasms	5	6	4	8
Total metastatic neoplasms	6	8	8	16

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

Table C2
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Drinking Water Study of Urethane and 5% Ethanol

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
Adrenal Cortex: Adenoma				
Overall rate[a]	3/46 (6.5%)	3/47 (6.4%)	1/47 (2.1%)	0/45 (0.0%)
Adjusted rate[b]	3/41.9 (7.2%)	3/38.6 (7.8%)	1/36.7 (2.7%)	0/31.5 (0.0%)
Terminal rate[c]	3/35 (8.6%)	3/29 (10.3%)	0/25 (0.0%)	0/12 (0.0%)
First incidence (days)	765 (T)	765 (T)	763	—[e]
Poly-3 test[d]	P=0.095N	P=0.624	P=0.354N	P=0.178N
Adrenal Medulla: Benign Pheochromocytoma				
Overall rate	2/46 (4.3%)	6/46 (13.0%)	3/46 (6.5%)	2/45 (4.4%)
Adjusted rate	2/41.9 (4.8%)	6/37.7 (15.9%)	3/36.6 (8.2%)	2/31.6 (6.3%)
Terminal rate	2/35 (5.7%)	5/28 (17.9%)	1/24 (4.2%)	1/12 (8.3%)
First incidence (days)	765 (T)	739	507	753
Poly-3 test	P=0.456N	P=0.100	P=0.438	P=0.587
Adrenal Medulla: Benign or Malignant Pheochromocytoma				
Overall rate	2/46 (4.3%)	6/46 (13.0%)	3/46 (6.5%)	3/45 (6.7%)
Adjusted rate	2/41.9 (4.8%)	6/37.7 (15.9%)	3/36.6 (8.2%)	3/31.8 (9.4%)
Terminal rate	2/35 (5.7%)	5/28 (17.9%)	1/24 (4.2%)	1/12 (8.3%)
First incidence (days)	765 (T)	739	507	691
Poly-3 test	P=0.535	P=0.100	P=0.438	P=0.377
Harderian Gland: Adenoma				
Overall rate	5/47 (10.6%)	12/48 (25.0%)	15/48 (31.3%)	26/45 (57.8%)
Adjusted rate	5/42.9 (11.7%)	12/40.0 (30.0%)	15/39.1 (38.4%)	26/38.3 (67.9%)
Terminal rate	5/35 (14.3%)	10/29 (34.5%)	10/25 (40.0%)	6/12 (50.0%)
First incidence (days)	765 (T)	517	507	444
Poly-3 test	P=0.001	P=0.034	P=0.004	P=0.001
Harderian Gland: Carcinoma				
Overall rate	0/47 (0.0%)	2/48 (4.2%)	2/48 (4.2%)	10/45 (22.2%)
Adjusted rate	0/42.9 (0.0%)	2/38.7 (5.2%)	2/37.7 (5.3%)	10/33.8 (29.6%)
Terminal rate	0/35 (0.0%)	1/29 (3.4%)	1/25 (4.0%)	4/12 (33.3%)
First incidence (days)	—	748	539	478
Poly-3 test	P=0.001	P=0.215	P=0.210	P=0.001
Harderian Gland: Adenoma or Carcinoma				
Overall rate	5/47 (10.6%)	14/48 (29.2%)	17/48 (35.4%)	35/45 (77.8%)
Adjusted rate	5/42.9 (11.7%)	14/40.1 (34.9%)	17/39.7 (42.8%)	35/39.8 (87.9%)
Terminal rate	5/35 (14.3%)	11/29 (37.9%)	11/25 (44.0%)	10/12 (83.3%)
First incidence (days)	765 (T)	517	507	444
Poly-3 test	P=0.001	P=0.010	P=0.001	P=0.001
Heart: Hemangiosarcoma				
Overall rate	0/47 (0.0%)	0/48 (0.0%)	1/48 (2.1%)	4/48 (8.3%)
Adjusted rate	0/43.5 (0.0%)	0/38.7 (0.0%)	1/37.4 (2.7%)	4/33.9 (11.8%)
Terminal rate	0/36 (0.0%)	0/29 (0.0%)	0/25 (0.0%)	2/12 (16.7%)
First incidence (days)	—	—	660	670
Poly-3 test	P=0.003	—[f]	P=0.470	P=0.035
Kidney: Hemangiosarcoma				
Overall rate	0/48 (0.0%)	0/47 (0.0%)	0/48 (0.0%)	3/48 (6.3%)
Adjusted rate	0/43.9 (0.0%)	0/38.6 (0.0%)	0/37.1 (0.0%)	3/34.0 (8.8%)
Terminal rate	0/36 (0.0%)	0/29 (0.0%)	0/25 (0.0%)	1/12 (8.3%)
First incidence (days)	—	—	—	643
Poly-3 test	P=0.006	—	—	P=0.079

Table C2
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Drinking Water Study of Urethane and 5% Ethanol

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
Liver: Hemangiosarcoma				
Overall rate	2/48 (4.2%)	2/46 (4.3%)	4/48 (8.3%)	13/48 (27.1%)
Adjusted rate	2/44.6 (4.5%)	2/38.4 (5.2%)	4/37.4 (10.7%)	13/35.2 (36.9%)
Terminal rate	1/36 (2.8%)	1/29 (3.4%)	3/25 (12.0%)	5/12 (41.7%)
First incidence (days)	464	620	660	507
Poly-3 test	P=0.001	P=0.638	P=0.260	P=0.001
Liver: Hemangioma or Hemangiosarcoma				
Overall rate	2/48 (4.2%)	4/46 (8.7%)	6/48 (12.5%)	13/48 (27.1%)
Adjusted rate	2/44.6 (4.5%)	4/38.4 (10.4%)	6/37.4 (16.0%)	13/35.2 (36.9%)
Terminal rate	1/36 (2.8%)	3/29 (10.3%)	5/25 (20.0%)	5/12 (41.7%)
First incidence (days)	464	620	660	507
Poly-3 test	P=0.001	P=0.270	P=0.083	P=0.001
Liver: Histiocytic Sarcoma				
Overall rate	2/48 (4.2%)	0/46 (0.0%)	4/48 (8.3%)	5/48 (10.4%)
Adjusted rate	2/44.9 (4.5%)	0/37.9 (0.0%)	4/37.8 (10.6%)	5/35.2 (14.2%)
Terminal rate	0/36 (0.0%)	0/29 (0.0%)	1/25 (4.0%)	1/12 (8.3%)
First incidence (days)	542	—	625	577
Poly-3 test	P=0.029	P=0.276N	P=0.262	P=0.131
Liver: Hepatocellular Adenoma				
Overall rate	19/48 (39.6%)	9/46 (19.6%)	16/48 (33.3%)	12/48 (25.0%)
Adjusted rate	19/44.6 (42.6%)	9/38.1 (23.7%)	16/38.2 (41.9%)	12/35.1 (34.2%)
Terminal rate	16/36 (44.4%)	7/29 (24.1%)	12/25 (48.0%)	6/12 (50.0%)
First incidence (days)	607	747	570	570
Poly-3 test	P=0.475N	P=0.054N	P=0.563N	P=0.296N
Liver: Hepatocellular Carcinoma				
Overall rate	7/48 (14.6%)	9/46 (19.6%)	2/48 (4.2%)	9/48 (18.8%)
Adjusted rate	7/44.9 (15.6%)	9/39.2 (23.0%)	2/37.9 (5.3%)	9/36.5 (24.7%)
Terminal rate	3/36 (8.3%)	6/29 (20.7%)	0/25 (0.0%)	1/12 (8.3%)
First incidence (days)	447	542	570	553
Poly-3 test	P=0.264	P=0.281	P=0.127N	P=0.229
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rate	25/48 (52.1%)	16/46 (34.8%)	17/48 (35.4%)	18/48 (37.5%)
Adjusted rate	25/45.6 (54.8%)	16/39.2 (40.8%)	17/38.4 (44.3%)	18/37.1 (48.6%)
Terminal rate	19/36 (52.8%)	12/29 (41.4%)	12/25 (48.0%)	7/12 (58.3%)
First incidence (days)	447	542	570	553
Poly-3 test	P=0.482N	P=0.140N	P=0.227N	P=0.365N
Liver: Hepatocellular Carcinoma or Hepatoblastoma				
Overall rate	7/48 (14.6%)	9/46 (19.6%)	2/48 (4.2%)	10/48 (20.8%)
Adjusted rate	7/44.9 (15.6%)	9/39.2 (23.0%)	2/37.9 (5.3%)	10/36.5 (27.4%)
Terminal rate	3/36 (8.3%)	6/29 (20.7%)	0/25 (0.0%)	2/12 (16.7%)
First incidence (days)	447	542	570	553
Poly-3 test	P=0.168	P=0.281	P=0.127N	P=0.152
Lung: Histiocytic Sarcoma				
Overall rate	0/48 (0.0%)	0/48 (0.0%)	3/48 (6.3%)	3/48 (6.3%)
Adjusted rate	0/43.9 (0.0%)	0/38.7 (0.0%)	3/37.8 (7.9%)	3/34.4 (8.7%)
Terminal rate	0/36 (0.0%)	0/29 (0.0%)	0/25 (0.0%)	1/12 (8.3%)
First incidence (days)	—	—	625	593
Poly-3 test	P=0.029	—	P=0.094	P=0.081

Table C2
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Drinking Water Study of Urethane and 5% Ethanol

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
Lung: Alveolar/bronchiolar Adenoma				
Overall rate	6/48 (12.5%)	8/48 (16.7%)	9/48 (18.8%)	33/48 (68.8%)
Adjusted rate	6/44.1 (13.6%)	8/38.7 (20.7%)	9/38.1 (23.6%)	33/42.2 (78.2%)
Terminal rate	5/36 (13.9%)	8/29 (27.6%)	6/25 (24.0%)	9/12 (75.0%)
First incidence (days)	710	765 (T)	507	355
Poly-3 test	P=0.001	P=0.288	P=0.189	P=0.001
Lung: Alveolar/bronchiolar Carcinoma				
Overall rate	5/48 (10.4%)	4/48 (8.3%)	5/48 (10.4%)	17/48 (35.4%)
Adjusted rate	5/43.9 (11.4%)	4/38.7 (10.3%)	5/37.6 (13.3%)	17/37.1 (45.9%)
Terminal rate	5/36 (13.9%)	4/29 (13.8%)	3/25 (12.0%)	5/12 (41.7%)
First incidence (days)	765 (T)	765 (T)	671	478
Poly-3 test	P=0.001	P=0.578N	P=0.531	P=0.001
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rate	11/48 (22.9%)	11/48 (22.9%)	14/48 (29.2%)	40/48 (83.3%)
Adjusted rate	11/44.1 (25.0%)	11/38.7 (28.4%)	14/38.6 (36.2%)	40/44.5 (89.9%)
Terminal rate	10/36 (27.8%)	11/29 (37.9%)	9/25 (36.0%)	11/12 (91.7%)
First incidence (days)	710	765 (T)	507	355
Poly-3 test	P=0.001	P=0.457	P=0.190	P=0.001
Lymph Node (Mesenteric): Histiocytic Sarcoma				
Overall rate	0/46 (0.0%)	0/44 (0.0%)	3/42 (7.1%)	4/43 (9.3%)
Adjusted rate	0/42.0 (0.0%)	0/36.6 (0.0%)	3/34.8 (8.6%)	4/31.8 (12.6%)
Terminal rate	0/36 (0.0%)	0/28 (0.0%)	1/25 (4.0%)	1/12 (8.3%)
First incidence (days)	—	—	678	577
Poly-3 test	P=0.007	—	P=0.087	P=0.032
Skin: Sarcoma				
Overall rate	12/48 (25.0%)	10/47 (21.3%)	15/48 (31.3%)	12/45 (26.7%)
Adjusted rate	12/44.8 (26.8%)	10/40.8 (24.5%)	15/42.4 (35.4%)	12/34.4 (34.9%)
Terminal rate	6/36 (16.7%)	2/29 (6.9%)	3/25 (12.0%)	4/12 (33.3%)
First incidence (days)	607	517	368	467
Poly-3 test	P=0.205	P=0.504N	P=0.263	P=0.299
Skin: Fibroma or Sarcoma				
Overall rate	13/48 (27.1%)	12/47 (25.5%)	16/48 (33.3%)	13/45 (28.9%)
Adjusted rate	13/44.8 (29.0%)	12/40.8 (29.4%)	16/42.4 (37.7%)	13/34.4 (37.8%)
Terminal rate	7/36 (19.4%)	4/29 (13.8%)	4/25 (16.0%)	4/12 (33.3%)
First incidence (days)	607	517	368	467
Poly-3 test	P=0.221	P=0.577	P=0.262	P=0.282
Skin: Squamous Cell Papilloma				
Overall rate	0/48 (0.0%)	2/47 (4.3%)	0/48 (0.0%)	6/45 (13.3%)
Adjusted rate	0/43.9 (0.0%)	2/39.0 (5.1%)	0/37.1 (0.0%)	6/32.4 (18.5%)
Terminal rate	0/36 (0.0%)	1/29 (3.4%)	0/25 (0.0%)	2/12 (16.7%)
First incidence (days)	—	662	—	710
Poly-3 test	P=0.001	P=0.211	—	P=0.005
Skin: Squamous Cell Papilloma or Squamous Cell Carcinoma				
Overall rate	0/48 (0.0%)	2/47 (4.3%)	0/48 (0.0%)	7/45 (15.6%)
Adjusted rate	0/43.9 (0.0%)	2/39.0 (5.1%)	0/37.1 (0.0%)	7/32.4 (21.6%)
Terminal rate	0/36 (0.0%)	1/29 (3.4%)	0/25 (0.0%)	2/12 (16.7%)
First incidence (days)	—	662	—	710
Poly-3 test	P=0.001	P=0.211	—	P=0.002

Table C2
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Drinking Water Study of Urethane and 5% Ethanol

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
Skin: Squamous Cell Papilloma, Basal Cell Adenoma, or Squamous Cell Carcinoma				
Overall rate	0/48 (0.0%)	2/47 (4.3%)	0/48 (0.0%)	10/45 (22.2%)
Adjusted rate	0/43.9 (0.0%)	2/39.0 (5.1%)	0/37.1 (0.0%)	10/32.9 (30.4%)
Terminal rate	0/36 (0.0%)	1/29 (3.4%)	0/25 (0.0%)	3/12 (25.0%)
First incidence (days)	—	662	—	691
Poly-3 test	P=0.001	P=0.211	—	P=0.001
Spleen: Histiocytic Sarcoma				
Overall rate	2/48 (4.2%)	0/46 (0.0%)	3/46 (6.5%)	3/45 (6.7%)
Adjusted rate	2/44.9 (4.5%)	0/37.9 (0.0%)	3/37.1 (8.1%)	3/33.1 (9.1%)
Terminal rate	0/36 (0.0%)	0/29 (0.0%)	0/25 (0.0%)	1/12 (8.3%)
First incidence (days)	542	—	625	593
Poly-3 test	P=0.155	P=0.276N	P=0.415	P=0.366
Stomach (Forestomach): Squamous Cell Papilloma				
Overall rate	2/48 (4.2%)	2/47 (4.3%)	3/45 (6.7%)	5/48 (10.4%)
Adjusted rate	2/43.9 (4.6%)	2/38.0 (5.3%)	3/36.6 (8.2%)	5/33.8 (14.8%)
Terminal rate	2/36 (5.6%)	2/29 (6.9%)	2/25 (8.0%)	2/12 (16.7%)
First incidence (days)	765 (T)	765 (T)	614	697
Poly-3 test	P=0.067	P=0.641	P=0.418	P=0.125
Stomach (Forestomach): Squamous Cell Papilloma or Squamous Cell Carcinoma				
Overall rate	2/48 (4.2%)	2/47 (4.3%)	4/45 (8.9%)	5/48 (10.4%)
Adjusted rate	2/43.9 (4.6%)	2/38.0 (5.3%)	4/36.6 (10.9%)	5/33.8 (14.8%)
Terminal rate	2/36 (5.6%)	2/29 (6.9%)	2/25 (8.0%)	2/12 (16.7%)
First incidence (days)	765 (T)	765 (T)	614	697
Poly-3 test	P=0.070	P=0.641	P=0.257	P=0.125
All Organs: Hemangioma				
Overall rate	3/48 (6.3%)	3/48 (6.3%)	2/48 (4.2%)	2/48 (4.2%)
Adjusted rate	3/43.9 (6.8%)	3/38.7 (7.8%)	2/37.1 (5.4%)	2/33.6 (6.0%)
Terminal rate	3/36 (8.3%)	3/29 (10.3%)	2/25 (8.0%)	1/12 (8.3%)
First incidence (days)	765 (T)	765 (T)	765 (T)	748
Poly-3 test	P=0.508N	P=0.603	P=0.576N	P=0.619N
All Organs: Hemangiosarcoma				
Overall rate	3/48 (6.3%)	3/48 (6.3%)	5/48 (10.4%)	18/48 (37.5%)
Adjusted rate	3/44.6 (6.7%)	3/39.1 (7.7%)	5/37.4 (13.4%)	18/36.2 (49.7%)
Terminal rate	2/36 (5.6%)	2/29 (6.9%)	4/25 (16.0%)	7/12 (58.3%)
First incidence (days)	464	620	660	507
Poly-3 test	P=0.001	P=0.600	P=0.264	P=0.001
All Organs: Hemangioma or Hemangiosarcoma				
Overall rate	6/48 (12.5%)	6/48 (12.5%)	7/48 (14.6%)	19/48 (39.6%)
Adjusted rate	6/44.6 (13.4%)	6/39.1 (15.3%)	7/37.4 (18.7%)	19/36.3 (52.4%)
Terminal rate	5/36 (13.9%)	5/29 (17.2%)	6/25 (24.0%)	7/12 (58.3%)
First incidence (days)	464	620	660	507
Poly-3 test	P=0.001	P=0.526	P=0.366	P=0.001
All Organs: Histiocytic Sarcoma				
Overall rate	2/48 (4.2%)	0/48 (0.0%)	4/48 (8.3%)	5/48 (10.4%)
Adjusted rate	2/44.9 (4.5%)	0/38.7 (0.0%)	4/37.8 (10.6%)	5/35.2 (14.2%)
Terminal rate	0/36 (0.0%)	0/29 (0.0%)	1/25 (4.0%)	1/12 (8.3%)
First incidence (days)	542	—	625	577
Poly-3 test	P=0.028	P=0.272N	P=0.262	P=0.131

Table C2
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Drinking Water Study of Urethane and 5% Ethanol

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
All Organs: Malignant Lymphoma				
Overall rate	12/48 (25.0%)	10/48 (20.8%)	8/48 (16.7%)	14/48 (29.2%)
Adjusted rate	12/44.5 (27.0%)	10/38.9 (25.7%)	8/37.1 (21.6%)	14/37.1 (37.7%)
Terminal rate	11/36 (30.6%)	9/29 (31.0%)	8/25 (32.0%)	4/12 (33.3%)
First incidence (days)	542	701	765 (T)	296
Poly-3 test	P=0.137	P=0.547N	P=0.381N	P=0.210
All Organs: Benign Neoplasms				
Overall rate	30/48 (62.5%)	29/48 (60.4%)	32/48 (66.7%)	40/48 (83.3%)
Adjusted rate	30/45.0 (66.6%)	29/40.6 (71.4%)	32/41.2 (77.7%)	40/42.8 (93.5%)
Terminal rate	25/36 (69.4%)	23/29 (79.3%)	21/25 (84.0%)	12/12 (100.0%)
First incidence (days)	607	517	368	355
Poly-3 test	P=0.001	P=0.401	P=0.174	P=0.001
All Organs: Malignant Neoplasms				
Overall rate	31/48 (64.6%)	30/48 (62.5%)	37/48 (77.1%)	45/48 (93.8%)
Adjusted rate	31/47.5 (65.2%)	30/42.9 (70.0%)	37/44.8 (82.6%)	45/45.5 (98.9%)
Terminal rate	20/36 (55.6%)	18/29 (62.1%)	18/25 (72.0%)	12/12 (100.0%)
First incidence (days)	447	421	368	296
Poly-3 test	P=0.001	P=0.400	P=0.046	P=0.001
All Organs: Benign or Malignant Neoplasms				
Overall rate	42/48 (87.5%)	41/48 (85.4%)	44/48 (91.7%)	46/48 (95.8%)
Adjusted rate	42/47.5 (88.4%)	41/43.2 (94.8%)	44/45.2 (97.4%)	46/46.3 (99.4%)
Terminal rate	31/36 (86.1%)	28/29 (96.6%)	24/25 (96.0%)	12/12 (100.0%)
First incidence (days)	447	421	368	296
Poly-3 test	P=0.023	P=0.224	P=0.096	P=0.030

(T) Terminal sacrifice
a Number of neoplasm-bearing animals/number of animals with tissue examined microscopically
b Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
c Observed incidence at terminal kill
d Beneath the control incidence (0 ppm urethane) is the P value associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and that exposed group. The Poly-3 test accounts for the differential mortality in animals that do not reach terminal sacrifice. A negative trend or a lower incidence in an exposed group is indicated by **N**.
e Not applicable; no neoplasms in animal group
f Value of statistic cannot be computed.

Table C3
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Drinking Water Study of Urethane and 5% Ethanol[a]

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
Disposition Summary				
Animals initially in study	48	48	48	48
Early deaths				
Moribund	5	6	6	15
Natural deaths	7	13	17	21
Survivors				
Terminal sacrifice	36	29	25	12
Animals examined microscopically	48	48	48	48
Alimentary System				
Gallbladder	(42)	(37)	(30)	(32)
Cyst, mild, mucosa			1 (3%)	
Cytoplasmic alteration, moderate, epithelium			1 (3%)	
Inflammation, acute, minimal		2 (5%)		
Inflammation, chronic, mild	1 (2%)			1 (3%)
Inflammation, chronic, minimal	1 (2%)			
Inflammation, subacute, minimal		1 (3%)		
Intestine large	(48)	(47)	(48)	(46)
Hyperplasia, mild, anus, epithelium				1 (2%)
Inflammation, chronic active, mild, anus			1 (2%)	
Ulcer, moderate, anus			1 (2%)	
Intestine large, cecum	(45)	(45)	(38)	(39)
Hyperplasia, mild, lymphoid tissue		1 (2%)		
Hyperplasia, moderate, lymphoid tissue			1 (3%)	
Intestine large, rectum	(47)	(46)	(48)	(46)
Cyst, minimal, anus		1 (2%)		
Erosion, moderate			1 (2%)	
Hyperplasia, mild, epithelium				1 (2%)
Inflammation, acute, minimal, anus		1 (2%)		
Inflammation, acute, moderate				1 (2%)
Inflammation, chronic active, moderate				1 (2%)
Inflammation, chronic, mild			1 (2%)	
Intestine small, duodenum	(46)	(43)	(36)	(38)
Hyperplasia, marked, lymphoid tissue	1 (2%)			
Intestine small, ileum	(42)	(43)	(36)	(39)
Inflammation, chronic, mild	1 (2%)			
Liver	(48)	(46)	(48)	(48)
Amyloid deposition, mild			1 (2%)	
Amyloid deposition, minimal		1 (2%)		
Angiectasis	1 (2%)	1 (2%)	8 (17%)	19 (40%)
Basophilic focus	1 (2%)	4 (9%)	1 (2%)	
Clear cell focus	2 (4%)	4 (9%)	4 (8%)	
Cyst, mild, bile duct	1 (2%)			
Cyst, moderate, bile duct				1 (2%)
Eosinophilic focus	10 (21%)	9 (20%)	18 (38%)	25 (52%)
Hematopoietic cell proliferation, mild			2 (4%)	5 (10%)
Hematopoietic cell proliferation, minimal			3 (6%)	8 (17%)
Hematopoietic cell proliferation, moderate	1 (2%)	1 (2%)		
Hyperplasia, marked, Kupffer cell	1 (2%)			1 (2%)
Hyperplasia, mild, bile duct				1 (2%)
Hyperplasia, mild, Kupffer cell	1 (2%)	3 (7%)	4 (8%)	5 (10%)

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

TABLE C3
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Drinking Water Study of Urethane and 5% Ethanol

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
Alimentary System (continued)				
Liver (continued)	(48)	(46)	(48)	(48)
Hyperplasia, mild, oval cell	1 (2%)			1 (2%)
Hyperplasia, minimal, bile duct				1 (2%)
Hyperplasia, minimal, Kupffer cell	3 (6%)	6 (13%)	5 (10%)	2 (4%)
Hyperplasia, moderate, Kupffer cell	2 (4%)		1 (2%)	5 (10%)
Infarct, median lobe	1 (2%)			
Infiltration cellular, lymphocytic, minimal		2 (4%)		
Infiltration cellular, mixed cell, minimal	4 (8%)	3 (7%)	2 (4%)	
Inflammation, chronic active, marked				1 (2%)
Mixed cell focus	1 (2%)	4 (9%)	5 (10%)	
Necrosis, marked	1 (2%)			2 (4%)
Necrosis, mild			1 (2%)	
Necrosis, mild, hepatocyte	2 (4%)	2 (4%)		3 (6%)
Necrosis, minimal	2 (4%)		2 (4%)	
Necrosis, minimal, hepatocyte	5 (10%)	2 (4%)	2 (4%)	
Necrosis, moderate		1 (2%)		2 (4%)
Necrosis, moderate, hepatocyte		1 (2%)		2 (4%)
Nuclear alteration, mild, hepatocyte	1 (2%)	3 (7%)	3 (6%)	2 (4%)
Nuclear alteration, minimal, hepatocyte			3 (6%)	
Nuclear alteration, moderate, hepatocyte				1 (2%)
Regeneration			3 (6%)	5 (10%)
Syncytial alteration, mild, hepatocyte	5 (10%)	5 (11%)	4 (8%)	4 (8%)
Syncytial alteration, minimal, hepatocyte	10 (21%)	8 (17%)	4 (8%)	1 (2%)
Syncytial alteration, moderate, hepatocyte	1 (2%)		2 (4%)	
Tension lipidosis	1 (2%)			
Vacuolization cytoplasmic, mild, hepatocyte		3 (7%)	3 (6%)	1 (2%)
Vacuolization cytoplasmic, minimal, hepatocyte	2 (4%)	1 (2%)		
Vacuolization cytoplasmic, moderate, hepatocyte		1 (2%)	1 (2%)	
Mesentery	(4)	(1)	(2)	
Inflammation, chronic, moderate			1 (50%)	
Necrosis, fat	3 (75%)	1 (100%)		
Pancreas	(48)	(46)	(45)	(44)
Atrophy, marked, acinar cell				1 (2%)
Atrophy, mild, acinar cell	1 (2%)			
Degeneration, minimal, acinar cell		1 (2%)		
Dilatation, mild, duct			1 (2%)	
Infiltration cellular, lymphocytic, minimal	1 (2%)	7 (15%)	4 (9%)	1 (2%)
Inflammation, chronic active, marked				1 (2%)
Necrosis, mild				1 (2%)
Vacuolization cytoplasmic, mild, acinar cell				2 (5%)
Vacuolization cytoplasmic, minimal, acinar cell			1 (2%)	
Salivary glands	(48)	(48)	(48)	(48)
Atrophy, mild	4 (8%)	2 (4%)	2 (4%)	7 (15%)
Atrophy, minimal	3 (6%)		1 (2%)	
Atrophy, moderate	1 (2%)			1 (2%)
Hyperplasia, moderate, duct	1 (2%)			
Infiltration cellular, lymphocytic, mild	21 (44%)	19 (40%)	17 (35%)	6 (13%)
Infiltration cellular, lymphocytic, minimal	18 (38%)	18 (38%)	16 (33%)	10 (21%)
Infiltration cellular, lymphocytic, moderate	1 (2%)	1 (2%)	1 (2%)	
Inflammation, chronic, mild	1 (2%)			
Mineralization, minimal			1 (2%)	
Stomach, forestomach	(48)	(47)	(45)	(48)
Cyst, mild	1 (2%)			
Cyst, minimal	1 (2%)		1 (2%)	

Table C3
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Drinking Water Study of Urethane and 5% Ethanol

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
Alimentary System (continued)				
Stomach, forestomach (continued)	(48)	(47)	(45)	(48)
Hyperplasia, mild, epithelium	1 (2%)			2 (4%)
Hyperplasia, minimal, epithelium			1 (2%)	
Hyperplasia, moderate, epithelium			2 (4%)	
Inflammation, chronic active, mild			1 (2%)	
Stomach, glandular	(48)	(46)	(45)	(45)
Cyst, minimal		1 (2%)	1 (2%)	
Erosion, mild		1 (2%)		
Erosion, minimal	1 (2%)			1 (2%)
Hyperplasia, moderate, epithelium	1 (2%)			1 (2%)
Infiltration cellular, lymphocytic, minimal	1 (2%)		1 (2%)	
Inflammation, chronic, minimal	1 (2%)			
Inflammation, subacute, minimal	1 (2%)			
Metaplasia, squamous, minimal	1 (2%)			
Mineralization, minimal		1 (2%)		
Ulcer, mild		1 (2%)		
Tongue	(48)	(48)	(48)	(48)
Foreign body	1 (2%)			2 (4%)
Inflammation, chronic, mild, artery		1 (2%)		
Inflammation, chronic, minimal	1 (2%)			2 (4%)
Cardiovascular System				
Heart	(47)	(48)	(48)	(48)
Abscess, moderate		1 (2%)		
Angiectasis, mild				2 (4%)
Angiectasis, minimal			1 (2%)	3 (6%)
Bacterium		3 (6%)		
Cardiomyopathy, mild			1 (2%)	
Cardiomyopathy, minimal	3 (6%)		1 (2%)	
Hyperplasia, mild, endothelium				1 (2%)
Hyperplasia, minimal, endothelium				1 (2%)
Hypertrophy, mild, parenchymal cell				1 (2%)
Hypertrophy, minimal, parenchymal cell			1 (2%)	2 (4%)
Inflammation, acute, marked, valve		2 (4%)		
Inflammation, chronic, mild, artery		1 (2%)		
Inflammation, chronic, minimal		1 (2%)		
Inflammation, chronic, minimal, myocardium		1 (2%)		
Inflammation, chronic, minimal, valve			1 (2%)	
Inflammation, subacute, minimal, epicardium			1 (2%)	
Mineralization, mild	1 (2%)	1 (2%)		
Mineralization, minimal		1 (2%)		
Mineralization, moderate				1 (2%)
Necrosis, mild				1 (2%)
Thrombosis, mild, atrium				1 (2%)
Thrombosis, moderate, atrium			1 (2%)	
Endocrine System				
Adrenal gland, cortex	(46)	(47)	(47)	(45)
Cyst, mild		1 (2%)		
Cyst, minimal			1 (2%)	
Hyperplasia, focal, marked		1 (2%)		
Hyperplasia, focal, mild				1 (2%)

Table C3
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Drinking Water Study of Urethane and 5% Ethanol

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
Endocrine System (continued)				
Adrenal gland, cortex (continued)	(46)	(47)	(47)	(45)
Hyperplasia, focal, mild, subcapsular			1 (2%)	
Hyperplasia, focal, minimal			1 (2%)	
Hyperplasia, focal, moderate	1 (2%)	1 (2%)		
Hyperplasia, marked, subcapsular	1 (2%)		1 (2%)	
Hyperplasia, mild, subcapsular	11 (24%)	17 (36%)	9 (19%)	10 (22%)
Hyperplasia, minimal, subcapsular	25 (54%)	24 (51%)	27 (57%)	29 (64%)
Hyperplasia, moderate, subcapsular	2 (4%)		1 (2%)	
Hypertrophy, marked			1 (2%)	
Hypertrophy, mild	5 (11%)	4 (9%)	1 (2%)	3 (7%)
Hypertrophy, minimal	2 (4%)	2 (4%)	2 (4%)	1 (2%)
Hypertrophy, moderate	2 (4%)		1 (2%)	1 (2%)
Necrosis, marked			1 (2%)	
Necrosis, mild		1 (2%)		
Adrenal gland, medulla	(46)	(46)	(46)	(45)
Amyloid deposition, mild			1 (2%)	
Hyperplasia, minimal		1 (2%)		
Islets, pancreatic	(48)	(46)	(46)	(44)
Hyperplasia, marked				1 (2%)
Hyperplasia, mild	1 (2%)	1 (2%)	1 (2%)	2 (5%)
Hyperplasia, minimal		1 (2%)	1 (2%)	
Infiltration cellular, lymphocytic, minimal	1 (2%)			
Parathyroid gland	(38)	(38)	(41)	(37)
Cyst, mild			1 (2%)	1 (3%)
Infiltration cellular, lymphocytic, minimal				1 (3%)
Pituitary gland	(39)	(39)	(42)	(42)
Cyst, mild, pars distalis		1 (3%)		1 (2%)
Cyst, minimal, pars distalis		3 (8%)		
Thyroid gland	(45)	(47)	(48)	(47)
Crystals	1 (2%)		1 (2%)	1 (2%)
Cyst, mild, follicle			1 (2%)	
Hyperplasia, focal, mild, C-cell				1 (2%)
Hyperplasia, minimal, follicular cell	1 (2%)			1 (2%)
Hyperplasia, moderate, follicular cell			1 (2%)	
Infiltration cellular, lymphocytic, minimal	1 (2%)	1 (2%)		
Infiltration cellular, mixed cell, mild			1 (2%)	
Ultimobranchial cyst	10 (22%)	11 (23%)	12 (25%)	10 (21%)
General Body System				
None				
Genital System				
Coagulating gland	(47)	(47)	(48)	(44)
Atrophy, mild	3 (6%)	4 (9%)	4 (8%)	4 (9%)
Atrophy, minimal		1 (2%)		4 (9%)
Cyst, marked		1 (2%)		
Dilatation, mild		1 (2%)	1 (2%)	1 (2%)
Infiltration cellular, lymphocytic, mild		1 (2%)		
Infiltration cellular, lymphocytic, minimal	3 (6%)	1 (2%)		
Inflammation, acute, marked			1 (2%)	
Inflammation, chronic active, moderate				1 (2%)

Table C3
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Drinking Water Study of Urethane and 5% Ethanol

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
Genital System (continued)				
Epididymis	(48)	(48)	(48)	(47)
Atrophy, mild		1 (2%)		
Granuloma sperm, mild	1 (2%)			3 (6%)
Infiltration cellular, lymphocytic, mild	1 (2%)	3 (6%)		1 (2%)
Infiltration cellular, lymphocytic, minimal	3 (6%)	4 (8%)	2 (4%)	2 (4%)
Inflammation, chronic active, mild				1 (2%)
Inflammation, chronic, mild		1 (2%)	2 (4%)	2 (4%)
Inflammation, chronic, minimal			1 (2%)	1 (2%)
Penis			(2)	
Inflammation, chronic, mild, adventitia			1 (50%)	
Preputial gland	(45)	(46)	(45)	(44)
Atrophy, marked	1 (2%)	3 (7%)	6 (13%)	10 (23%)
Atrophy, mild	5 (11%)	7 (15%)	4 (9%)	4 (9%)
Atrophy, minimal			1 (2%)	2 (5%)
Atrophy, moderate	7 (16%)	7 (15%)	2 (4%)	13 (30%)
Cyst, marked				1 (2%)
Cyst, mild			2 (4%)	1 (2%)
Cyst, minimal		1 (2%)		
Dilatation, marked		1 (2%)	1 (2%)	
Dilatation, mild	9 (20%)	7 (15%)	9 (20%)	6 (14%)
Dilatation, minimal	5 (11%)	3 (7%)	1 (2%)	1 (2%)
Dilatation, moderate	6 (13%)	6 (13%)	4 (9%)	5 (11%)
Hyperplasia, mild		2 (4%)		
Inflammation, chronic active, marked	2 (4%)	2 (4%)	3 (7%)	1 (2%)
Inflammation, chronic active, mild	2 (4%)	3 (7%)	4 (9%)	3 (7%)
Inflammation, chronic active, moderate	6 (13%)	2 (4%)	4 (9%)	7 (16%)
Inflammation, chronic, marked			1 (2%)	
Inflammation, chronic, mild	4 (9%)	3 (7%)	4 (9%)	
Inflammation, chronic, minimal	5 (11%)	4 (9%)	5 (11%)	2 (5%)
Inflammation, subacute, mild	1 (2%)			
Inflammation, subacute, minimal	3 (7%)	1 (2%)		
Prostate	(46)	(46)	(45)	(48)
Atrophy, mild			1 (2%)	3 (6%)
Atrophy, minimal	1 (2%)	1 (2%)		2 (4%)
Hyperplasia, mild, epithelium	1 (2%)			
Infiltration cellular, lymphocytic, mild	1 (2%)			
Inflammation, acute, marked			1 (2%)	
Inflammation, acute, mild				1 (2%)
Inflammation, acute, moderate		1 (2%)		1 (2%)
Inflammation, chronic active, mild	1 (2%)		1 (2%)	1 (2%)
Inflammation, chronic, mild			1 (2%)	
Inflammation, subacute, mild		3 (7%)	2 (4%)	
Inflammation, subacute, minimal	19 (41%)	14 (30%)	7 (16%)	7 (15%)
Seminal vesicle	(47)	(47)	(48)	(45)
Atrophy, mild	3 (6%)	3 (6%)	3 (6%)	4 (9%)
Atrophy, minimal		2 (4%)		6 (13%)
Dilatation, mild		1 (2%)	1 (2%)	2 (4%)
Dilatation, minimal		2 (4%)		
Dilatation, moderate			1 (2%)	
Infiltration cellular, lymphocytic, minimal	1 (2%)		1 (2%)	1 (2%)
Inflammation, acute, mild			1 (2%)	2 (4%)
Inflammation, chronic active, mild				1 (2%)
Inflammation, chronic, mild		1 (2%)		
Inflammation, chronic, moderate			1 (2%)	

Table C3
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Drinking Water Study of Urethane and 5% Ethanol

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
Genital System (continued)				
Testes	(48)	(48)	(48)	(48)
Atrophy, marked, germinal epithelium		1 (2%)		
Atrophy, mild, germinal epithelium	1 (2%)	1 (2%)	1 (2%)	
Atrophy, minimal, germinal epithelium			3 (6%)	
Atrophy, moderate, germinal epithelium	1 (2%)	1 (2%)		2 (4%)
Degeneration, mild, germinal epithelium		1 (2%)	1 (2%)	1 (2%)
Degeneration, minimal, germinal epithelium		3 (6%)	1 (2%)	3 (6%)
Fibrosis, marked			1 (2%)	
Mineralization, minimal	1 (2%)	1 (2%)	2 (4%)	
Mineralization, moderate			1 (2%)	
Hematopoietic System				
Bone marrow	(48)	(46)	(46)	(46)
Depletion, minimal				1 (2%)
Fibrosis, mild	1 (2%)			
Hemorrhage, moderate			1 (2%)	
Hyperplasia, mild	3 (6%)	2 (4%)		1 (2%)
Hyperplasia, minimal	2 (4%)	3 (7%)	3 (7%)	2 (4%)
Hyperplasia, moderate			1 (2%)	2 (4%)
Myelofibrosis, moderate			1 (2%)	
Necrosis, mild	1 (2%)			1 (2%)
Necrosis, moderate				1 (2%)
Lymph node	(48)	(47)	(48)	(47)
Hyperplasia, lymphoid, mild, inguinal			1 (2%)	
Hyperplasia, lymphoid, mild, lumbar		1 (2%)		
Hyperplasia, moderate, renal			1 (2%)	
Infiltration cellular, histiocytic, mild, inguinal		1 (2%)		
Infiltration cellular, histiocytic, minimal, inguinal				1 (2%)
Pigmentation, mild, inguinal				1 (2%)
Lymph node, mandibular	(48)	(47)	(48)	(47)
Angiectasis, minimal			1 (2%)	
Atrophy, moderate			1 (2%)	1 (2%)
Cyst, moderate		1 (2%)		
Hemorrhage, minimal				1 (2%)
Hemorrhage, moderate		1 (2%)		
Hyperplasia, lymphoid, marked		3 (6%)		
Hyperplasia, lymphoid, mild	2 (4%)	1 (2%)	1 (2%)	1 (2%)
Hyperplasia, lymphoid, minimal	7 (15%)	5 (11%)	6 (13%)	
Hyperplasia, lymphoid, moderate	1 (2%)	1 (2%)	1 (2%)	
Infiltration cellular, histiocytic, mild	2 (4%)	1 (2%)		3 (6%)
Infiltration cellular, histiocytic, minimal				1 (2%)
Infiltration cellular, histiocytic, moderate				1 (2%)
Inflammation, chronic, mild		1 (2%)		
Pigmentation, mild			1 (2%)	
Lymph node, mesenteric	(46)	(44)	(42)	(43)
Angiectasis, marked		1 (2%)		1 (2%)
Angiectasis, mild	10 (22%)	11 (25%)	9 (21%)	9 (21%)
Angiectasis, minimal	12 (26%)	6 (14%)	6 (14%)	4 (9%)
Angiectasis, moderate	4 (9%)	4 (9%)	2 (5%)	3 (7%)
Depletion lymphoid, mild		1 (2%)		
Hematopoietic cell proliferation, mild	1 (2%)			
Hematopoietic cell proliferation, minimal		1 (2%)		
Hematopoietic cell proliferation, moderate		1 (2%)		

Table C3
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Drinking Water Study of Urethane and 5% Ethanol

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
Hematopoietic System (continued)				
Lymph node, mesenteric (continued)	(46)	(44)	(42)	(43)
Hemorrhage, mild	1 (2%)		1 (2%)	
Hemorrhage, moderate			1 (2%)	1 (2%)
Hyperplasia, lymphoid, marked	1 (2%)	1 (2%)		
Hyperplasia, lymphoid, mild	3 (7%)	4 (9%)	3 (7%)	
Hyperplasia, lymphoid, minimal	7 (15%)	4 (9%)	3 (7%)	
Hyperplasia, lymphoid, moderate	1 (2%)	1 (2%)		
Infiltration cellular, histiocytic, marked				1 (2%)
Infiltration cellular, histiocytic, mild	1 (2%)			1 (2%)
Infiltration cellular, histiocytic, minimal	2 (4%)	1 (2%)	1 (2%)	
Thrombosis, marked, vein				1 (2%)
Spleen	(48)	(46)	(46)	(45)
Atrophy, mild, lymphoid follicle		1 (2%)	3 (7%)	1 (2%)
Congestion, mild			1 (2%)	
Hematopoietic cell proliferation, marked	4 (8%)	5 (11%)	6 (13%)	5 (11%)
Hematopoietic cell proliferation, mild	5 (10%)	2 (4%)	2 (4%)	6 (13%)
Hematopoietic cell proliferation, minimal			1 (2%)	4 (9%)
Hematopoietic cell proliferation, moderate	5 (10%)	5 (11%)	7 (15%)	12 (27%)
Hyperplasia, marked, lymphoid follicle	3 (6%)	8 (17%)	6 (13%)	1 (2%)
Hyperplasia, mild, lymphoid follicle	7 (15%)	6 (13%)	6 (13%)	2 (4%)
Hyperplasia, minimal, lymphoid follicle	4 (8%)	4 (9%)	1 (2%)	2 (4%)
Hyperplasia, moderate, lymphoid follicle	10 (21%)	4 (9%)	6 (13%)	
Metaplasia, osseous, minimal	1 (2%)			
Thymus	(34)	(33)	(32)	(35)
Atrophy, marked	3 (9%)	4 (12%)	4 (13%)	13 (37%)
Atrophy, mild	5 (15%)	3 (9%)	3 (9%)	
Atrophy, minimal	2 (6%)	4 (12%)		1 (3%)
Atrophy, moderate	1 (3%)	2 (6%)	6 (19%)	5 (14%)
Cyst, minimal	3 (9%)	4 (12%)	3 (9%)	2 (6%)
Hemorrhage, minimal			1 (3%)	
Integumentary System				
Mammary gland	(1)	(1)	(2)	(1)
Cyst, mild				1 100%)
Skin	(48)	(47)	(48)	(45)
Edema, mild	2 (4%)	1 (2%)		1 (2%)
Edema, minimal			1 (2%)	
Edema, moderate				1 (2%)
Hyperplasia, marked, epithelium	1 (2%)			
Hyperplasia, mild, epithelium			1 (2%)	1 (2%)
Hyperplasia, minimal, epithelium				1 (2%)
Hyperplasia, moderate, epithelium				1 (2%)
Inflammation, acute, moderate				1 (2%)
Inflammation, chronic active, marked			1 (2%)	
Inflammation, chronic active, mild	1 (2%)		1 (2%)	1 (2%)
Inflammation, chronic active, mild, prepuce			1 (2%)	
Inflammation, chronic active, moderate			1 (2%)	
Inflammation, chronic, mild		1 (2%)	2 (4%)	
Inflammation, chronic, minimal		1 (2%)	1 (2%)	1 (2%)
Inflammation, chronic, moderate				2 (4%)
Metaplasia, osseous, marked			1 (2%)	
Necrosis, moderate, fat			1 (2%)	
Ulcer, mild	2 (4%)		1 (2%)	
Ulcer, moderate			2 (4%)	

Table C3
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Drinking Water Study of Urethane and 5% Ethanol

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
Musculoskeletal System				
Bone	(48)	(48)	(47)	(48)
Degeneration, marked, cartilage, sternum				1 (2%)
Hyperostosis, mild, calvarium			1 (2%)	
Hyperostosis, mild, cranium	1 (2%)			
Hyperostosis, mild, sternum			1 (2%)	
Hyperostosis, moderate, calvarium				1 (2%)
Inflammation, acute, moderate, sternum				1 (2%)
Inflammation, chronic, mild, periosteum, sternum				1 (2%)
Bone, femur	(48)	(48)	(47)	(47)
Degeneration, mild, joint, cartilage	9 (19%)	8 (17%)	6 (13%)	7 (15%)
Degeneration, minimal, joint, cartilage	6 (13%)	3 (6%)	2 (4%)	
Degeneration, moderate, joint, cartilage		1 (2%)	1 (2%)	1 (2%)
Hyperostosis, mild			1 (2%)	
Inflammation, chronic, mild, joint				1 (2%)
Skeletal muscle	(48)	(48)	(48)	(47)
Infiltration cellular, lymphocytic, mild	1 (2%)			
Infiltration cellular, lymphocytic, minimal	1 (2%)	1 (2%)	1 (2%)	
Necrosis, mild				1 (2%)
Necrosis, minimal				1 (2%)
Necrosis, moderate			1 (2%)	
Regeneration, moderate			1 (2%)	
Nervous System				
Brain, cerebellum	(47)	(48)	(46)	(46)
Mineralization, minimal, meninges		1 (2%)		
Brain, cerebrum	(48)	(48)	(48)	(48)
Inflammation, acute, marked, meninges		1 (2%)		
Mineralization, mild, thalamus	1 (2%)	1 (2%)		3 (6%)
Mineralization, minimal, thalamus	34 (71%)	23 (48%)	26 (54%)	21 (44%)
Peripheral nerve	(47)	(48)	(48)	(47)
Degeneration, mild				1 (2%)
Degeneration, minimal	3 (6%)	3 (6%)	2 (4%)	3 (6%)
Spinal cord, thoracic	(48)	(48)	(48)	(48)
Inflammation, acute, moderate, meninges		1 (2%)		
Respiratory System				
Larynx	(46)	(47)	(45)	(47)
Atrophy, mild			1 (2%)	
Infiltration cellular, lymphocytic, minimal			1 (2%)	
Inflammation, acute, mild				1 (2%)
Inflammation, acute, minimal		1 (2%)		
Inflammation, subacute, minimal		1 (2%)		
Lung	(48)	(48)	(48)	(48)
Foreign body		1 (2%)		
Hemorrhage, mild		1 (2%)		
Hyperplasia, marked, alveolar epithelium		1 (2%)	1 (2%)	2 (4%)
Hyperplasia, mild, alveolar epithelium		1 (2%)	4 (8%)	4 (8%)
Hyperplasia, minimal, alveolar epithelium	1 (2%)		1 (2%)	
Hyperplasia, moderate, alveolar epithelium		1 (2%)	1 (2%)	6 (13%)
Hyperplasia, moderate, bronchiole, epithelium	1 (2%)			
Infiltration cellular, histiocytic, mild				1 (2%)
Infiltration cellular, histiocytic, minimal	1 (2%)			

Table C3
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Drinking Water Study of Urethane and 5% Ethanol

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
Respiratory System (continued)				
Lung (continued)	(48)	(48)	(48)	(48)
Infiltration cellular, lymphocytic, mild	3 (6%)	3 (6%)	1 (2%)	
Infiltration cellular, lymphocytic, minimal	11 (23%)	8 (17%)	3 (6%)	2 (4%)
Inflammation, chronic active, minimal		1 (2%)		
Inflammation, chronic, mild	2 (4%)			
Inflammation, chronic, minimal	2 (4%)	1 (2%)	1 (2%)	1 (2%)
Inflammation, chronic, minimal, vein	1 (2%)			
Parasite protozoan	1 (2%)			
Nose	(48)	(48)	(48)	(46)
Cyst, minimal, mucosa	1 (2%)			
Cytoplasmic alteration, mild, olfactory epithelium		1 (2%)	1 (2%)	1 (2%)
Cytoplasmic alteration, mild, respiratory epithelium	1 (2%)	3 (6%)	2 (4%)	
Cytoplasmic alteration, minimal, olfactory epithelium	1 (2%)	2 (4%)	2 (4%)	3 (7%)
Cytoplasmic alteration, minimal, respiratory epithelium	4 (8%)	2 (4%)	6 (13%)	1 (2%)
Inflammation, acute, mild, nasolacrimal duct	1 (2%)			
Inflammation, chronic, mild, nasolacrimal duct		1 (2%)		
Inflammation, mild			1 (2%)	
Special Senses System				
Eye	(48)	(48)	(48)	(46)
Cataract, marked, lens				1 (2%)
Cataract, mild, lens			2 (4%)	
Cataract, minimal, lens		1 (2%)	1 (2%)	2 (4%)
Cataract, moderate, lens		1 (2%)		1 (2%)
Hyperplasia, mild, cornea			1 (2%)	
Inflammation, acute, mild, cornea	1 (2%)			
Inflammation, acute, mild, iris				1 (2%)
Inflammation, acute, minimal, cornea				1 (2%)
Inflammation, acute, moderate, cornea	1 (2%)		1 (2%)	1 (2%)
Inflammation, acute, moderate, optic nerve		1 (2%)		
Inflammation, chronic active, marked, cornea				2 (4%)
Inflammation, chronic active, mild, cornea	1 (2%)			1 (2%)
Inflammation, chronic active, moderate, cornea			1 (2%)	2 (4%)
Inflammation, chronic, mild, cornea				3 (7%)
Inflammation, chronic, minimal, cornea			1 (2%)	
Inflammation, chronic, moderate, cornea		1 (2%)	1 (2%)	1 (2%)
Harderian gland	(47)	(48)	(48)	(45)
Hyperplasia, focal, mild			1 (2%)	
Hyperplasia, focal, moderate			1 (2%)	
Infiltration cellular, lymphocytic, mild	2 (4%)		2 (4%)	
Infiltration cellular, lymphocytic, minimal	15 (32%)	17 (35%)	17 (35%)	2 (4%)
Lacrimal gland	(47)	(47)	(48)	(47)
Amyloid deposition, minimal				1 (2%)
Atrophy, marked				1 (2%)
Atrophy, mild	3 (6%)	3 (6%)		4 (9%)
Atrophy, minimal	3 (6%)	6 (13%)	5 (10%)	5 (11%)
Atrophy, moderate		2 (4%)	2 (4%)	
Degeneration, mild		1 (2%)		
Hyperplasia, focal, mild	1 (2%)			
Hyperplasia, mild, duct			1 (2%)	
Infiltration cellular, lymphocytic, mild	2 (4%)	5 (11%)	2 (4%)	2 (4%)
Infiltration cellular, lymphocytic, minimal	14 (30%)	11 (23%)	11 (23%)	9 (19%)
Infiltration cellular, lymphocytic, moderate			1 (2%)	
Necrosis, mild	1 (2%)			

Table C3
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Drinking Water Study of Urethane and 5% Ethanol

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
Special Senses System (continued)				
Zymbal's gland	(46)	(45)	(47)	(42)
Hyperplasia, mild		1 (2%)		
Infiltration cellular, lymphocytic, minimal	1 (2%)			
Inflammation, subacute, minimal				1 (2%)
Urinary System				
Kidney	(48)	(47)	(48)	(48)
Accumulation, hyaline droplet, mild, renal tubule			1 (2%)	2 (4%)
Accumulation, hyaline droplet, moderate, renal tubule			1 (2%)	
Amyloid deposition, mild		2 (4%)		
Amyloid deposition, minimal	4 (8%)	3 (6%)	1 (2%)	1 (2%)
Amyloid deposition, moderate		1 (2%)		
Atrophy, focal, mild				1 (2%)
Bacterium		1 (2%)		
Cyst, mild	1 (2%)	1 (2%)		1 (2%)
Cyst, minimal	6 (13%)	2 (4%)	4 (8%)	3 (6%)
Degeneration, mild, renal tubule	4 (8%)	4 (9%)		1 (2%)
Degeneration, minimal, renal tubule	12 (25%)	16 (34%)	10 (21%)	6 (13%)
Degeneration, moderate, renal tubule	1 (2%)		1 (2%)	1 (2%)
Dilatation, marked, pelvis		1 (2%)		
Dilatation, mild, pelvis				1 (2%)
Dilatation, moderate, pelvis			1 (2%)	
Glomerulosclerosis, mild	12 (25%)	10 (21%)	8 (17%)	9 (19%)
Glomerulosclerosis, minimal	30 (63%)	22 (47%)	26 (54%)	17 (35%)
Glomerulosclerosis, moderate	2 (4%)	1 (2%)		3 (6%)
Hyperplasia, focal, mild, renal tubule			1 (2%)	
Hyperplasia, focal, minimal, renal tubule	3 (6%)	1 (2%)		1 (2%)
Hypoplasia, focal, mild	1 (2%)			
Infarct, mild		1 (2%)	1 (2%)	
Infarct, minimal				1 (2%)
Infiltration cellular, lymphocytic, mild	12 (25%)	7 (15%)	5 (10%)	
Infiltration cellular, lymphocytic, minimal	19 (40%)	20 (43%)	18 (38%)	15 (31%)
Infiltration cellular, lymphocytic, moderate			2 (4%)	
Inflammation, acute, mild, pelvis			1 (2%)	
Inflammation, chronic active, mild			1 (2%)	
Inflammation, chronic active, mild, pelvis			1 (2%)	
Inflammation, chronic, mild			1 (2%)	
Inflammation, chronic, mild, artery			1 (2%)	
Inflammation, chronic, mild, pelvis			1 (2%)	
Inflammation, chronic, moderate		1 (2%)		
Metaplasia, osseous, minimal		1 (2%)		
Mineralization, mild		1 (2%)		
Mineralization, minimal	5 (10%)	8 (17%)	4 (8%)	2 (4%)
Urethra		(1)	(3)	
Inflammation, acute, marked, bulbourethral gland			2 (67%)	
Urinary bladder	(48)	(47)	(48)	(45)
Calculus gross observation			1 (2%)	
Dilatation, marked				1 (2%)
Dilatation, moderate			1 (2%)	
Edema, moderate				1 (2%)

Table C3
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Drinking Water Study of Urethane and 5% Ethanol

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
Urinary System (continued)				
Urinary bladder (continued)	(48)	(47)	(48)	(45)
Infiltration cellular, lymphocytic, mild	6 (13%)	1 (2%)	2 (4%)	1 (2%)
Infiltration cellular, lymphocytic, minimal	19 (40%)	22 (47%)	15 (31%)	22 (49%)
Infiltration cellular, lymphocytic, moderate	2 (4%)	1 (2%)		
Inflammation, acute, mild			2 (4%)	1 (2%)
Inflammation, chronic active, marked			1 (2%)	
Inflammation, chronic active, mild			1 (2%)	
Ulcer, marked			1 (2%)	

APPENDIX D
SUMMARY OF LESIONS IN FEMALE MICE IN THE 2-YEAR DRINKING WATER STUDY OF URETHANE, ETHANOL, AND URETHANE/ETHANOL

Table D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Drinking Water Study of Urethane and 0% Ethanol[a]

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
Disposition Summary				
Animals initially in study	48	48	48	48
Early deaths				
Moribund	1	3	5	18
Natural deaths	9	8	16	29
Survivors				
Terminal sacrifice	38	37	27	1
Animals examined microscopically	48	48	48	48
Alimentary System				
Esophagus	(48)	(47)	(47)	(47)
Lymphoma malignant		1 (2%)		
Gallbladder	(47)	(45)	(46)	(43)
Leiomyosarcoma, metastatic, uterus			1 (2%)	
Lymphoma malignant	1 (2%)	1 (2%)	1 (2%)	
Sarcoma, metastatic, skin				1 (2%)
Intestine large, cecum	(48)	(45)	(46)	(45)
Lymphoma malignant		1 (2%)		
Intestine large, colon	(48)	(44)	(46)	(46)
Lymphoma malignant	1 (2%)			
Sarcoma, metastatic, skin				1 (2%)
Sarcoma, metastatic, uncertain primary site				1 (2%)
Sarcoma, metastatic, uterus			1 (2%)	
Intestine large, rectum	(48)	(45)	(45)	(46)
Histiocytic sarcoma			1 (2%)	1 (2%)
Leiomyosarcoma, metastatic, uterus			1 (2%)	
Lymphoma malignant				2 (4%)
Sarcoma, metastatic, uterus			1 (2%)	
Intestine small	(48)	(44)	(46)	(44)
Polyp adenomatous		1 (2%)		
Intestine small, ileum	(48)	(44)	(46)	(44)
Histiocytic sarcoma				1 (2%)
Lymphoma malignant	1 (2%)	1 (2%)	1 (2%)	
Intestine small, jejunum	(48)	(44)	(46)	(44)
Leiomyosarcoma, metastatic, uterus			1 (2%)	
Lymphoma malignant	1 (2%)			
Liver	(48)	(47)	(47)	(47)
Hemangiosarcoma			1 (2%)	7 (15%)
Hepatocellular adenoma	3 (6%)	8 (17%)	10 (21%)	2 (4%)
Hepatocellular adenoma, multiple	2 (4%)	2 (4%)	9 (19%)	16 (34%)
Hepatocellular carcinoma		1 (2%)	2 (4%)	1 (2%)
Histiocytic sarcoma	1 (2%)	2 (4%)	3 (6%)	3 (6%)
Leiomyosarcoma, metastatic, uterus			1 (2%)	
Lymphoma malignant	11 (23%)	3 (6%)	5 (11%)	10 (21%)
Sarcoma, metastatic, skin				1 (2%)
Mesentery	(3)	(4)	(7)	(6)
Lymphoma malignant			1 (14%)	
Sarcoma, metastatic, skin				2 (33%)
Pancreas	(48)	(43)	(47)	(44)
Histiocytic sarcoma				2 (5%)
Leiomyosarcoma, metastatic, uterus			1 (2%)	
Lymphoma malignant	7 (15%)	1 (2%)	3 (6%)	6 (14%)
Sarcoma, metastatic, skin				1 (2%)
Sarcoma, metastatic, uncertain primary site				1 (2%)

Table D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Drinking Water Study of Urethane and 0% Ethanol

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
Alimentary System (continued)				
Salivary glands	(48)	(48)	(48)	(47)
Lymphoma malignant	7 (15%)	3 (6%)	3 (6%)	8 (17%)
Stomach, forestomach	(48)	(46)	(46)	(46)
Lymphoma malignant	1 (2%)	1 (2%)		1 (2%)
Mast cell tumor malignant			1 (2%)	
Squamous cell carcinoma		1 (2%)		1 (2%)
Squamous cell papilloma	2 (4%)	3 (7%)	3 (7%)	3 (7%)
Stomach, glandular	(47)	(46)	(46)	(47)
Leiomyosarcoma, metastatic, uterus			1 (2%)	
Lymphoma malignant	1 (2%)	1 (2%)		1 (2%)
Cardiovascular System				
Blood vessel	(47)	(47)	(48)	(46)
Lymphoma malignant				2 (4%)
Heart	(48)	(48)	(48)	(48)
Hemangioma			1 (2%)	
Hemangiosarcoma			1 (2%)	
Histiocytic sarcoma	1 (2%)		2 (4%)	3 (6%)
Lymphoma malignant	3 (6%)	2 (4%)		3 (6%)
Endocrine System				
Adrenal gland, cortex	(48)	(45)	(45)	(47)
Adenoma				1 (2%)
Adenoma, bilateral				1 (2%)
Adenoma, subcapsular	1 (2%)		1 (2%)	
Hemangiosarcoma				1 (2%)
Histiocytic sarcoma			1 (2%)	
Lymphoma malignant	1 (2%)	2 (4%)	2 (4%)	2 (4%)
Sarcoma, metastatic, uncertain primary site				1 (2%)
Adrenal gland, medulla	(47)	(42)	(43)	(47)
Lymphoma malignant	1 (2%)	1 (2%)		1 (2%)
Islets, pancreatic	(48)	(43)	(47)	(44)
Adenoma	1 (2%)			
Histiocytic sarcoma				1 (2%)
Lymphoma malignant	3 (6%)	1 (2%)	3 (6%)	2 (5%)
Parathyroid gland	(32)	(38)	(31)	(40)
Lymphoma malignant		1 (3%)	1 (3%)	
Pituitary gland	(42)	(42)	(40)	(39)
Adenoma, pars distalis	7 (17%)	4 (10%)	5 (13%)	1 (3%)
Lymphoma malignant				2 (5%)
Thyroid gland	(47)	(47)	(47)	(45)
Adenoma, follicular cell	1 (2%)		1 (2%)	2 (4%)
Carcinoma, follicular cell				1 (2%)
Lymphoma malignant	1 (2%)	1 (2%)		
General Body System				
Tissue NOS	(1)	(1)	(1)	(4)
Histiocytic sarcoma				1 (25%)
Lymphoma malignant		1 (100%)		1 (25%)
Lymphoma malignant, abdominal	1 (100%)			1 (25%)
Sarcoma				1 (25%)
Sarcoma, abdominal			1 (100%)	

Table D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Drinking Water Study of Urethane and 0% Ethanol

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
Genital System				
Ovary	(48)	(46)	(46)	(39)
Adenoma, tubular			2 (4%)	1 (3%)
Cystadenoma	2 (4%)		1 (2%)	1 (3%)
Granulosa cell tumor benign			2 (4%)	3 (8%)
Granulosa cell tumor malignant				3 (8%)
Hemangioma	1 (2%)			
Histiocytic sarcoma	1 (2%)	1 (2%)	3 (7%)	
Luteoma		1 (2%)		
Lymphoma malignant	4 (8%)	3 (7%)	3 (7%)	8 (21%)
Uterus	(48)	(47)	(48)	(46)
Adenoma, endometrium		1 (2%)		1 (2%)
Hemangioma		1 (2%)	2 (4%)	
Hemangiosarcoma				2 (4%)
Histiocytic sarcoma	1 (2%)	1 (2%)	3 (6%)	2 (4%)
Leiomyosarcoma			1 (2%)	
Lymphoma malignant	2 (4%)	2 (4%)		3 (7%)
Polyp stromal			1 (2%)	1 (2%)
Sarcoma			1 (2%)	1 (2%)
Sarcoma stromal	1 (2%)		1 (2%)	
Vagina	(48)	(47)	(46)	(43)
Basosquamous tumor benign		1 (2%)		
Leiomyosarcoma, metastatic, uterus			1 (2%)	
Lymphoma malignant	3 (6%)	2 (4%)		4 (9%)
Sarcoma, metastatic, skin	1 (2%)			
Sarcoma, metastatic, uterus			1 (2%)	
Squamous cell carcinoma				1 (2%)
Squamous cell papilloma				1 (2%)
Hematopoietic System				
Bone marrow	(48)	(47)	(46)	(47)
Histiocytic sarcoma			1 (2%)	
Lymphoma malignant			1 (2%)	1 (2%)
Lymph node	(48)	(47)	(47)	(46)
Histiocytic sarcoma, iliac			1 (2%)	
Histiocytic sarcoma, inguinal			1 (2%)	
Histiocytic sarcoma, lumbar			1 (2%)	1 (2%)
Histiocytic sarcoma, renal				1 (2%)
Leiomyosarcoma, metastatic, renal, uterus			1 (2%)	
Lymphangioma, renal				1 (2%)
Lymphoma malignant, axillary	2 (4%)	1 (2%)		
Lymphoma malignant, inguinal		1 (2%)		
Lymphoma malignant, lumbar	3 (6%)	3 (6%)	3 (6%)	5 (11%)
Lymphoma malignant, pancreatic	1 (2%)	1 (2%)		
Lymphoma malignant, renal	4 (8%)	1 (2%)	2 (4%)	3 (7%)
Lymphoma malignant, thoracic	1 (2%)	2 (4%)	1 (2%)	2 (4%)
Lymph node, mandibular	(45)	(47)	(45)	(42)
Adenocarcinoma, metastatic, uncertain primary site				1 (2%)
Histiocytic sarcoma		1 (2%)	1 (2%)	1 (2%)
Lymphoma malignant	9 (20%)	4 (9%)	5 (11%)	11 (26%)

Table D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Drinking Water Study of Urethane and 0% Ethanol

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
Hematopoietic System (continued)				
Lymph node, mesenteric	(47)	(45)	(42)	(39)
Histiocytic sarcoma		2 (4%)	2 (5%)	3 (8%)
Leiomyosarcoma, metastatic, uterus			1 (2%)	
Lymphoma malignant	13 (28%)	6 (13%)	7 (17%)	11 (28%)
Sarcoma		1 (2%)		
Sarcoma, metastatic, uncertain primary site				1 (3%)
Spleen	(48)	(45)	(47)	(46)
Hemangiosarcoma			1 (2%)	4 (9%)
Histiocytic sarcoma			2 (4%)	2 (4%)
Leiomyosarcoma, metastatic, uterus			1 (2%)	
Lymphoma malignant	15 (31%)	4 (9%)	7 (15%)	13 (28%)
Sarcoma, metastatic, lymph node		1 (2%)		
Sarcoma, metastatic, skin				1 (2%)
Thymus	(40)	(37)	(32)	(38)
Alveolar/bronchiolar carcinoma, metastatic, lung				4 (11%)
Histiocytic sarcoma		1 (3%)	3 (9%)	1 (3%)
Leiomyosarcoma, metastatic, uterus			1 (3%)	
Lymphoma malignant	10 (25%)	3 (8%)	7 (22%)	10 (26%)
Sarcoma, metastatic, skin				1 (3%)
Sarcoma, metastatic, uncertain primary site				1 (3%)
Integumentary System				
Mammary gland	(47)	(46)	(46)	(48)
Adenoacanthoma		1 (2%)	1 (2%)	11 (23%)
Adenocarcinoma	4 (9%)	3 (7%)	3 (7%)	11 (23%)
Adenoma			2 (4%)	1 (2%)
Basosquamous tumor malignant			1 (2%)	
Fibroadenoma				1 (2%)
Lymphoma malignant	1 (2%)			1 (2%)
Sarcoma, metastatic, skin				1 (2%)
Skin	(48)	(48)	(46)	(48)
Basal cell carcinoma			1 (2%)	1 (2%)
Basosquamous tumor malignant			1 (2%)	
Fibrous histiocytoma		1 (2%)		
Hemangiosarcoma				2 (4%)
Lymphoma malignant		1 (2%)		3 (6%)
Papilloma		1 (2%)		
Sarcoma	4 (8%)	3 (6%)		6 (13%)
Musculoskeletal System				
Bone	(48)	(48)	(48)	(48)
Lymphoma malignant, sternum	1 (2%)			
Osteosarcoma, right, rib				1 (2%)
Sarcoma, metastatic, sternum, skin				1 (2%)
Sarcoma, sternum				1 (2%)
Bone, femur	(48)	(48)	(48)	(48)
Hemangioma				1 (2%)
Lymphoma malignant				1 (2%)

Table D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Drinking Water Study of Urethane and 0% Ethanol

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
Musculoskeletal System (continued)				
Skeletal muscle	(48)	(48)	(48)	(48)
Alveolar/bronchiolar carcinoma, metastatic, lung				1 (2%)
Hemangiosarcoma			1 (2%)	
Lymphoma malignant	1 (2%)	2 (4%)		3 (6%)
Rhabdomyosarcoma		1 (2%)		
Sarcoma, metastatic, diaphragm, skin				1 (2%)
Sarcoma, metastatic, skin	1 (2%)			
Sarcoma, metastatic, uncertain primary site				1 (2%)
Nervous System				
Brain, cerebrum	(48)	(48)	(48)	(48)
Lymphoma malignant				1 (2%)
Respiratory System				
Larynx	(48)	(46)	(46)	(45)
Lymphoma malignant		1 (2%)		
Lung	(48)	(48)	(48)	(47)
Adenoacanthoma, metastatic, mammary gland		1 (2%)		5 (11%)
Alveolar/bronchiolar adenoma	4 (8%)	6 (13%)	13 (27%)	12 (26%)
Alveolar/bronchiolar adenoma, multiple			4 (8%)	17 (36%)
Alveolar/bronchiolar carcinoma	2 (4%)	4 (8%)	10 (21%)	6 (13%)
Alveolar/bronchiolar carcinoma, multiple			3 (6%)	13 (28%)
Basal cell carcinoma, metastatic, skin			1 (2%)	
Basosquamous tumor malignant, metastatic, mammary gland			1 (2%)	
Basosquamous tumor malignant, metastatic, Zymbal's gland				1 (2%)
Carcinoma, metastatic, harderian gland				1 (2%)
Carcinoma, metastatic, mammary gland				1 (2%)
Granulosa cell tumor malignant, metastatic, ovary				1 (2%)
Hemangiosarcoma				1 (2%)
Hepatocellular carcinoma, metastatic, liver				1 (2%)
Histiocytic sarcoma		1 (2%)	3 (6%)	1 (2%)
Lymphoma malignant	8 (17%)	3 (6%)	4 (8%)	8 (17%)
Special Senses System				
Harderian gland	(48)	(48)	(48)	(48)
Adenoma	3 (6%)	10 (21%)	8 (17%)	20 (42%)
Adenoma, bilateral				1 (2%)
Carcinoma		1 (2%)	11 (23%)	7 (15%)
Carcinoma, bilateral				4 (8%)
Lymphoma malignant		2 (4%)		1 (2%)
Lacrimal gland	(45)	(47)	(43)	(40)
Lymphoma malignant	4 (9%)	2 (4%)	3 (7%)	1 (3%)
Zymbal's gland	(46)	(43)	(46)	(46)
Basosquamous tumor malignant				1 (2%)
Lymphoma malignant		1 (2%)		1 (2%)

Table D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Drinking Water Study of Urethane and 0% Ethanol

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
Urinary System				
Kidney	(48)	(48)	(48)	(48)
Histiocytic sarcoma			2 (4%)	1 (2%)
Lymphoma malignant	6 (13%)	2 (4%)	2 (4%)	8 (17%)
Sarcoma				1 (2%)
Sarcoma, metastatic, skin				2 (4%)
Urinary bladder	(48)	(46)	(45)	(41)
Leiomyosarcoma, metastatic, uterus			1 (2%)	
Lymphoma malignant	2 (4%)	1 (2%)	1 (2%)	5 (12%)
Neoplasm Summary				
Total animals with primary neoplasms[b]	37	35	45	47
Total primary neoplasms	173	135	203	348
Total animals with benign neoplasms	22	26	38	42
Total benign neoplasms	27	39	65	88
Total animals with malignant neoplasms	26	20	37	46
Total malignant neoplasms	146	96	138	260
Total animals with metastatic neoplasms	1	2	4	20
Total metastatic neoplasms	2	2	17	35

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

Table D2a
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Drinking Water Study of Urethane and 0% Ethanol

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
Adrenal Cortex: Adenoma or Hemangiosarcoma				
Overall rate[a]	1/48 (2.1%)	0/45 (0.0%)	2/45 (4.4%)	3/47 (6.4%)
Adjusted rate[b]	1/45.6 (2.2%)	0/41.3 (0.0%)	2/37.5 (5.3%)	3/28.9 (10.4%)
Terminal rate[c]	0/38 (0.0%)	0/35 (0.0%)	1/25 (4.0%)	0/1 (0.0%)
First incidence (days)	642	—[e]	678	676
Poly-3 test[d]	P=0.046	P=0.520N	P=0.432	P=0.169
Harderian Gland: Adenoma				
Overall rate	3/48 (6.3%)	10/48 (20.8%)	8/48 (16.7%)	21/48 (43.8%)
Adjusted rate	3/45.3 (6.6%)	10/45.0 (22.2%)	8/41.1 (19.5%)	21/36.1 (58.2%)
Terminal rate	2/38 (5.3%)	7/37 (18.9%)	4/27 (14.8%)	0/1 (0.0%)
First incidence (days)	747	648	554	466
Poly-3 test	P=0.001	P=0.033	P=0.070	P=0.001
Harderian Gland: Carcinoma				
Overall rate	0/48 (0.0%)	1/48 (2.1%)	11/48 (22.9%)	11/48 (22.9%)
Adjusted rate	0/45.2 (0.0%)	1/44.2 (2.3%)	11/40.7 (27.0%)	11/32.0 (34.3%)
Terminal rate	0/38 (0.0%)	1/37 (2.7%)	7/27 (25.9%)	1/1 (100.0%)
First incidence (days)	—	765 (T)	616	548
Poly-3 test	P=0.001	P=0.495	P=0.001	P=0.001
Harderian Gland: Adenoma or Carcinoma				
Overall rate	3/48 (6.3%)	11/48 (22.9%)	19/48 (39.6%)	30/48 (62.5%)
Adjusted rate	3/45.3 (6.6%)	11/45.0 (24.4%)	19/42.3 (45.0%)	30/39.0 (76.8%)
Terminal rate	2/38 (5.3%)	8/37 (21.6%)	11/27 (40.7%)	1/1 (100.0%)
First incidence (days)	747	648	554	466
Poly-3 test	P=0.001	P=0.018	P=0.001	P=0.001
Heart: Histiocytic Sarcoma				
Overall rate	1/48 (2.1%)	0/48 (0.0%)	2/48 (4.2%)	3/48 (6.3%)
Adjusted rate	1/45.7 (2.2%)	0/44.2 (0.0%)	2/39.8 (5.0%)	3/29.4 (10.2%)
Terminal rate	0/38 (0.0%)	0/37 (0.0%)	1/27 (3.7%)	0/1 (0.0%)
First incidence (days)	616	—	678	650
Poly-3 test	P=0.045	P=0.507N	P=0.452	P=0.173
Liver: Hemangiosarcoma				
Overall rate	0/48 (0.0%)	0/47 (0.0%)	1/47 (2.1%)	7/47 (14.9%)
Adjusted rate	0/45.2 (0.0%)	0/43.3 (0.0%)	1/39.2 (2.6%)	7/30.3 (23.1%)
Terminal rate	0/38 (0.0%)	0/37 (0.0%)	1/27 (3.7%)	0/1 (0.0%)
First incidence (days)	—	—	765 (T)	551
Poly-3 test	P=0.001	—[f]	P=0.471	P=0.001
Liver: Hemangioma or Hemangiosarcoma				
Overall rate	0/48 (0.0%)	0/47 (0.0%)	1/47 (2.1%)	7/47 (14.9%)
Adjusted rate	0/45.2 (0.0%)	0/43.3 (0.0%)	1/39.2 (2.6%)	7/30.3 (23.1%)
Terminal rate	0/38 (0.0%)	0/37 (0.0%)	1/27 (3.7%)	0/1 (0.0%)
First incidence (days)	—	—	765 (T)	551
Poly-3 test	P=0.001	—	P=0.471	P=0.001
Liver: Histiocytic Sarcoma				
Overall rate	1/48 (2.1%)	2/47 (4.3%)	3/47 (6.4%)	3/47 (6.4%)
Adjusted rate	1/45.7 (2.2%)	2/44.2 (4.5%)	3/39.5 (7.6%)	3/29.0 (10.3%)
Terminal rate	0/38 (0.0%)	0/37 (0.0%)	1/27 (3.7%)	0/1 (0.0%)
First incidence (days)	616	594	678	650
Poly-3 test	P=0.120	P=0.489	P=0.255	P=0.169

Table D2a
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Drinking Water Study of Urethane and 0% Ethanol

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
Liver: Hepatocellular Adenoma				
Overall rate	5/48 (10.4%)	10/47 (21.3%)	19/47 (40.4%)	18/47 (38.3%)
Adjusted rate	5/45.2 (11.1%)	10/43.6 (22.9%)	19/39.7 (47.8%)	18/33.4 (54.0%)
Terminal rate	5/38 (13.2%)	9/37 (24.3%)	16/27 (59.3%)	0/1 (0.0%)
First incidence (days)	765 (T)	684	696	590
Poly-3 test	P=0.001	P=0.112	P=0.001	P=0.001
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rate	5/48 (10.4%)	11/47 (23.4%)	20/47 (42.6%)	19/47 (40.4%)
Adjusted rate	5/45.2 (11.1%)	11/43.7 (25.2%)	20/39.7 (50.3%)	19/33.7 (56.4%)
Terminal rate	5/38 (13.2%)	9/37 (24.3%)	17/27 (63.0%)	0/1 (0.0%)
First incidence (days)	765 (T)	684	696	590
Poly-3 test	P=0.001	P=0.071	P=0.001	P=0.001
Lung: Histiocytic Sarcoma				
Overall rate	0/48 (0.0%)	1/48 (2.1%)	3/48 (6.3%)	1/47 (2.1%)
Adjusted rate	0/45.2 (0.0%)	1/44.7 (2.2%)	3/39.9 (7.5%)	1/28.5 (3.5%)
Terminal rate	0/38 (0.0%)	0/37 (0.0%)	1/27 (3.7%)	0/1 (0.0%)
First incidence (days)	—	594	678	650
Poly-3 test	P=0.267	P=0.498	P=0.097	P=0.412
Lung: Alveolar/bronchiolar Adenoma				
Overall rate	4/48 (8.3%)	6/48 (12.5%)	17/48 (35.4%)	29/47 (61.7%)
Adjusted rate	4/45.2 (8.8%)	6/44.3 (13.5%)	17/42.4 (40.1%)	29/38.8 (74.8%)
Terminal rate	4/38 (10.5%)	5/37 (13.5%)	9/27 (33.3%)	1/1 (100.0%)
First incidence (days)	765 (T)	741	438	391
Poly-3 test	P=0.001	P=0.356	P=0.001	P=0.001
Lung: Alveolar/bronchiolar Carcinoma				
Overall rate	2/48 (4.2%)	4/48 (8.3%)	13/48 (27.1%)	19/47 (40.4%)
Adjusted rate	2/45.6 (4.4%)	4/44.4 (9.0%)	13/40.5 (32.1%)	19/32.9 (57.8%)
Terminal rate	1/38 (2.6%)	2/37 (5.4%)	9/27 (33.3%)	1/1 (100.0%)
First incidence (days)	642	741	635	548
Poly-3 test	P=0.001	P=0.324	P=0.001	P=0.001
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rate	6/48 (12.5%)	8/48 (16.7%)	28/48 (58.3%)	39/47 (83.0%)
Adjusted rate	6/45.6 (13.1%)	8/44.4 (18.0%)	28/43.3 (64.6%)	39/41.9 (93.2%)
Terminal rate	5/38 (13.2%)	6/37 (16.2%)	16/27 (59.3%)	1/1 (100.0%)
First incidence (days)	642	741	438	391
Poly-3 test	P=0.001	P=0.365	P=0.001	P=0.001
Lymph Node (Mesenteric): Histiocytic Sarcoma				
Overall rate	0/47 (0.0%)	2/45 (4.4%)	2/42 (4.8%)	3/39 (7.7%)
Adjusted rate	0/44.3 (0.0%)	2/43.0 (4.7%)	2/36.3 (5.5%)	3/24.7 (12.1%)
Terminal rate	0/38 (0.0%)	0/36 (0.0%)	0/25 (0.0%)	0/1 (0.0%)
First incidence (days)	—	594	678	650
Poly-3 test	P=0.043	P=0.230	P=0.195	P=0.045
Mammary Gland: Adenoacanthoma				
Overall rate	0/47 (0.0%)	1/46 (2.2%)	1/46 (2.2%)	11/48 (22.9%)
Adjusted rate	0/44.2 (0.0%)	1/42.6 (2.3%)	1/39.2 (2.6%)	11/32.6 (33.8%)
Terminal rate	0/37 (0.0%)	0/36 (0.0%)	0/27 (0.0%)	0/1 (0.0%)
First incidence (days)	—	684	675	523
Poly-3 test	P=0.001	P=0.492	P=0.476	P=0.001

Table D2a
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Drinking Water Study of Urethane and 0% Ethanol

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
Mammary Gland: Adenocarcinoma				
Overall rate	4/47 (8.5%)	3/46 (6.5%)	3/46 (6.5%)	11/48 (22.9%)
Adjusted rate	4/44.2 (9.0%)	3/42.3 (7.1%)	3/39.3 (7.6%)	11/32.8 (33.6%)
Terminal rate	4/37 (10.8%)	3/36 (8.3%)	1/27 (3.7%)	1/1 (100.0%)
First incidence (days)	765 (T)	765 (T)	696	391
Poly-3 test	P=0.001	P=0.524N	P=0.564N	P=0.007
Mammary Gland: Adenoacanthoma or Adenocarcinoma				
Overall rate	4/47 (8.5%)	4/46 (8.7%)	4/46 (8.7%)	22/48 (45.8%)
Adjusted rate	4/44.2 (9.0%)	4/42.6 (9.4%)	4/39.6 (10.1%)	22/36.6 (60.1%)
Terminal rate	4/37 (10.8%)	3/36 (8.3%)	1/27 (3.7%)	1/1 (100.0%)
First incidence (days)	765 (T)	684	675	391
Poly-3 test	P=0.001	P=0.622	P=0.582	P=0.001
Ovary: Histiocytic Sarcoma				
Overall rate	1/48 (2.1%)	1/46 (2.2%)	3/46 (6.5%)	0/39 (0.0%)
Adjusted rate	1/45.7 (2.2%)	1/42.8 (2.3%)	3/38.8 (7.7%)	0/22.8 (0.0%)
Terminal rate	0/38 (0.0%)	0/36 (0.0%)	1/27 (3.7%)	0/1 (0.0%)
First incidence (days)	616	594	678	—
Poly-3 test	P=0.608N	P=0.746	P=0.249	P=0.628N
Ovary: Benign Granulosa Cell Tumor				
Overall rate	0/48 (0.0%)	0/46 (0.0%)	2/46 (4.3%)	3/39 (7.7%)
Adjusted rate	0/45.2 (0.0%)	0/42.3 (0.0%)	2/38.5 (5.2%)	3/23.8 (12.6%)
Terminal rate	0/38 (0.0%)	0/36 (0.0%)	2/27 (7.4%)	0/1 (0.0%)
First incidence (days)	—	—	765 (T)	576
Poly-3 test	P=0.006	—	P=0.203	P=0.041
Ovary: Malignant Granulosa Cell Tumor				
Overall rate	0/48 (0.0%)	0/46 (0.0%)	0/46 (0.0%)	3/39 (7.7%)
Adjusted rate	0/45.2 (0.0%)	0/42.3 (0.0%)	0/38.5 (0.0%)	3/23.8 (12.6%)
Terminal rate	0/38 (0.0%)	0/36 (0.0%)	0/27 (0.0%)	0/1 (0.0%)
First incidence (days)	—	—	—	635
Poly-3 test	P=0.002	—	—	P=0.040
Ovary: Benign or Malignant Granulosa Cell Tumor				
Overall rate	0/48 (0.0%)	0/46 (0.0%)	2/46 (4.3%)	5/39 (12.8%)
Adjusted rate	0/45.2 (0.0%)	0/42.3 (0.0%)	2/38.5 (5.2%)	5/24.5 (20.4%)
Terminal rate	0/38 (0.0%)	0/36 (0.0%)	2/27 (7.4%)	0/1 (0.0%)
First incidence (days)	—	—	765 (T)	576
Poly-3 test	P=0.001	—	P=0.203	P=0.004
Pituitary Gland (Pars Distalis): Adenoma or Carcinoma				
Overall rate	7/42 (16.7%)	4/42 (9.5%)	5/40 (12.5%)	1/39 (2.6%)
Adjusted rate	7/40.5 (17.3%)	4/38.3 (10.4%)	5/33.8 (14.8%)	1/24.0 (4.2%)
Terminal rate	6/35 (17.1%)	3/31 (9.7%)	4/23 (17.4%)	0/1 (0.0%)
First incidence (days)	642	728	649	678
Poly-3 test	P=0.158N	P=0.291N	P=0.510N	P=0.136N
Skin: Sarcoma				
Overall rate	4/48 (8.3%)	3/48 (6.3%)	0/46 (0.0%)	6/48 (12.5%)
Adjusted rate	4/45.2 (8.8%)	3/44.4 (6.8%)	0/38.8 (0.0%)	6/30.3 (19.8%)
Terminal rate	4/38 (10.5%)	1/37 (2.7%)	0/27 (0.0%)	0/1 (0.0%)
First incidence (days)	765 (T)	728	—	590
Poly-3 test	P=0.090	P=0.510N	P=0.082N	P=0.158

Table D2a
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Drinking Water Study of Urethane and 0% Ethanol

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
Skin: Sarcoma or Fibrous Histiocytoma				
Overall rate	4/48 (8.3%)	4/48 (8.3%)	0/46 (0.0%)	6/48 (12.5%)
Adjusted rate	4/45.2 (8.8%)	4/44.4 (9.0%)	0/38.8 (0.0%)	6/30.3 (19.8%)
Terminal rate	4/38 (10.5%)	2/37 (5.4%)	0/27 (0.0%)	0/1 (0.0%)
First incidence (days)	765 (T)	728	—	590
Poly-3 test	P=0.124	P=0.634	P=0.082N	P=0.158
Spleen: Hemangiosarcoma				
Overall rate	0/48 (0.0%)	0/45 (0.0%)	1/47 (2.1%)	4/46 (8.7%)
Adjusted rate	0/45.2 (0.0%)	0/42.5 (0.0%)	1/39.2 (2.6%)	4/28.2 (14.2%)
Terminal rate	0/38 (0.0%)	0/37 (0.0%)	1/27 (3.7%)	0/1 (0.0%)
First incidence (days)	—	—	765 (T)	605
Poly-3 test	P=0.001	—	P=0.471	P=0.021
Stomach (Forestomach): Squamous Cell Papilloma				
Overall rate	2/48 (4.2%)	3/46 (6.5%)	3/46 (6.5%)	3/46 (6.5%)
Adjusted rate	2/45.2 (4.4%)	3/42.7 (7.0%)	3/39.0 (7.7%)	3/28.6 (10.5%)
Terminal rate	2/38 (5.3%)	3/37 (8.1%)	2/27 (7.4%)	0/1 (0.0%)
First incidence (days)	765 (T)	765 (T)	712	605
Poly-3 test	P=0.260	P=0.474	P=0.433	P=0.305
Stomach (Forestomach): Squamous Cell Papilloma or Squamous Cell Carcinoma				
Overall rate	2/48 (4.2%)	4/46 (8.7%)	3/46 (6.5%)	4/46 (8.7%)
Adjusted rate	2/45.2 (4.4%)	4/42.7 (9.4%)	3/39.0 (7.7%)	4/29.0 (13.8%)
Terminal rate	2/38 (5.3%)	4/37 (10.8%)	2/27 (7.4%)	0/1 (0.0%)
First incidence (days)	765 (T)	765 (T)	712	605
Poly-3 test	P=0.173	P=0.311	P=0.433	P=0.165
Thymus: Histiocytic Sarcoma				
Overall rate	0/40 (0.0%)	1/37 (2.7%)	3/32 (9.4%)	1/38 (2.6%)
Adjusted rate	0/37.6 (0.0%)	1/34.6 (2.9%)	3/26.7 (11.3%)	1/22.7 (4.4%)
Terminal rate	0/31 (0.0%)	0/29 (0.0%)	1/16 (6.3%)	0/1 (0.0%)
First incidence (days)	—	594	678	744
Poly-3 test	P=0.251	P=0.483	P=0.064	P=0.404
Thyroid Gland (Follicular Cell): Adenoma or Carcinoma				
Overall rate	1/47 (2.1%)	0/47 (0.0%)	1/47 (2.1%)	3/45 (6.7%)
Adjusted rate	1/44.2 (2.3%)	0/43.2 (0.0%)	1/39.3 (2.5%)	3/27.9 (10.7%)
Terminal rate	1/37 (2.7%)	0/36 (0.0%)	0/27 (0.0%)	1/1 (100.0%)
First incidence (days)	765 (T)	—	719	466
Poly-3 test	P=0.038	P=0.505N	P=0.734	P=0.167
Uterus: Histiocytic Sarcoma				
Overall rate	1/48 (2.1%)	1/47 (2.1%)	3/48 (6.3%)	2/46 (4.3%)
Adjusted rate	1/45.7 (2.2%)	1/43.7 (2.3%)	3/39.9 (7.5%)	2/28.1 (7.1%)
Terminal rate	0/38 (0.0%)	0/37 (0.0%)	1/27 (3.7%)	0/1 (0.0%)
First incidence (days)	616	643	678	694
Poly-3 test	P=0.193	P=0.751	P=0.258	P=0.341
All Organs: Hemangioma				
Overall rate	1/48 (2.1%)	1/48 (2.1%)	3/48 (6.3%)	1/48 (2.1%)
Adjusted rate	1/45.2 (2.2%)	1/44.2 (2.3%)	3/39.7 (7.6%)	1/28.9 (3.5%)
Terminal rate	1/38 (2.6%)	1/37 (2.7%)	2/27 (7.4%)	0/1 (0.0%)
First incidence (days)	765 (T)	765 (T)	719	725
Poly-3 test	P=0.423	P=0.755	P=0.260	P=0.651

Table D2a
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Drinking Water Study of Urethane and 0% Ethanol

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
All Organs: Hemangiosarcoma				
Overall rate	0/48 (0.0%)	0/48 (0.0%)	4/48 (8.3%)	11/48 (22.9%)
Adjusted rate	0/45.2 (0.0%)	0/44.2 (0.0%)	4/39.5 (10.1%)	11/31.8 (34.6%)
Terminal rate	0/38 (0.0%)	0/37 (0.0%)	4/27 (14.8%)	0/1 (0.0%)
First incidence (days)	—	—	765 (T)	551
Poly-3 test	P=0.001	—	P=0.045	P=0.001
All Organs: Hemangioma or Hemangiosarcoma				
Overall rate	1/48 (2.1%)	1/48 (2.1%)	6/48 (12.5%)	11/48 (22.9%)
Adjusted rate	1/45.2 (2.2%)	1/44.2 (2.3%)	6/39.7 (15.1%)	11/31.8 (34.6%)
Terminal rate	1/38 (2.6%)	1/37 (2.7%)	5/27 (18.5%)	0/1 (0.0%)
First incidence (days)	765 (T)	765 (T)	719	551
Poly-3 test	P=0.001	P=0.755	P=0.037	P=0.001
All Organs: Histiocytic Sarcoma				
Overall rate	1/48 (2.1%)	2/48 (4.2%)	3/48 (6.3%)	3/48 (6.3%)
Adjusted rate	1/45.7 (2.2%)	2/45.1 (4.4%)	3/39.9 (7.5%)	3/29.4 (10.2%)
Terminal rate	0/38 (0.0%)	0/37 (0.0%)	1/27 (3.7%)	0/1 (0.0%)
First incidence (days)	616	594	678	650
Poly-3 test	P=0.121	P=0.496	P=0.258	P=0.173
All Organs: Malignant Lymphoma				
Overall rate	16/48 (33.3%)	6/48 (12.5%)	8/48 (16.7%)	15/48 (31.3%)
Adjusted rate	16/46.0 (34.8%)	6/45.3 (13.2%)	8/42.0 (19.0%)	15/35.1 (42.7%)
Terminal rate	11/38 (28.9%)	3/37 (8.1%)	2/27 (7.4%)	1/1 (100.0%)
First incidence (days)	636	510	549	193
Poly-3 test	P=0.067	P=0.013N	P=0.076N	P=0.308
All Organs: Benign Neoplasms				
Overall rate	22/48 (45.8%)	26/48 (54.2%)	38/48 (79.2%)	42/48 (87.5%)
Adjusted rate	22/45.7 (48.1%)	26/45.1 (57.6%)	38/44.6 (85.2%)	42/44.3 (94.9%)
Terminal rate	20/38 (52.6%)	22/37 (59.5%)	23/27 (85.2%)	1/1 (100.0%)
First incidence (days)	642	648	438	391
Poly-3 test	P=0.001	P=0.241	P=0.001	P=0.001
All Organs: Malignant Neoplasms				
Overall rate	26/48 (54.2%)	20/48 (41.7%)	37/48 (77.1%)	46/48 (95.8%)
Adjusted rate	26/46.9 (55.5%)	20/46.9 (42.7%)	37/46.8 (79.1%)	46/46.8 (98.2%)
Terminal rate	19/38 (50.0%)	11/37 (29.7%)	18/27 (66.7%)	1/1 (100.0%)
First incidence (days)	616	510	438	193
Poly-3 test	P=0.001	P=0.150N	P=0.011	P=0.001

Table D2a
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Drinking Water Study of Urethane and 0% Ethanol

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
All Organs: Benign or Malignant Neoplasms				
Overall rate	37/48 (77.1%)	35/48 (72.9%)	45/48 (93.8%)	47/48 (97.9%)
Adjusted rate	37/46.9 (78.8%)	35/47.3 (74.1%)	45/47.2 (95.4%)	47/47.3 (99.3%)
Terminal rate	29/38 (76.3%)	25/37 (67.6%)	25/27 (92.6%)	1/1 (100.0%)
First incidence (days)	616	510	438	193
Poly-3 test	P=0.001	P=0.381N	P=0.014	P=0.001

(T) Terminal sacrifice
a Number of neoplasm-bearing animals/number of animals with tissue examined microscopically
b Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
c Observed incidence at terminal kill
d Beneath the control incidence (0 ppm urethane) is the P value associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and that exposed group. The Poly-3 test accounts for the differential mortality in animals that do not reach terminal sacrifice. A negative trend or a lower incidence in an exposed group is indicated by **N**.
e Not applicable; no neoplasms in animal group
f Value of statistic cannot be computed.

Table D2b
Statistical Analysis of Primary Neoplasms in Female Mice Exposed to Ethanol and 0 ppm Urethane in Drinking Water for 2 Years

	0% Ethanol	2.5% Ethanol	5% Ethanol
Harderian Gland: Adenoma			
Overall rate[a]	3/48 (6.3%)	2/47 (4.3%)	4/48 (8.3%)
Adjusted rate[b]	3/45.3 (6.6%)	2/44.5 (4.5%)	4/40.8 (9.8%)
Terminal rate[c]	2/38 (5.3%)	2/39 (5.1%)	3/31 (9.7%)
First incidence (days)	747	765 (T)	718
Poly-3 test[d]	P=0.825	P=0.977	P=0.985
Harderian Gland: Adenoma or Carcinoma			
Overall rate	3/48 (6.3%)	3/47 (6.4%)	5/48 (10.4%)
Adjusted rate	3/45.3 (6.6%)	3/44.5 (6.7%)	5/40.8 (12.3%)
Terminal rate	2/38 (5.3%)	3/39 (7.7%)	4/31 (12.9%)
First incidence (days)	747	765 (T)	718
Poly-3 test	P=0.557	P=1.000	P=0.698
Liver: Histiocytic Sarcoma			
Overall rate	1/48 (2.1%)	0/47 (0.0%)	4/48 (8.3%)
Adjusted rate	1/45.7 (2.2%)	0/44.5 (0.0%)	4/41.7 (9.6%)
Terminal rate	0/38 (0.0%)	0/39 (0.0%)	0/31 (0.0%)
First incidence (days)	616	—[e]	515
Poly-3 test	P=0.160	P=0.993	P=0.356
Liver: Hepatocellular Adenoma			
Overall rate	5/48 (10.4%)	6/47 (12.8%)	3/48 (6.3%)
Adjusted rate	5/45.2 (11.1%)	6/44.5 (13.5%)	3/40.6 (7.4%)
Terminal rate	5/38 (13.2%)	6/39 (15.4%)	3/31 (9.7%)
First incidence (days)	765 (T)	765 (T)	765 (T)
Poly-3 test	P=0.628	P=1.000	P=0.730
Liver: Hepatocellular Adenoma or Carcinoma			
Overall rate	5/48 (10.4%)	7/47 (14.9%)	3/48 (6.3%)
Adjusted rate	5/45.2 (11.1%)	7/44.5 (15.7%)	3/40.6 (7.4%)
Terminal rate	5/38 (13.2%)	6/39 (15.4%)	3/31 (9.7%)
First incidence (days)	765 (T)	752	765 (T)
Poly-3 test	P=0.641	P=0.798	P=0.730
Lung: Histiocytic Sarcoma			
Overall rate	0/48 (0.0%)	0/47 (0.0%)	4/48 (8.3%)
Adjusted rate	0/45.2 (0.0%)	0/44.5 (0.0%)	4/41.7 (9.6%)
Terminal rate	0/38 (0.0%)	0/39 (0.0%)	0/31 (0.0%)
First incidence (days)	—	—	515
Poly-3 test	P=0.027	—[f]	P=0.123
Lung: Alveolar/bronchiolar Adenoma			
Overall rate	4/48 (8.3%)	5/47 (10.6%)	5/48 (10.4%)
Adjusted rate	4/45.2 (8.8%)	5/44.5 (11.2%)	5/40.6 (12.3%)
Terminal rate	4/38 (10.5%)	5/39 (12.8%)	5/31 (16.1%)
First incidence (days)	765 (T)	765 (T)	765 (T)
Poly-3 test	P=0.846	P=1.000	P=0.980
Lung: Alveolar/bronchiolar Adenoma or Carcinoma			
Overall rate	6/48 (12.5%)	5/47 (10.6%)	5/48 (10.4%)
Adjusted rate	6/45.6 (13.1%)	5/44.5 (11.2%)	5/40.6 (12.3%)
Terminal rate	5/38 (13.2%)	5/39 (12.8%)	5/31 (16.1%)
First incidence (days)	642	765 (T)	765 (T)
Poly-3 test	P=0.906	P=0.975	P=1.000

Table D2b
Statistical Analysis of Primary Neoplasms in Female Mice Exposed to Ethanol and 0 ppm Urethane in Drinking Water for 2 Years

	0% Ethanol	2.5% Ethanol	5% Ethanol
Lymph Node (Mesenteric): Histiocytic Sarcoma			
Overall rate	0/47 (0.0%)	0/43 (0.0%)	4/45 (8.9%)
Adjusted rate	0/44.3 (0.0%)	0/41.0 (0.0%)	4/38.8 (10.3%)
Terminal rate	0/38 (0.0%)	0/36 (0.0%)	0/29 (0.0%)
First incidence (days)	—	—	515
Poly-3 test	P=0.026	—	P=0.110
Mammary Gland: Adenocarcinoma			
Overall rate	4/47 (8.5%)	4/47 (8.5%)	3/47 (6.4%)
Adjusted rate	4/44.2 (9.0%)	4/44.7 (9.0%)	3/40.2 (7.5%)
Terminal rate	4/37 (10.8%)	2/39 (5.1%)	2/31 (6.5%)
First incidence (days)	765 (T)	718	754
Poly-3 test	P=0.851	P=1.000	P=1.000
Ovary: Histiocytic Sarcoma			
Overall rate	1/48 (2.1%)	0/47 (0.0%)	4/46 (8.7%)
Adjusted rate	1/45.7 (2.2%)	0/44.5 (0.0%)	4/39.9 (10.0%)
Terminal rate	0/38 (0.0%)	0/39 (0.0%)	0/31 (0.0%)
First incidence (days)	616	—	515
Poly-3 test	P=0.147	P=0.993	P=0.332
Pancreas: Histocytic Sarcoma			
Overall rate	0/48 (0.0%)	0/47 (0.0%)	3/47 (6.4%)
Adjusted rate	0/45.2 (0.0%)	0/44.5 (0.0%)	3/40.1 (7.5%)
Terminal rate	0/38 (0.0%)	0/39 (0.0%)	0/31 (0.0%)
First incidence (days)	—	—	706
Poly-3 test	P=0.068	—	P=0.227
Pituitary Gland (Pars Distalis): Adenoma or Carcinoma			
Overall rate	7/42 (16.7%)	7/44 (15.9%)	7/40 (17.5%)
Adjusted rate	7/40.5 (17.3%)	7/42.5 (16.5%)	7/33.8 (20.7%)
Terminal rate	6/35 (17.1%)	5/37 (13.5%)	6/25 (24.0%)
First incidence (days)	642	677	718
Poly-3 test	P=0.972	P=1.000	P=1.000
Skin: Sarcoma			
Overall rate	4/48 (8.3%)	2/47 (4.3%)	3/48 (6.3%)
Adjusted rate	4/45.2 (8.8%)	2/44.5 (4.5%)	3/41.4 (7.2%)
Terminal rate	4/38 (10.5%)	2/39 (5.1%)	0/31 (0.0%)
First incidence (days)	765 (T)	765 (T)	571
Poly-3 test	P=0.832	P=0.650	P=0.997
Spleen: Histiocytic Sarcoma			
Overall rate	0/48 (0.0%)	0/47 (0.0%)	4/48 (8.3%)
Adjusted rate	0/45.2 (0.0%)	0/44.5 (0.0%)	4/41.7 (9.6%)
Terminal rate	0/38 (0.0%)	0/39 (0.0%)	0/31 (0.0%)
First incidence (days)	—	—	515
Poly-3 test	P=0.027	—	P=0.123
Thymus: Histiocytic Sarcoma			
Overall rate	0/40 (0.0%)	0/41 (0.0%)	2/39 (5.1%)
Adjusted rate	0/37.6 (0.0%)	0/39.0 (0.0%)	2/33.1 (6.0%)
Terminal rate	0/31 (0.0%)	0/34 (0.0%)	0/24 (0.0%)
First incidence (days)	—	—	515
Poly-3 test	P=0.181	—	P=0.466

Table D2b
Statistical Analysis of Primary Neoplasms in Female Mice Exposed to Ethanol and 0 ppm Urethane in Drinking Water for 2 Years

	0% Ethanol	2.5% Ethanol	5% Ethanol
Uterus: Histiocytic Sarcoma			
Overall rate	1/48 (2.1%)	0/47 (0.0%)	3/48 (6.3%)
Adjusted rate	1/45.7 (2.2%)	0/44.5 (0.0%)	3/41.5 (7.2%)
Terminal rate	0/38 (0.0%)	0/39 (0.0%)	0/31 (0.0%)
First incidence (days)	616	—	515
Poly-3 test	P=0.351	P=0.993	P=0.606
All Organs: Histiocytic Sarcoma			
Overall rate	1/48 (2.1%)	0/47 (0.0%)	4/48 (8.3%)
Adjusted rate	1/45.7 (2.2%)	0/44.5 (0.0%)	4/41.7 (9.6%)
Terminal rate	0/38 (0.0%)	0/39 (0.0%)	0/31 (0.0%)
First incidence (days)	616	—	515
Poly-3 test	P=0.160	P=0.993	P=0.356
All Organs: Malignant Lymphoma			
Overall rate	16/48 (33.3%)	9/47 (19.1%)	5/48 (10.4%)
Adjusted rate	16/46.0 (34.8%)	9/44.8 (20.1%)	5/40.8 (12.2%)
Terminal rate	11/38 (28.9%)	7/39 (17.9%)	3/31 (9.7%)
First incidence (days)	636	677	718
Poly-3 test	P=0.008	P=0.143	P=0.012
All Organs: Benign Neoplasms			
Overall rate	22/48 (45.8%)	21/47 (44.7%)	22/48 (45.8%)
Adjusted rate	22/45.7 (48.1%)	21/45.0 (46.7%)	22/41.1 (53.5%)
Terminal rate	20/38 (52.6%)	18/39 (46.2%)	18/31 (58.1%)
First incidence (days)	642	677	718
Poly-3 test	P=1.000	P=0.904	P=1.000
All Organs: Malignant Neoplasms			
Overall rate	26/48 (54.2%)	14/47 (29.8%)	17/48 (35.4%)
Adjusted rate	26/46.9 (55.5%)	14/45.0 (31.1%)	17/43.1 (39.5%)
Terminal rate	19/38 (50.0%)	10/39 (25.6%)	8/31 (25.8%)
First incidence (days)	616	677	515
Poly-3 test	P=0.069	P=0.018	P=0.091
All Organs: Benign or Malignant Neoplasms			
Overall rate	37/48 (77.1%)	29/47 (61.7%)	32/48 (66.7%)
Adjusted rate	37/46.9 (78.8%)	29/45.0 (64.4%)	32/43.3 (73.8%)
Terminal rate	29/38 (76.3%)	25/39 (64.1%)	21/31 (67.7%)
First incidence (days)	616	677	515
Poly-3 test	P=0.290	P=0.107	P=0.320

(T) Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals with tissue examined microscopically
[b] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] P values are two sided. Beneath the control incidence (0% ethanol) is the P value associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and that exposed group. The Poly-3 test accounts for the differential mortality in animals that do not reach terminal sacrifice.
[e] Not applicable; no neoplasms in animal group
[f] Value of statistic cannot be computed.

Table D2c
Statistical Analysis of Primary Neoplasms in Female Mice Exposed to Ethanol and 10 ppm Urethane in Drinking Water for 2 Years

	0% Ethanol	2.5% Ethanol	5% Ethanol
Harderian Gland: Adenoma			
Overall rate[a]	10/48 (20.8%)	3/47 (6.4%)	7/48 (14.6%)
Adjusted rate[b]	10/45.0 (22.2%)	3/42.5 (7.1%)	7/42.0 (16.7%)
Terminal rate[c]	7/37 (18.9%)	3/33 (9.1%)	5/32 (15.6%)
First incidence (days)	648	765 (T)	721
Poly-3 test[d]	P=0.522	P=0.085	P=0.703
Harderian Gland: Carcinoma			
Overall rate	1/48 (2.1%)	3/47 (6.4%)	11/48 (22.9%)
Adjusted rate	1/44.2 (2.3%)	3/42.5 (7.1%)	11/41.9 (26.2%)
Terminal rate	1/37 (2.7%)	3/33 (9.1%)	10/32 (31.3%)
First incidence (days)	765 (T)	765 (T)	738
Poly-3 test	P=0.001	P=0.585	P=0.002
Harderian Gland: Adenoma or Carcinoma			
Overall rate	11/48 (22.9%)	5/47 (10.6%)	18/48 (37.5%)
Adjusted rate	11/45.0 (24.4%)	5/42.5 (14.8%)	18/42.1 (42.7%)
Terminal rate	8/37 (21.6%)	5/33 (15.2%)	15/32 (46.9%)
First incidence (days)	648	765 (T)	721
Poly-3 test	P=0.076	P=0.203	P=0.108
Liver: Hepatocellular Adenoma			
Overall rate	10/47 (21.3%)	5/47 (10.6%)	6/47 (12.8%)
Adjusted rate	10/43.6 (22.9%)	5/42.5 (11.8%)	6/41.2 (14.6%)
Terminal rate	9/37 (24.3%)	5/33 (15.2%)	4/32 (12.5%)
First incidence (days)	684	765 (T)	738
Poly-3 test	P=0.356	P=0.273	P=0.478
Liver: Hepatocellular Adenoma or Carcinoma			
Overall rate	11/47 (23.4%)	5/47 (10.6%)	7/47 (14.9%)
Adjusted rate	11/43.7 (25.2%)	5/42.5 (11.8%)	7/41.2 (17.0%)
Terminal rate	9/37 (24.3%)	5/33 (15.2%)	5/32 (15.6%)
First incidence (days)	684	765 (T)	738
Poly-3 test	P=0.377	P=0.179	P=0.510
Lung: Alveolar/bronchiolar Adenoma			
Overall rate	6/48 (12.5%)	10/47 (21.3%)	10/48 (20.8%)
Adjusted rate	6/44.3 (13.5%)	10/43.6 (22.9%)	10/42.1 (23.8%)
Terminal rate	5/37 (13.5%)	6/33 (18.2%)	7/32 (21.9%)
First incidence (days)	741	611	721
Poly-3 test	P=0.289	P=0.391	P=0.344
Lung: Alveolar/bronchiolar Carcinoma			
Overall rate	4/48 (8.3%)	2/47 (4.3%)	7/48 (14.6%)
Adjusted rate	4/44.4 (9.0%)	2/42.5 (4.7%)	7/42.1 (16.6%)
Terminal rate	2/37 (5.4%)	2/33 (6.1%)	5/32 (15.6%)
First incidence (days)	741	765 (T)	703
Poly-3 test	P=0.341	P=0.710	P=0.460
Lung: Alveolar/bronchiolar Adenoma or Carcinoma			
Overall rate	8/48 (16.7%)	11/47 (23.4%)	17/48 (35.4%)
Adjusted rate	8/44.4 (18.0%)	10/43.6 (25.2%)	17/42.3 (40.2%)
Terminal rate	6/37 (16.2%)	7/33 (21.2%)	12/32 (37.5%)
First incidence (days)	741	611	703
Poly-3 test	P=0.028	P=0.580	P=0.037

Table D2c
Statistical Analysis of Primary Neoplasms in Female Mice Exposed to Ethanol and 10 ppm Urethane in Drinking Water for 2 Years

	0% Ethanol	2.5% Ethanol	5% Ethanol
Lymph Node (Mandibular): Histiocytic Sarcoma			
Overall rate	1/47 (2.1%)	2/44 (4.5%)	0/46 (0.0%)
Adjusted rate	1/43.8 (2.3%)	2/41.1 (4.9%)	0/40.0 (0.0%)
Terminal rate	0/37 (0.0%)	1/33 (3.0%)	0/31 (0.0%)
First incidence (days)	594	698	—[e]
Poly-3 test	P=0.802	P=0.958	P=1.000
Mammary Gland: Adenocarcinoma			
Overall rate	3/46 (6.5%)	3/45 (6.7%)	4/48 (8.3%)
Adjusted rate	3/42.3 (7.1%)	3/41.0 (7.3%)	4/42.2 (9.5%)
Terminal rate	3/36 (8.3%)	3/32 (9.4%)	3/32 (9.4%)
First incidence (days)	765 (T)	765 (T)	644
Poly-3 test	P=0.846	P=1.000	P=0.998
Mammary Gland: Adenoacanthoma or Adenocarcinoma			
Overall rate	4/46 (8.7%)	3/45 (6.7%)	4/48 (8.3%)
Adjusted rate	4/42.6 (9.4%)	3/41.0 (7.3%)	4/42.2 (9.5%)
Terminal rate	3/36 (8.3%)	3/32 (9.4%)	3/32 (9.4%)
First incidence (days)	684	765 (T)	644
Poly-3 test	P=1.000	P=1.000	P=1.000
Pituitary Gland (Pars Distalis): Adenoma			
Overall rate	4/42 (9.5%)	2/41 (4.9%)	6/41 (14.6%)
Adjusted rate	4/38.3 (10.4%)	2/37.3 (5.4%)	6/35.5 (16.9%)
Terminal rate	3/31 (9.7%)	2/30 (6.7%)	6/27 (22.2%)
First incidence (days)	728	765 (T)	765 (T)
Poly-3 test	P=0.517	P=0.695	P=0.640
Skin: Sarcoma			
Overall rate	3/48 (6.3%)	1/47 (2.1%)	7/48 (14.6%)
Adjusted rate	3/44.4 (6.8%)	1/42.5 (2.4%)	7/42.2 (16.6%)
Terminal rate	1/37 (2.7%)	1/33 (3.0%)	3/32 (9.4%)
First incidence (days)	728	765 (T)	721
Poly-3 test	P=0.160	P=0.639	P=0.272
Skin: Fibrous Histiocytoma or Sarcoma			
Overall rate	4/48 (8.3%)	1/47 (2.1%)	7/48 (14.6%)
Adjusted rate	4/44.4 (9.0%)	1/42.5 (2.4%)	7/42.2 (16.6%)
Terminal rate	2/37 (5.4%)	1/33 (3.0%)	3/32 (9.4%)
First incidence (days)	728	765 (T)	721
Poly-3 test	P=0.329	P=0.381	P=0.462
Stomach (Forestomach): Squamous Cell Papilloma			
Overall rate	3/46 (6.5%)	4/46 (8.7%)	3/47 (6.4%)
Adjusted rate	3/42.7 (7.0%)	4/42.1 (9.5%)	3/41.1 (7.3%)
Terminal rate	3/37 (8.1%)	3/33 (9.1%)	3/32 (9.4%)
First incidence (days)	765 (T)	736	765 (T)
Poly-3 test	P=1.000	P=0.989	P=1.000

Table D2c
Statistical Analysis of Primary Neoplasms in Female Mice Exposed to Ethanol and 10 ppm Urethane in Drinking Water for 2 Years

	0% Ethanol	2.5% Ethanol	5% Ethanol
Stomach (Forestomach): Squamous Cell Papilloma or Squamous Cell Carcinoma			
Overall rate	4/46 (8.7%)	4/46 (8.7%)	3/47 (6.4%)
Adjusted rate	4/42.7 (9.4%)	4/42.1 (9.5%)	3/41.1 (7.3%)
Terminal rate	4/37 (10.8%)	3/33 (9.1%)	3/32 (9.4%)
First incidence (days)	765 (T)	736	765 (T)
Poly-3 test	P=0.898	P=1.000	P=1.000
Uterus: Hemangioma or Hemangiosarcoma			
Overall rate	1/47 (2.1%)	0/47 (0.0%)	3/48 (6.3%)
Adjusted rate	1/43.3 (2.3%)	0/42.5 (0.0%)	3/41.9 (7.2%)
Terminal rate	1/37 (2.7%)	0/33 (0.0%)	2/32 (6.3%)
First incidence (days)	765 (T)	—	754
Poly-3 test	P=0.352	P=1.000	P=0.586
All Organs: Hemangiosarcoma			
Overall rate	0/48 (0.0%)	2/47 (4.3%)	3/48 (6.3%)
Adjusted rate	0/44.2 (0.0%)	2/42.5 (4.7%)	3/41.9 (7.2%)
Terminal rate	0/37 (0.0%)	2/33 (6.1%)	2/32 (6.3%)
First incidence (days)	—	765 (T)	754
Poly-3 test	P=0.150	P=0.458	P=0.218
All Organs: Hemangioma or Hemangiosarcoma			
Overall rate	1/48 (2.1%)	3/47 (6.4%)	4/48 (8.3%)
Adjusted rate	1/44.2 (2.3%)	3/42.5 (7.1%)	4/41.9 (9.6%)
Terminal rate	1/37 (2.7%)	3/33 (9.1%)	3/32 (9.4%)
First incidence (days)	765 (T)	765 (T)	754
Poly-3 test	P=0.240	P=0.585	P=0.324
All Organs: Malignant Lymphoma			
Overall rate	6/48 (12.5%)	10/47 (21.3%)	6/48 (12.5%)
Adjusted rate	6/45.3 (13.2%)	10/43.6 (22.9%)	6/42.8 (14.0%)
Terminal rate	3/37 (8.1%)	7/33 (21.2%)	4/32 (12.5%)
First incidence (days)	510	611	553
Poly-3 test	P=1.000	P=0.366	P=1.000
All Organs: Benign Neoplasms			
Overall rate	26/48 (54.2%)	21/47 (44.7%)	26/48 (54.2%)
Adjusted rate	26/45.1 (57.6%)	21/44.4 (47.3%)	26/42.6 (61.1%)
Terminal rate	22/37 (59.5%)	15/33 (45.5%)	20/32 (62.5%)
First incidence (days)	648	529	662
Poly-3 test	P=0.867	P=0.431	P=0.913
All Organs: Malignant Neoplasms			
Overall rate	20/48 (41.7%)	22/47 (46.8%)	35/48 (72.9%)
Adjusted rate	20/46.9 (42.7%)	22/44.4 (49.6%)	35/44.8 (78.2%)
Terminal rate	11/37 (29.7%)	16/33 (48.5%)	24/32 (75.0%)
First incidence (days)	510	611	531
Poly-3 test	P=0.001	P=0.666	P=0.001

Table D2c
Statistical Analysis of Primary Neoplasms in Female Mice Exposed to Ethanol and 10 ppm Urethane in Drinking Water for 2 Years

	0% Ethanol	2.5% Ethanol	5% Ethanol
All Organs: Benign or Malignant Neoplasms			
Overall rate	35/48 (72.9%)	33/47 (70.2%)	43/48 (89.6%)
Adjusted rate	35/47.3 (74.1%)	33/45.2 (73.0%)	43/45.1 (95.2%)
Terminal rate	25/37 (67.6%)	24/33 (72.7%)	30/32 (93.8%)
First incidence (days)	510	529	531
Poly-3 test	P=0.013	P=1.000	P=0.009

(T) Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals with tissue examined microscopically
[b] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] P values are two sided. Beneath the control incidence (0% ethanol) is the P value associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and that exposed group. The Poly-3 test accounts for the differential mortality in animals that do not reach terminal sacrifice.
[e] Not applicable; no neoplasms in animal group

Table D2d
Statistical Analysis of Primary Neoplasms in Female Mice Exposed to Ethanol and 30 ppm Urethane in Drinking Water for 2 Years

	0% Ethanol	2.5% Ethanol	5% Ethanol
Adrenal Cortex: Adenoma			
Overall rate[a]	1/45 (2.2%)	0/46 (0.0%)	3/47 (6.4%)
Adjusted rate[b]	1/37.2 (2.7%)	0/34.4 (0.0%)	3/39.6 (7.6%)
Terminal rate[c]	1/25 (4.0%)	0/18 (0.0%)	3/27 (11.1%)
First incidence (days)	765 (T)	—[e]	765 (T)
Poly-3 test[d]	P=0.375	P=1.000	P=0.655
Harderian Gland: Adenoma			
Overall rate	8/48 (16.7%)	9/46 (19.6%)	6/46 (13.0%)
Adjusted rate	8/41.1 (19.5%)	9/36.3 (24.8%)	6/39.5 (15.2%)
Terminal rate	4/27 (14.8%)	3/19 (15.8%)	3/26 (11.5%)
First incidence (days)	554	594	663
Poly-3 test	P=0.736	P=0.770	P=0.833
Harderian Gland: Carcinoma			
Overall rate	11/48 (22.9%)	6/46 (13.0%)	7/46 (15.2%)
Adjusted rate	11/40.7 (27.0%)	6/35.6 (16.8%)	7/38.8 (18.0%)
Terminal rate	7/27 (25.9%)	4/19 (21.1%)	7/26 (26.9%)
First incidence (days)	616	584	765 (T)
Poly-3 test	P=0.380	P=0.424	P=0.487
Harderian Gland: Adenoma or Carcinoma			
Overall rate	19/48 (39.6%)	15/46 (32.6%)	13/46 (28.3%)
Adjusted rate	19/42.3 (45.0%)	15/37.1 (40.4%)	13/39.5 (32.9%)
Terminal rate	11/27 (40.7%)	7/19 (36.8%)	10/26 (38.5%)
First incidence (days)	554	584	663
Poly-3 test	P=0.304	P=0.855	P=0.366
Liver: Histiocytic Sarcoma			
Overall rate	3/47 (6.4%)	2/47 (4.3%)	3/48 (6.3%)
Adjusted rate	3/39.5 (7.6%)	2/36.0 (5.5%)	3/41.0 (7.3%)
Terminal rate	1/27 (3.7%)	0/19 (0.0%)	0/27 (0.0%)
First incidence (days)	678	607	687
Poly-3 test	P=1.000	P=1.000	P=1.000
Liver: Hepatocellular Adenoma			
Overall rate	19/47 (40.4%)	15/47 (31.9%)	16/48 (33.3%)
Adjusted rate	19/39.7 (47.8%)	15/36.2 (41.4%)	16/41.1 (38.9%)
Terminal rate	16/27 (59.3%)	13/19 (68.4%)	12/27 (44.4%)
First incidence (days)	696	600	685
Poly-3 test	P=0.469	P=0.735	P=0.551
Liver: Hepatocellular Carcinoma			
Overall rate	2/47 (4.3%)	3/47 (6.4%)	0/48 (0.0%)
Adjusted rate	2/39.2 (5.1%)	3/36.0 (8.3%)	0/40.6 (0.0%)
Terminal rate	2/27 (7.4%)	2/19 (10.5%)	0/27 (0.0%)
First incidence (days)	765 (T)	584	—
Poly-3 test	P=0.380	P=0.922	P=0.458
Liver: Hepatocellular Adenoma or Carcinoma			
Overall rate	20/47 (42.6%)	16/47 (34.0%)	16/48 (33.3%)
Adjusted rate	20/39.7 (50.3%)	16/36.8 (43.5%)	16/41.1 (38.9%)
Terminal rate	17/27 (63.0%)	13/19 (68.4%)	12/27 (44.4%)
First incidence (days)	696	584	685
Poly-3 test	P=0.337	P=0.704	P=0.406

Table D2d
Statistical Analysis of Primary Neoplasms in Female Mice Exposed to Ethanol and 30 ppm Urethane in Drinking Water for 2 Years

	0% Ethanol	2.5% Ethanol	5% Ethanol
Lung: Histiocytic Sarcoma			
Overall rate	3/48 (6.3%)	1/48 (2.1%)	3/48 (6.3%)
Adjusted rate	3/39.9 (7.5%)	1/36.3 (2.8%)	3/41.0 (7.3%)
Terminal rate	1/27 (3.7%)	0/19 (0.0%)	0/27 (0.0%)
First incidence (days)	678	738	687
Poly-3 test	P=1.000	P=0.678	P=1.000
Lung: Alveolar/bronchiolar Adenoma			
Overall rate	17/48 (35.4%)	16/48 (33.3%)	18/48 (37.5%)
Adjusted rate	17/42.4 (40.1%)	16/39.2 (40.8%)	18/42.2 (42.7%)
Terminal rate	9/27 (33.3%)	7/19 (36.8%)	14/27 (51.9%)
First incidence (days)	438	306	380
Poly-3 test	P=0.894	P=1.000	P=0.985
Lung: Alveolar/bronchiolar Carcinoma			
Overall rate	13/48 (27.1%)	6/48 (12.5%)	9/48 (18.8%)
Adjusted rate	13/40.5 (32.1%)	6/37.0 (16.2%)	9/40.9 (22.0%)
Terminal rate	9/27 (33.3%)	3/19 (15.8%)	8/27 (29.6%)
First incidence (days)	635	640	670
Poly-3 test	P=0.336	P=0.167	P=0.434
Lung: Alveolar/bronchiolar Adenoma or Carcinoma			
Overall rate	28/48 (58.3%)	21/48 (43.8%)	24/48 (50.0%)
Adjusted rate	28/43.3 (64.6%)	21/39.7 (52.9%)	24/42.5 (56.5%)
Terminal rate	16/27 (59.3%)	10/19 (52.6%)	19/27 (70.4%)
First incidence (days)	438	306	380
Poly-3 test	P=0.486	P=0.367	P=0.570
Lymph Node (Mesenteric): Histiocytic Sarcoma			
Overall rate	2/42 (4.8%)	1/42 (2.4%)	3/46 (6.5%)
Adjusted rate	2/36.3 (5.5%)	1/31.5 (3.2%)	3/39.6 (7.6%)
Terminal rate	0/25 (0.0%)	0/17 (0.0%)	0/26 (0.0%)
First incidence (days)	678	738	687
Poly-3 test	P=0.875	P=1.000	P=1.000
Mammary Gland: Adenocarcinoma			
Overall rate	3/46 (6.5%)	11/48 (22.9%)	6/48 (12.5%)
Adjusted rate	3/39.3 (7.6%)	11/38.2 (28.8%)	6/41.7 (14.4%)
Terminal rate	1/27 (3.7%)	4/19 (21.1%)	2/27 (7.4%)
First incidence (days)	696	607	642
Poly-3 test	P=0.526	P=0.028	P=0.541
Mammary Gland: Adenoacanthoma or Adenocarcinoma			
Overall rate	4/46 (8.7%)	12/48 (25.0%)	7/48 (14.6%)
Adjusted rate	4/39.6 (10.1%)	12/38.5 (31.2%)	7/41.7 (16.8%)
Terminal rate	1/27 (3.7%)	4/19 (21.1%)	3/27 (11.1%)
First incidence (days)	675	607	642
Poly-3 test	P=0.545	P=0.036	P=0.578
Ovary: Cystadenoma			
Overall rate	1/46 (2.2%)	0/47 (0.0%)	3/46 (6.5%)
Adjusted rate	1/38.5 (2.6%)	0/35.8 (0.0%)	3/38.8 (7.7%)
Terminal rate	1/27 (3.7%)	0/19 (0.0%)	3/26 (11.5%)
First incidence (days)	765 (T)	—	765 (T)
Poly-3 test	P=0.348	P=1.000	P=0.614

Table D2d
Statistical Analysis of Primary Neoplasms in Female Mice Exposed to Ethanol and 30 ppm Urethane in Drinking Water for 2 Years

	0% Ethanol	2.5% Ethanol	5% Ethanol
Ovary: Histiocytic Sarcoma			
Overall rate	3/46 (6.5%)	1/47 (2.1%)	2/46 (4.3%)
Adjusted rate	3/38.8 (7.7%)	1/35.9 (2.8%)	2/38.9 (5.1%)
Terminal rate	1/27 (3.7%)	0/19 (0.0%)	0/26 (0.0%)
First incidence (days)	678	738	745
Poly-3 test	P=0.796	P=0.665	P=0.998
Ovary: Benign Granulosa Cell Tumor			
Overall rate	2/46 (4.3%)	3/47 (6.4%)	5/46 (10.9%)
Adjusted rate	2/38.5 (5.2%)	3/36.0 (8.3%)	5/39.3 (12.7%)
Terminal rate	2/27 (7.4%)	2/19 (10.5%)	3/26 (11.5%)
First incidence (days)	765 (T)	696	685
Poly-3 test	P=0.323	P=0.940	P=0.444
Ovary: Benign or Malignant Granulosa Cell Tumor			
Overall rate	2/46 (4.3%)	3/47 (6.4%)	6/46 (13.0%)
Adjusted rate	2/38.5 (5.2%)	3/36.0 (8.3%)	6/39.5 (15.2%)
Terminal rate	2/27 (7.4%)	2/19 (10.5%)	3/26 (11.5%)
First incidence (days)	765 (T)	696	685
Poly-3 test	P=0.184	P=0.940	P=0.278
Pancreatic Islets: Adenoma			
Overall rate	0/47 (0.0%)	1/46 (2.2%)	3/48 (6.3%)
Adjusted rate	0/39.2 (0.0%)	1/35.4 (2.8%)	3/40.6 (7.4%)
Terminal rate	0/27 (0.0%)	0/19 (0.0%)	2/27 (7.4%)
First incidence (days)	—	681	745
Poly-3 test	P=0.128	P=0.959	P=0.249
Pituitary Gland (Pars Distalis): Adenoma or Carcinoma			
Overall rate	5/40 (12.5%)	3/41 (7.3%)	5/40 (12.5%)
Adjusted rate	5/33.8 (14.8%)	3/30.9 (9.7%)	5/34.4 (14.5%)
Terminal rate	4/23 (17.4%)	1/15 (6.7%)	5/25 (20.0%)
First incidence (days)	649	594	765 (T)
Poly-3 test	P=1.000	P=0.808	P=1.000
Skin: Sarcoma			
Overall rate	0/46 (0.0%)	6/48 (12.5%)	4/48 (8.3%)
Adjusted rate	0/38.8 (0.0%)	6/37.2 (16.1%)	4/41.1 (9.7%)
Terminal rate	0/27 (0.0%)	2/19 (10.5%)	2/27 (7.4%)
First incidence (days)	—	636	685
Poly-3 test	P=0.174	P=0.025	P=0.134
Spleen: Histiocytic Sarcoma			
Overall rate	2/47 (4.3%)	1/46 (2.2%)	3/48 (6.3%)
Adjusted rate	2/39.5 (5.1%)	1/35.2 (2.8%)	3/41.0 (7.3%)
Terminal rate	0/27 (0.0%)	0/19 (0.0%)	0/27 (0.0%)
First incidence (days)	678	738	687
Poly-3 test	P=0.830	P=1.000	P=1.000
Stomach (Forestomach): Squamous Cell Papilloma			
Overall rate	3/46 (6.5%)	0/47 (0.0%)	2/48 (4.2%)
Adjusted rate	3/39.0 (7.7%)	0/35.4 (0.0%)	2/40.8 (4.9%)
Terminal rate	2/27 (7.4%)	0/19 (0.0%)	1/27 (3.7%)
First incidence (days)	712	—	702
Poly-3 test	P=0.745	P=0.271	P=0.959

Table D2d
Statistical Analysis of Primary Neoplasms in Female Mice Exposed to Ethanol and 30 ppm Urethane in Drinking Water for 2 Years

	0% Ethanol	2.5% Ethanol	5% Ethanol
Thymus: Histiocytic Sarcoma			
Overall rate	3/32 (9.4%)	1/34 (2.9%)	0/43 (0.0%)
Adjusted rate	3/26.7 (11.3%)	1/26.7 (3.7%)	0/36.1 (0.0%)
Terminal rate	1/16 (6.3%)	0/14 (0.0%)	0/24 (0.0%)
First incidence (days)	678	738	—
Poly-3 test	P=0.067	P=0.603	P=0.136
Uterus: Hemangioma or Hemangiosarcoma			
Overall rate	2/48 (4.2%)	2/48 (4.2%)	3/47 (6.4%)
Adjusted rate	2/39.5 (5.1%)	2/36.4 (5.5%)	3/40.0 (7.5%)
Terminal rate	2/27 (7.4%)	1/19 (5.3%)	1/26 (3.8%)
First incidence (days)	765 (T)	696	675
Poly-3 test	P=0.824	P=1.000	P=1.000
Uterus: Histiocytic Sarcoma			
Overall rate	3/48 (6.3%)	2/48 (4.2%)	1/47 (2.1%)
Adjusted rate	3/39.9 (7.5%)	2/36.9 (5.4%)	1/39.6 (2.5%)
Terminal rate	1/27 (3.7%)	0/19 (0.0%)	0/26 (0.0%)
First incidence (days)	678	607	746
Poly-3 test	P=0.447	P=1.000	P=0.613
All Organs: Hemangioma			
Overall rate	3/48 (6.3%)	2/48 (4.2%)	6/48 (12.5%)
Adjusted rate	3/39.7 (7.6%)	2/36.2 (5.5%)	6/41.0 (14.6%)
Terminal rate	2/27 (7.4%)	2/19 (10.5%)	4/27 (14.8%)
First incidence (days)	719	765 (T)	675
Poly-3 test	P=0.353	P=1.000	P=0.512
All Organs: Hemangiosarcoma			
Overall rate	4/48 (8.3%)	1/48 (2.1%)	1/48 (2.1%)
Adjusted rate	4/39.5 (10.1%)	1/36.4 (2.7%)	1/40.6 (2.5%)
Terminal rate	4/27 (14.8%)	0/19 (0.0%)	1/27 (3.7%)
First incidence (days)	765 (T)	696	765 (T)
Poly-3 test	P=0.191	P=0.406	P=0.339
All Organs: Hemangioma or Hemangiosarcoma			
Overall rate	6/48 (12.5%)	3/48 (6.3%)	7/48 (14.6%)
Adjusted rate	6/39.7 (15.1%)	3/36.4 (8.2%)	7/41.0 (17.1%)
Terminal rate	5/27 (18.5%)	2/19 (10.5%)	5/27 (18.5%)
First incidence (days)	719	696	675
Poly-3 test	P=0.910	P=0.567	P=1.000
All Organs: Histiocytic Sarcoma			
Overall rate	3/48 (6.3%)	3/48 (6.3%)	3/48 (6.3%)
Adjusted rate	3/39.9 (7.5%)	3/37.0 (8.1%)	3/41.0 (7.3%)
Terminal rate	1/27 (3.7%)	0/19 (0.0%)	0/27 (0.0%)
First incidence (days)	678	607	687
Poly-3 test	P=1.000	P=1.000	P=1.000
All Organs: Malignant Lymphoma			
Overall rate	8/48 (16.7%)	11/48 (22.9%)	15/48 (31.3%)
Adjusted rate	8/42.0 (19.0%)	11/38.7 (28.4%)	15/43.8 (34.3%)
Terminal rate	2/27 (7.4%)	5/19 (26.3%)	6/27 (22.2%)
First incidence (days)	549	593	285
Poly-3 test	P=0.134	P=0.461	P=0.172

Table D2d
Statistical Analysis of Primary Neoplasms in Female Mice Exposed to Ethanol and 30 ppm Urethane in Drinking Water for 2 Years

	0% Ethanol	2.5% Ethanol	5% Ethanol
All Organs: Benign Neoplasms			
Overall rate	38/48 (79.2%)	31/48 (64.6%)	37/48 (77.1%)
Adjusted rate	38/44.6 (85.2%)	31/40.5 (76.6%)	37/44.0 (84.2%)
Terminal rate	23/27 (85.2%)	18/19 (94.7%)	25/27 (92.6%)
First incidence (days)	438	306	380
Poly-3 test	P=1.000	P=0.411	P=1.000
All Organs: Malignant Neoplasms			
Overall rate	37/48 (77.1%)	38/48 (79.2%)	37/48 (77.1%)
Adjusted rate	37/46.8 (79.1%)	38/44.5 (85.4%)	37/46.2 (80.1%)
Terminal rate	18/27 (66.7%)	15/19 (78.9%)	20/27 (74.1%)
First incidence (days)	438	468	285
Poly-3 test	P=1.000	P=0.601	P=1.000
All Organs: Benign or Malignant Neoplasms			
Overall rate	45/48 (93.8%)	45/48 (93.8%)	47/48 (97.9%)
Adjusted rate	45/47.2 (95.4%)	45/46.5 (96.8%)	47/47.5 (98.9%)
Terminal rate	25/27 (92.6%)	18/19 (94.7%)	27/27 (100.0%)
First incidence (days)	438	306	285
Poly-3 test	P=0.440	P=1.000	P=0.658

(T) Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals with tissue examined microscopically
[b] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] P values are two sided. Beneath the control incidence (0% ethanol) is the P value associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and that exposed group. The Poly-3 test accounts for the differential mortality in animals that do not reach terminal sacrifice.
[e] Not applicable; no neoplasms in animal group

Table D2e
Statistical Analysis of Primary Neoplasms in Female Mice Exposed to Ethanol and 90 ppm Urethane in Drinking Water for 2 Years

	0% Ethanol	2.5% Ethanol	5% Ethanol
Adrenal Cortex: Adenoma			
Overall rate[a]	2/47 (4.3%)	0/44 (0.0%)	3/46 (6.5%)
Adjusted rate[b]	2/28.6 (7.0%)	0/29.8 (0.0%)	3/29.7 (10.1%)
Terminal rate[c]	0/1 (0.0%)	0/7 (0.0%)	1/4 (25.0%)
First incidence (days)	710	—[e]	700
Poly-3 test[d]	P=0.787	P=0.452	P=1.000
Adrenal Cortex: Adenoma or Carcinoma			
Overall rate	2/47 (4.3%)	1/44 (2.3%)	3/46 (6.5%)
Adjusted rate	2/28.6 (7.0%)	1/30.0 (3.3%)	3/29.7 (10.1%)
Terminal rate	0/1 (0.0%)	0/7 (0.0%)	1/4 (25.0%)
First incidence (days)	710	715	700
Poly-3 test	P=0.818	P=0.967	P=1.000
Harderian Gland: Adenoma			
Overall rate	21/48 (43.8%)	19/47 (40.4%)	20/46 (43.5%)
Adjusted rate	21/36.1 (58.2%)	19/37.9 (50.1%)	20/36.5 (54.7%)
Terminal rate	0/1 (0.0%)	2/8 (25.0%)	2/4 (50.0%)
First incidence (days)	466	542	433
Poly-3 test	P=0.865	P=0.622	P=0.949
Harderian Gland: Carcinoma			
Overall rate	11/48 (22.9%)	16/47 (34.0%)	10/46 (21.7%)
Adjusted rate	11/32.0 (34.3%)	16/36.1 (44.4%)	10/32.7 (30.5%)
Terminal rate	1/1 (100.0%)	3/8 (37.5%)	0/4 (0.0%)
First incidence (days)	548	599	559
Poly-3 test	P=0.825	P=0.530	P=0.951
Harderian Gland: Adenoma or Carcinoma			
Overall rate	30/48 (62.5%)	35/47 (74.5%)	29/46 (63.0%)
Adjusted rate	30/39.0 (76.8%)	35/41.5 (84.3%)	29/39.7 (73.0%)
Terminal rate	1/1 (100.0%)	5/8 (62.5%)	2/4 (50.0%)
First incidence (days)	466	542	433
Poly-3 test	P=0.739	P=0.512	P=0.883
Heart: Hemangiosarcoma			
Overall rate	0/48 (0.0%)	3/48 (6.3%)	6/47 (12.8%)
Adjusted rate	0/28.7 (0.0%)	3/34.2 (8.8%)	6/31.5 (19.1%)
Terminal rate	0/1 (0.0%)	0/8 (0.0%)	1/4 (25.0%)
First incidence (days)	—	565	603
Poly-3 test	P=0.021	P=0.300	P=0.035
Heart: Histiocytic Sarcoma			
Overall rate	3/48 (6.3%)	0/48 (0.0%)	0/47 (0.0%)
Adjusted rate	3/29.4 (10.2%)	0/33.0 (0.0%)	0/30.0 (0.0%)
Terminal rate	0/1 (0.0%)	0/8 (0.0%)	0/4 (0.0%)
First incidence (days)	650	—	—
Poly-3 test	P=0.069	P=0.193	P=0.222
Kidney: Hemangiosarcoma			
Overall rate	0/48 (0.0%)	3/48 (6.3%)	1/47 (2.1%)
Adjusted rate	0/28.7 (0.0%)	3/34.6 (8.7%)	1/30.4 (3.3%)
Terminal rate	0/1 (0.0%)	0/8 (0.0%)	0/4 (0.0%)
First incidence (days)	—	508	675
Poly-3 test	P=0.830	P=0.306	P=1.000

Table D2e
Statistical Analysis of Primary Neoplasms in Female Mice Exposed to Ethanol and 90 ppm Urethane in Drinking Water for 2 Years

	0% Ethanol	2.5% Ethanol	5% Ethanol
Liver: Hemangiosarcoma			
Overall rate	7/47 (14.9%)	7/46 (15.2%)	6/48 (12.5%)
Adjusted rate	7/30.3 (23.1%)	7/32.6 (21.5%)	6/32.1 (18.7%)
Terminal rate	0/1 (0.0%)	1/8 (12.5%)	0/4 (0.0%)
First incidence (days)	551	677	485
Poly-3 test	P=0.782	P=1.000	P=0.901
Liver: Histiocytic Sarcoma			
Overall rate	3/47 (6.4%)	1/46 (2.2%)	2/48 (4.2%)
Adjusted rate	3/29.0 (10.3%)	1/31.8 (3.1%)	2/31.1 (6.4%)
Terminal rate	0/1 (0.0%)	1/8 (12.5%)	0/4 (0.0%)
First incidence (days)	650	765 (T)	674
Poly-3 test	P=0.760	P=0.539	P=0.936
Liver: Hepatocellular Adenoma			
Overall rate	18/47 (38.3%)	23/46 (50.0%)	16/48 (33.3%)
Adjusted rate	18/33.4 (54.0%)	23/36.4 (63.2%)	16/35.5 (45.0%)
Terminal rate	0/1 (0.0%)	8/8 (100.0%)	3/4 (75.0%)
First incidence (days)	590	608	559
Poly-3 test	P=0.474	P=0.550	P=0.590
Liver: Hepatocellular Adenoma or Carcinoma			
Overall rate	19/47 (40.4%)	23/46 (50.0%)	17/48 (35.4%)
Adjusted rate	19/33.7 (56.4%)	23/36.4 (63.2%)	17/35.7 (47.6%)
Terminal rate	0/1 (0.0%)	8/8 (100.0%)	3/4 (75.0%)
First incidence (days)	590	608	559
Poly-3 test	P=0.483	P=0.711	P=0.592
Lung: Alveolar/bronchiolar Adenoma			
Overall rate	29/47 (61.7%)	28/48 (58.3%)	30/48 (62.5%)
Adjusted rate	29/38.8 (74.8%)	28/39.4 (71.1%)	30/38.9 (77.1%)
Terminal rate	1/1 (100.0%)	6/8 (75.0%)	4/4 (100.0%)
First incidence (days)	391	593	433
Poly-3 test	P=0.905	P=0.899	P=1.000
Lung: Alveolar/bronchiolar Carcinoma			
Overall rate	19/47 (40.4%)	23/48 (47.9%)	23/48 (47.9%)
Adjusted rate	19/32.9 (57.8%)	23/37.3 (61.7%)	23/37.7 (61.1%)
Terminal rate	1/1 (100.0%)	6/8 (75.0%)	3/4 (75.0%)
First incidence (days)	548	499	485
Poly-3 test	P=0.885	P=0.924	P=0.971
Lung: Alveolar/bronchiolar Adenoma or Carcinoma			
Overall rate	39/47 (83.0%)	38/48 (79.2%)	37/48 (77.1%)
Adjusted rate	39/41.9 (93.2%)	38/42.0 (90.6%)	37/41.8 (88.5%)
Terminal rate	1/1 (100.0%)	8/8 (100.0%)	4/4 (100.0%)
First incidence (days)	391	499	433
Poly-3 test	P=0.459	P=0.962	P=0.627
Lymph Node (Mesenteric): Histiocytic Sarcoma			
Overall rate	3/39 (7.7%)	2/38 (5.3%)	2/38 (5.3%)
Adjusted rate	3/24.7 (12.1%)	2/27.0 (7.4%)	2/25.2 (7.9%)
Terminal rate	0/1 (0.0%)	1/8 (12.5%)	0/4 (0.0%)
First incidence (days)	650	762	674
Poly-3 test	P=0.801	P=0.917	P=0.981

Table D2e
Statistical Analysis of Primary Neoplasms in Female Mice Exposed to Ethanol and 90 ppm Urethane in Drinking Water for 2 Years

	0% Ethanol	2.5% Ethanol	5% Ethanol
Mammary Gland: Adenoacanthoma			
Overall rate	11/48 (22.9%)	3/47 (6.4%)	9/45 (20.0%)
Adjusted rate	11/32.6 (33.8%)	3/33.4 (9.0%)	9/32.0 (28.1%)
Terminal rate	0/1 (0.0%)	0/8 (0.0%)	2/4 (50.0%)
First incidence (days)	523	599	459
Poly-3 test	P=0.705	P=0.023	P=0.819
Mammary Gland: Adenocarcinoma			
Overall rate	11/48 (22.9%)	14/47 (29.8%)	15/45 (33.3%)
Adjusted rate	11/32.8 (33.6%)	14/35.6 (39.3%)	15/33.8 (44.3%)
Terminal rate	1/1 (100.0%)	2/8 (25.0%)	1/4 (25.0%)
First incidence (days)	391	648	559
Poly-3 test	P=0.426	P=0.800	P=0.494
Mammary Gland: Adenoacanthoma or Adenocarcinoma			
Overall rate	22/48 (45.8%)	16/47 (34.0%)	23/45 (51.1%)
Adjusted rate	22/36.6 (60.1%)	16/36.3 (44.1%)	23/36.9 (62.4%)
Terminal rate	1/1 (100.0%)	2/8 (25.0%)	2/4 (50.0%)
First incidence (days)	391	599	459
Poly-3 test	P=0.900	P=0.222	P=1.000
Ovary: Hemangioma or Hemangiosarcoma			
Overall rate	0/39 (0.0%)	3/48 (6.3%)	0/45 (0.0%)
Adjusted rate	0/22.8 (0.0%)	3/33.8 (8.9%)	0/28.9 (0.0%)
Terminal rate	0/1 (0.0%)	0/8 (0.0%)	0/4 (0.0%)
First incidence (days)	—	611	—
Poly-3 test	P=1.000	P=0.396	—[f]
Ovary: Benign Granulosa Cell Tumor			
Overall rate	3/39 (7.7%)	3/48 (6.3%)	3/45 (6.7%)
Adjusted rate	3/23.8 (12.6%)	3/33.9 (8.9%)	3/28.9 (10.4%)
Terminal rate	0/1 (0.0%)	1/8 (12.5%)	3/4 (75.0%)
First incidence (days)	576	614	765 (T)
Poly-3 test	P=1.000	P=0.982	P=1.000
Ovary: Malignant Granulosa Cell Tumor			
Overall rate	3/39 (7.7%)	0/48 (0.0%)	0/45 (0.0%)
Adjusted rate	3/23.8 (12.6%)	0/33.0 (0.0%)	0/28.9 (0.0%)
Terminal rate	0/1 (0.0%)	0/8 (0.0%)	0/4 (0.0%)
First incidence (days)	635	—	—
Poly-3 test	P=0.048	P=0.130	P=0.163
Ovary: Benign or Malignant Granulosa Cell Tumor			
Overall rate	5/39 (12.8%)	3/48 (6.3%)	3/45 (6.7%)
Adjusted rate	5/24.5 (20.4%)	3/33.9 (8.9%)	3/28.9 (10.4%)
Terminal rate	0/1 (0.0%)	1/8 (12.5%)	3/4 (75.0%)
First incidence (days)	576	614	765 (T)
Poly-3 test	P=0.406	P=0.375	P=0.515
Pancreas: Histocytic Sarcoma			
Overall rate	2/44 (4.5%)	1/44 (2.3%)	1/44 (2.3%)
Adjusted rate	2/27.2 (7.4%)	1/30.5 (3.3%)	1/28.5 (3.5%)
Terminal rate	0/1 (0.0%)	0/8 (0.0%)	0/4 (0.0%)
First incidence (days)	650	762	762
Poly-3 test	P=0.738	P=0.918	P=0.967

Table D2e
Statistical Analysis of Primary Neoplasms in Female Mice Exposed to Ethanol and 90 ppm Urethane in Drinking Water for 2 Years

	0% Ethanol	2.5% Ethanol	5% Ethanol
Skin: Sarcoma			
Overall rate	6/48 (12.5%)	5/47 (10.6%)	7/47 (14.9%)
Adjusted rate	6/30.3 (19.8%)	5/33.5 (14.9%)	7/32.2 (21.7%)
Terminal rate	0/1 (0.0%)	0/8 (0.0%)	0/4 (0.0%)
First incidence (days)	590	626	573
Poly-3 test	P=0.955	P=0.853	P=1.000
Skin: Fibroma or Sarcoma			
Overall rate	6/48 (12.5%)	6/47 (12.8%)	7/47 (14.9%)
Adjusted rate	6/30.3 (19.8%)	6/33.7 (17.8%)	7/32.2 (21.7%)
Terminal rate	0/1 (0.0%)	0/8 (0.0%)	0/4 (0.0%)
First incidence (days)	590	626	573
Poly-3 test	P=0.968	P=1.000	P=1.000
Spleen: Hemangiosarcoma			
Overall rate	4/46 (8.7%)	3/46 (6.5%)	1/45 (2.2%)
Adjusted rate	4/28.2 (14.2%)	3/32.7 (9.2%)	1/29.0 (3.4%)
Terminal rate	0/1 (0.0%)	0/8 (0.0%)	0/4 (0.0%)
First incidence (days)	605	626	749
Poly-3 test	P=0.241	P=0.835	P=0.326
Stomach (Forestomach): Squamous Cell Papilloma			
Overall rate	3/46 (6.5%)	0/46 (0.0%)	0/45 (0.0%)
Adjusted rate	3/28.6 (10.5%)	0/31.7 (0.0%)	0/28.8 (0.0%)
Terminal rate	0/1 (0.0%)	0/8 (0.0%)	0/4 (0.0%)
First incidence (days)	605	—	—
Poly-3 test	P=0.069	P=0.196	P=0.226
Stomach (Forestomach): Squamous Cell Papilloma or Squamous Cell Carcinoma			
Overall rate	4/46 (8.7%)	1/46 (2.2%)	0/45 (0.0%)
Adjusted rate	4/29.0 (13.8%)	1/32.1 (3.1%)	0/28.8 (0.0%)
Terminal rate	0/1 (0.0%)	0/8 (0.0%)	0/4 (0.0%)
First incidence (days)	605	659	—
Poly-3 test	P=0.045	P=0.287	P=0.113
Thymus: Histiocytic Sarcoma			
Overall rate	1/38 (2.6%)	0/36 (0.0%)	2/39 (5.1%)
Adjusted rate	1/22.7 (4.4%)	0/25.0 (0.0%)	2/24.3 (8.2%)
Terminal rate	0/1 (0.0%)	0/5 (0.0%)	0/2 (0.0%)
First incidence (days)	744	—	674
Poly-3 test	P=0.750	P=0.961	P=1.000
Thyroid Gland (Follicular Cell): Adenoma or Carcinoma			
Overall rate	3/45 (6.7%)	0/46 (0.0%)	1/46 (2.2%)
Adjusted rate	3/27.9 (10.7%)	0/32.2 (0.0%)	1/30.1 (3.3%)
Terminal rate	1/1 (100.0%)	0/8 (0.0%)	0/4 (0.0%)
First incidence (days)	466	—	629
Poly-3 test	P=0.330	P=0.183	P=0.550
Uterus: Hemangioma			
Overall rate	0/46 (0.0%)	3/48 (6.3%)	1/45 (2.2%)
Adjusted rate	0/27.8 (0.0%)	3/34.3 (8.7%)	1/29.0 (3.4%)
Terminal rate	0/1 (0.0%)	0/8 (0.0%)	0/4 (0.0%)
First incidence (days)	—	608	751
Poly-3 test	P=0.811	P=0.315	P=1.000

Table D2e
Statistical Analysis of Primary Neoplasms in Female Mice Exposed to Ethanol and 90 ppm Urethane in Drinking Water for 2 Years

	0% Ethanol	2.5% Ethanol	5% Ethanol
Uterus: Hemangioma or Hemangiosarcoma			
Overall rate	2/46 (4.3%)	4/48 (8.3%)	2/45 (4.4%)
Adjusted rate	2/28.3 (7.1%)	4/34.3 (11.7%)	2/29.1 (6.9%)
Terminal rate	0/1 (0.0%)	1/8 (12.5%)	0/4 (0.0%)
First incidence (days)	676	608	749
Poly-3 test	P=1.000	P=0.854	P=1.000
All Organs: Hemangioma			
Overall rate	1/48 (2.1%)	4/48 (8.3%)	2/48 (4.2%)
Adjusted rate	1/28.9 (3.5%)	4/34.5 (11.6%)	2/31.2 (6.4%)
Terminal rate	0/1 (0.0%)	0/8 (0.0%)	0/4 (0.0%)
First incidence (days)	725	608	643
Poly-3 test	P=0.908	P=0.466	P=1.000
All Organs: Hemangiosarcoma			
Overall rate	11/48 (22.9%)	17/48 (35.4%)	13/48 (27.1%)
Adjusted rate	11/31.8 (34.6%)	17/37.8 (45.0%)	13/33.8 (38.5%)
Terminal rate	0/1 (0.0%)	2/8 (25.0%)	2/4 (50.0%)
First incidence (days)	551	508	485
Poly-3 test	P=0.875	P=0.508	P=0.945
All Organs: Hemangioma or Hemangiosarcoma			
Overall rate	11/48 (22.9%)	21/48 (43.8%)	14/48 (29.2%)
Adjusted rate	11/31.8 (34.6%)	21/39.3 (53.5%)	14/34.2 (40.9%)
Terminal rate	0/1 (0.0%)	2/8 (25.0%)	2/4 (50.0%)
First incidence (days)	551	508	485
Poly-3 test	P=0.750	P=0.152	P=0.773
All Organs: Histiocytic Sarcoma			
Overall rate	3/48 (6.3%)	2/48 (4.2%)	2/48 (4.2%)
Adjusted rate	3/29.4 (10.2%)	2/33.0 (6.1%)	2/31.1 (6.4%)
Terminal rate	0/1 (0.0%)	1/8 (12.5%)	0/4 (0.0%)
First incidence (days)	650	762	674
Poly-3 test	P=0.775	P=0.894	P=0.950
All Organs: Malignant Lymphoma			
Overall rate	15/48 (31.3%)	6/48 (12.5%)	10/48 (20.8%)
Adjusted rate	15/35.1 (42.7%)	6/35.4 (17.0%)	10/35.2 (28.4%)
Terminal rate	1/1 (100.0%)	0/8 (0.0%)	1/4 (25.0%)
First incidence (days)	193	360	433
Poly-3 test	P=0.211	P=0.025	P=0.287
All Organs: Benign Neoplasms			
Overall rate	42/48 (87.5%)	39/48 (81.3%)	41/48 (85.4%)
Adjusted rate	42/44.3 (94.9%)	39/42.7 (91.4%)	41/44.0 (93.2%)
Terminal rate	1/1 (100.0%)	8/8 (100.0%)	4/4 (100.0%)
First incidence (days)	391	542	433
Poly-3 test	P=0.898	P=0.764	P=1.000
All Organs: Malignant Neoplasms			
Overall rate	46/48 (95.8%)	45/48 (93.8%)	46/48 (95.8%)
Adjusted rate	46/46.8 (98.2%)	45/46.3 (97.1%)	46/47.0 (97.8%)
Terminal rate	1/1 (100.0%)	8/8 (100.0%)	3/4 (75.0%)
First incidence (days)	193	360	433
Poly-3 test	P=1.000	P=1.000	P=1.000

Table D2e
Statistical Analysis of Primary Neoplasms in Female Mice Exposed to Ethanol and 90 ppm Urethane in Drinking Water for 2 Years

	0% Ethanol	2.5% Ethanol	5% Ethanol
All Organs: Benign or Malignant Neoplasms			
Overall rate	47/48 (97.9%)	48/48 (100.0%)	47/48 (97.9%)
Adjusted rate	47/47.3 (99.3%)	48/48.0 (100.0%)	47/47.0 (99.9%)
Terminal rate	1/1 (100.0%)	8/8 (100.0%)	4/4 (100.0%)
First incidence (days)	193	360	433
Poly-3 test	P=1.000	P=1.000	P=1.000

(T) Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals with tissue examined microscopically
[b] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] P values are two sided. Beneath the control incidence (0% ethanol) is the P value associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and that exposed group. The Poly-3 test accounts for the differential mortality in animals that do not reach terminal sacrifice.
[e] Not applicable; no neoplasms in animal group
[f] Value of statistic cannot be computed.

Table D3a
Historical Incidence of Hemangiosarcoma (All Sites) in Control Female $B6C3F_1$/Nctr BR Mice[a]

Study	Incidence in Controls
Chloral hydrate (gavage)	2/144
Doxylamine	0/48
Fumonisin B_1	1/47
Pyrilamine	1/48
Sulfamethazine	1/184
Triprolidine	1/47
Total (%)	6/518 (1.2%)
Range	0%-2%

[a] Data as of January 2002. Studies were conducted at the National Center for Toxicological Research in animals given NIH-31 feed.

Table D3b
Historical Incidence of Hepatocellular Neoplasms in Control Female $B6C3F_1$/Nctr BR Mice[a]

	Incidence in Controls		
Study	Adenoma	Carcinoma	Adenoma or Carcinoma
Chloral hydrate (gavage)	5/144	4/144	9/144
Doxylamine	0/46	0/46	0/46
Fumonisin B_1	5/47	0/47	5/47
Pyrilamine	1/47	0/47	1/47
Sulfamethazine	8/184	2/184	10/184
Triprolidine	2/47	2/47	4/47
Total (%)	21/515 (4.1%)	8/515 (1.6%)	29/515 (5.6%)
Range	0%-11%	0%-4%	0%-11%

[a] Data as of January 2002. Studies were conducted at the National Center for Toxicological Research in animals given NIH-31 feed.

TABLE D3c
Historical Incidence of Alveolar/bronchiolar Neoplasms in Control Female $B6C3F_1$/Nctr BR Mice[a]

Study	Incidence in Controls: Adenoma	Carcinoma	Adenoma or Carcinoma
Chloral hydrate (gavage)	8/143	0/143	8/143
Doxylamine	3/48	0/48	3/48
Fumonisin B_1	2/47	0/47	2/47
Pyrilamine	1/48	0/48	1/48
Sulfamethazine	5/182	1/182	6/182
Triprolidine	3/47	2/47	5/47
Total (%)	22/515 (4.3%)	3/515 (0.6%)	25/515 (4.9%)
Range	2%-6%	0%-4%	2%-11%

[a] Data as of January 2002. Studies were conducted at the National Center for Toxicological Research in animals given NIH-31 feed.

TABLE D3d
Historical Incidence of Harderian Gland Neoplasms in Control Female $B6C3F_1$/Nctr BR Mice[a]

Study	Incidence in Controls: Adenoma	Carcinoma	Adenoma or Carcinoma
Chloral hydrate (gavage)	4/140	2/140	6/140
Fumonisin B_1	4/46	1/46	4/46
Sulfamethazine	13/182	0/182	13/182
Total (%)	21/368 (5.7%)	3/368 (0.8%)	23/368 (6.3%)
Range	3%-9%	1%-2%	4%-9%

[a] Data as of January 2002. Studies were conducted at the National Center for Toxicological Research in animals given NIH-31 feed.

TABLE D3e
Historical Incidence of Mammary Gland Neoplasms in Control Female $B6C3F_1$/Nctr BR Mice[a]

Study	Incidence in Controls		
	Adenoacanthoma	Adenocarcinoma	Adenoacanthoma or Adenocarcinoma
Chloral hydrate (gavage)	0/133	1/133	1/133
Fumonisin B_1	0/46	1/46	1/46
Total (%)	0/179	2/179 (1.1%)	2/179 (1.1%)
Range		1%-2%	1%-2%

[a] Data as of January 2002. Studies were conducted at the National Center for Toxicological Research in animals given NIH-31 feed.

TABLE D3f
Historical Incidence of Granulosa Cell Tumor in Control Female $B6C3F_1$/Nctr BR Mice[a]

Study	Incidence in Controls		
	Benign	Malignant	Benign or Malignant
Chloral hydrate (gavage)	0/141	0/141	0/141
Doxylamine	0/47	0/47	0/47
Fumonisin B_1	0/46	0/46	0/46
Pyrilamine	0/48	0/48	0/48
Sulfamethazine	0/177	1/177	1/177
Triprolidine	0/45	0/45	0/45
Total (%)	0/504	1/504 (0.2%)	1/504 (0.2%)
Range		0%-1%	0%-1%

[a] Data as of January 2002. Studies were conducted at the National Center for Toxicological Research in animals given NIH-31 feed.

Table D4
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Drinking Water Study of Urethane and 0% Ethanol[a]

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
Disposition Summary				
Animals initially in study	48	48	48	48
Early deaths				
Moribund	1	3	5	18
Natural deaths	9	8	16	29
Survivors				
Terminal sacrifice	38	37	27	1
Animals examined microscopically	48	48	48	48
Alimentary System				
Esophagus	(48)	(47)	(47)	(47)
Autolysis, marked				1 (2%)
Autolysis, moderate				1 (2%)
Gallbladder	(47)	(45)	(46)	(43)
Autolysis, marked				3 (7%)
Autolysis, moderate	7 (15%)	1 (2%)	2 (4%)	4 (9%)
Cytoplasmic alteration, mild, epithelium	1 (2%)			
Infiltration cellular, lymphocytic, minimal		1 (2%)		
Inflammation, chronic active, moderate	1 (2%)			
Intestine large, cecum	(48)	(45)	(46)	(45)
Autolysis, marked			1 (2%)	5 (11%)
Autolysis, moderate	5 (10%)	1 (2%)	2 (4%)	10 (22%)
Hyperplasia, mild, lymphoid tissue			1 (2%)	
Intestine large, colon	(48)	(44)	(46)	(46)
Autolysis, marked			1 (2%)	5 (11%)
Autolysis, moderate	5 (10%)	1 (2%)	2 (4%)	10 (22%)
Intestine large, rectum	(48)	(45)	(45)	(46)
Autolysis, marked				4 (9%)
Autolysis, moderate	1 (2%)		1 (2%)	7 (15%)
Intestine small	(48)	(44)	(46)	(44)
Intussusception		1 (2%)		
Intestine small, duodenum	(48)	(43)	(45)	(44)
Autolysis, marked			1 (2%)	5 (11%)
Autolysis, moderate	8 (17%)	2 (5%)	2 (4%)	13 (30%)
Hyperplasia, moderate, lymphoid tissue				1 (2%)
Infiltration cellular, lymphocytic, moderate		1 (2%)		
Intestine small, ileum	(48)	(44)	(46)	(44)
Autolysis, marked			1 (2%)	5 (11%)
Autolysis, moderate	8 (17%)	2 (5%)	2 (4%)	13 (30%)
Hyperplasia, marked, lymphoid tissue			1 (2%)	
Hyperplasia, mild, lymphoid tissue		3 (7%)	2 (4%)	
Hyperplasia, moderate, lymphoid tissue	1 (2%)	1 (2%)	1 (2%)	
Intestine small, jejunum	(48)	(44)	(46)	(44)
Autolysis, marked			1 (2%)	5 (11%)
Autolysis, moderate	8 (17%)	2 (5%)	2 (4%)	13 (30%)
Hyperplasia, mild, lymphoid tissue			1 (2%)	
Hyperplasia, moderate, lymphoid tissue		1 (2%)		
Liver	(48)	(47)	(47)	(47)
Angiectasis		3 (6%)	10 (21%)	24 (51%)
Autolysis, marked				1 (2%)
Autolysis, moderate				1 (2%)
Basophilic focus	1 (2%)	1 (2%)	1 (2%)	

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

Table D4
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Drinking Water Study of Urethane and 0% Ethanol

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
Alimentary System (continued)				
Liver (continued)	(48)	(47)	(47)	(47)
Clear cell focus	1 (2%)	2 (4%)		
Clear cell focus, multiple				1 (2%)
Degeneration, cystic, minimal		1 (2%)		
Eosinophilic focus	2 (4%)	8 (17%)	5 (11%)	
Eosinophilic focus, multiple	1 (2%)	6 (13%)	27 (57%)	20 (43%)
Granuloma, focal, minimal	4 (8%)	1 (2%)		
Hematopoietic cell proliferation granulocytic, moderate		1 (2%)		
Hematopoietic cell proliferation, marked				1 (2%)
Hematopoietic cell proliferation, mild	2 (4%)	5 (11%)	16 (34%)	7 (15%)
Hematopoietic cell proliferation, minimal	4 (8%)	1 (2%)	2 (4%)	
Hematopoietic cell proliferation, moderate	1 (2%)		2 (4%)	11 (23%)
Hyperplasia, mild, Kupffer cell			1 (2%)	
Hyperplasia, mild, oval cell	1 (2%)			
Hyperplasia, moderate, Kupffer cell		1 (2%)		
Hyperplasia, moderate, oval cell			1 (2%)	
Infiltration cellular, lymphocytic, mild	1 (2%)	4 (9%)	4 (9%)	1 (2%)
Infiltration cellular, lymphocytic, minimal	11 (23%)	12 (26%)	5 (11%)	
Infiltration cellular, lymphocytic, moderate			1 (2%)	
Inflammation, chronic active, mild	1 (2%)	2 (4%)		
Inflammation, chronic active, moderate			1 (2%)	
Mixed cell focus		5 (11%)	1 (2%)	
Mixed cell focus, multiple		1 (2%)		1 (2%)
Necrosis, mild	1 (2%)	1 (2%)	1 (2%)	5 (11%)
Necrosis, mild, centrilobular	1 (2%)			
Necrosis, mild, hepatocyte	1 (2%)			
Necrosis, minimal			2 (4%)	
Necrosis, minimal, centrilobular		1 (2%)		
Necrosis, moderate		1 (2%)	2 (4%)	6 (13%)
Necrosis, moderate, centrilobular		1 (2%)		2 (4%)
Necrosis, moderate, hepatocyte	1 (2%)			
Pigmentation, mild				1 (2%)
Regeneration			1 (2%)	2 (4%)
Thrombosis		1 (2%)	1 (2%)	11 (23%)
Vacuolization cytoplasmic, marked, hepatocyte				3 (6%)
Vacuolization cytoplasmic, mild, hepatocyte	3 (6%)	3 (6%)	1 (2%)	
Vacuolization cytoplasmic, minimal, hepatocyte	2 (4%)	2 (4%)	2 (4%)	
Vacuolization cytoplasmic, moderate, hepatocyte	2 (4%)	5 (11%)	1 (2%)	2 (4%)
Mesentery	(3)	(4)	(7)	(6)
Inflammation, mild, fat				1 (17%)
Necrosis, fat	3 (100%)	4 (100%)	6 (86%)	3 (50%)
Pancreas	(48)	(43)	(47)	(44)
Atrophy, mild, acinar cell			1 (2%)	
Atrophy, minimal, acinar cell		1 (2%)		
Atrophy, moderate, acinar cell	1 (2%)		1 (2%)	
Autolysis, marked				3 (7%)
Autolysis, mild				1 (2%)
Autolysis, moderate			1 (2%)	5 (11%)
Infiltration cellular, lymphocytic, mild	1 (2%)		2 (4%)	
Infiltration cellular, lymphocytic, minimal	11 (23%)	15 (35%)	9 (19%)	3 (7%)
Necrosis, mild		1 (2%)		
Vacuolization cytoplasmic, mild, acinar cell			1 (2%)	

TABLE D4
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Drinking Water Study of Urethane and 0% Ethanol

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
Alimentary System (continued)				
Salivary glands	(48)	(48)	(48)	(47)
Atrophy, mild		1 (2%)		1 (2%)
Atrophy, minimal				1 (2%)
Atrophy, moderate				1 (2%)
Autolysis, marked				1 (2%)
Hemorrhage, mild				1 (2%)
Infiltration cellular, lymphocytic, mild	17 (35%)	16 (33%)	12 (25%)	6 (13%)
Infiltration cellular, lymphocytic, minimal	19 (40%)	25 (52%)	24 (50%)	13 (28%)
Infiltration cellular, lymphocytic, moderate	1 (2%)	1 (2%)	1 (2%)	
Stomach, forestomach	(48)	(46)	(46)	(46)
Autolysis, marked				4 (9%)
Autolysis, moderate	1 (2%)		1 (2%)	5 (11%)
Cyst epithelial inclusion		1 (2%)		
Foreign body			2 (4%)	
Hyperkeratosis, mild			2 (4%)	1 (2%)
Hyperkeratosis, minimal	2 (4%)			
Hyperplasia, mild, epithelium	2 (4%)	7 (15%)	7 (15%)	3 (7%)
Hyperplasia, minimal, epithelium	1 (2%)	1 (2%)		1 (2%)
Hyperplasia, moderate, epithelium	3 (6%)	3 (7%)	3 (7%)	5 (11%)
Infiltration cellular, lymphocytic, mild		1 (2%)		
Infiltration cellular, lymphocytic, minimal				1 (2%)
Inflammation, mild	1 (2%)	2 (4%)	6 (13%)	2 (4%)
Inflammation, moderate			1 (2%)	
Ulcer, mild	1 (2%)	1 (2%)	1 (2%)	
Stomach, glandular	(47)	(46)	(46)	(47)
Autolysis, marked				4 (9%)
Autolysis, moderate	1 (2%)		1 (2%)	5 (11%)
Diverticulum			1 (2%)	
Hyperplasia, minimal, epithelium			1 (2%)	
Hypertrophy, mild, epithelium				1 (2%)
Infiltration cellular, lymphocytic, minimal				1 (2%)
Mineralization, minimal				1 (2%)
Thrombosis, minimal				1 (2%)
Tongue	(48)	(48)	(48)	(46)
Polyarteritis, mild				1 (2%)
Cardiovascular System				
Blood vessel	(47)	(47)	(48)	(46)
Infiltration cellular, lymphocytic, minimal				1 (2%)
Mineralization, minimal		1 (2%)		
Heart	(48)	(48)	(48)	(48)
Angiectasis, mild				1 (2%)
Cardiomyopathy, mild	1 (2%)		2 (4%)	1 (2%)
Cardiomyopathy, minimal	1 (2%)	2 (4%)	2 (4%)	2 (4%)
Cardiomyopathy, moderate			1 (2%)	1 (2%)
Hyperplasia, mild, endothelium	1 (2%)		2 (4%)	3 (6%)
Hyperplasia, minimal, endothelium			1 (2%)	3 (6%)
Inflammation, chronic, minimal, myocardium				1 (2%)
Inflammation, mild, artery				1 (2%)
Inflammation, mild, atrioventricular valve				1 (2%)
Inflammation, minimal, myocardium			1 (2%)	1 (2%)
Inflammation, moderate, myocardium				1 (2%)

Table D4
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Drinking Water Study of Urethane and 0% Ethanol

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
Cardiovascular System (continued)				
Heart (continued)	(48)	(48)	(48)	(48)
Mineralization, mild				1 (2%)
Mineralization, minimal		1 (2%)	1 (2%)	1 (2%)
Mineralization, moderate				2 (4%)
Necrosis, minimal				1 (2%)
Necrosis, moderate				1 (2%)
Thrombosis, mild, myocardium			1 (2%)	
Thrombosis, moderate, atrium				2 (4%)
Endocrine System				
Adrenal gland	(48)	(45)	(45)	(47)
Hyperplasia, mild, parenchymal cell				1 (2%)
Adrenal gland, cortex	(48)	(45)	(45)	(47)
Accessory adrenal cortical nodule	1 (2%)			
Angiectasis, mild		1 (2%)		1 (2%)
Angiectasis, minimal	1 (2%)			
Atrophy, mild			1 (2%)	
Atrophy, moderate				1 (2%)
Autolysis, marked				2 (4%)
Autolysis, moderate				2 (4%)
Hematopoietic cell proliferation, mild			1 (2%)	
Hematopoietic cell proliferation, minimal				2 (4%)
Hematopoietic cell proliferation, moderate		1 (2%)		
Hyperplasia, mild, subcapsular	36 (75%)	27 (60%)	24 (53%)	22 (47%)
Hyperplasia, minimal, subcapsular	7 (15%)	8 (18%)	6 (13%)	5 (11%)
Hyperplasia, moderate, subcapsular	2 (4%)	1 (2%)	3 (7%)	2 (4%)
Hypertrophy, moderate	1 (2%)			
Infiltration cellular, lymphocytic, minimal			1 (2%)	3 (6%)
Inflammation, acute, minimal			1 (2%)	
Thrombosis, moderate		1 (2%)		
Adrenal gland, medulla	(47)	(42)	(43)	(47)
Angiectasis, mild				1 (2%)
Autolysis, marked				2 (4%)
Autolysis, moderate				2 (4%)
Hyperplasia, mild	1 (2%)		2 (5%)	
Hyperplasia, moderate		1 (2%)		
Islets, pancreatic	(48)	(43)	(47)	(44)
Autolysis, marked				4 (9%)
Autolysis, moderate			1 (2%)	3 (7%)
Hyperplasia, mild		3 (7%)	1 (2%)	
Hyperplasia, minimal	2 (4%)	3 (7%)	4 (9%)	4 (9%)
Infiltration cellular, lymphocytic, minimal		1 (2%)	1 (2%)	
Parathyroid gland	(32)	(38)	(31)	(40)
Autolysis, marked				1 (3%)
Autolysis, moderate				1 (3%)
Infiltration cellular, lymphocytic, mild		1 (3%)		
Inflammation, mild	1 (3%)			
Pituitary gland	(42)	(42)	(40)	(39)
Angiectasis, mild	3 (7%)	4 (10%)		
Angiectasis, minimal		1 (2%)		
Hyperplasia, mild, pars distalis	1 (2%)	1 (2%)	2 (5%)	
Hyperplasia, minimal, pars distalis	4 (10%)		1 (3%)	

Table D4
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Drinking Water Study of Urethane and 0% Ethanol

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
Endocrine System (continued)				
Thyroid gland	(47)	(47)	(47)	(45)
Autolysis, marked				1 (2%)
Autolysis, moderate				3 (7%)
Cyst multilocular			3 (6%)	
Hyperplasia, mild, follicular cell	1 (2%)			
Hyperplasia, minimal, C-cell	1 (2%)		1 (2%)	
Hyperplasia, minimal, follicular cell				1 (2%)
Infiltration cellular, lymphocytic, minimal	2 (4%)			1 (2%)
Infiltration cellular, polymorphonuclear, minimal			1 (2%)	
Inflammation, minimal				1 (2%)
General Body System				
None				
Genital System				
Clitoral gland	(43)	(41)	(43)	(37)
Atrophy, mild	29 (67%)	38 (93%)	39 (91%)	22 (59%)
Atrophy, minimal	1 (2%)			4 (11%)
Atrophy, moderate	9 (21%)	1 (2%)	1 (2%)	6 (16%)
Autolysis, moderate			1 (2%)	
Ovary	(48)	(46)	(46)	(39)
Angiectasis, marked			1 (2%)	1 (3%)
Angiectasis, mild			2 (4%)	4 (10%)
Angiectasis, minimal	1 (2%)	2 (4%)	1 (2%)	
Angiectasis, moderate	1 (2%)		2 (4%)	1 (3%)
Atrophy, marked	9 (19%)	34 (74%)	32 (70%)	21 (54%)
Atrophy, mild	13 (27%)	1 (2%)	2 (4%)	1 (3%)
Atrophy, minimal	6 (13%)			
Atrophy, moderate	14 (29%)	5 (11%)	3 (7%)	8 (21%)
Autolysis, marked	1 (2%)			1 (3%)
Autolysis, moderate				1 (3%)
Cyst	10 (21%)	11 (24%)	12 (26%)	2 (5%)
Cyst, periovarian tissue	2 (4%)			1 (3%)
Hematocyst	9 (19%)	4 (9%)	3 (7%)	2 (5%)
Hemorrhage, moderate			1 (2%)	
Hyperplasia, tubular, mild			3 (7%)	1 (3%)
Hyperplasia, tubular, minimal				2 (5%)
Hyperplasia, tubular, moderate				1 (3%)
Infiltration cellular, histiocytic, marked				1 (3%)
Infiltration cellular, histiocytic, moderate		1 (2%)		
Infiltration cellular, lymphocytic, minimal		1 (2%)		
Inflammation, moderate	1 (2%)			
Mineralization, mild				1 (3%)
Mineralization, moderate				1 (3%)
Pigmentation, moderate		1 (2%)		
Thrombosis, marked			1 (2%)	1 (3%)
Thrombosis, marked, periovarian tissue				1 (3%)
Thrombosis, moderate			3 (7%)	

Table D4
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Drinking Water Study of Urethane and 0% Ethanol

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
Genital System (continued)				
Uterus	(48)	(47)	(48)	(46)
Amyloid deposition, moderate		1 (2%)		
Angiectasis, marked		1 (2%)	1 (2%)	3 (7%)
Angiectasis, mild			1 (2%)	2 (4%)
Angiectasis, minimal		2 (4%)		
Angiectasis, moderate		1 (2%)	4 (8%)	2 (4%)
Autolysis, moderate				1 (2%)
Dilatation, minimal	1 (2%)			
Dilatation, moderate	1 (2%)			
Hemorrhage, marked				2 (4%)
Hemorrhage, minimal		1 (2%)		
Hyperplasia, cystic, marked, endometrium		1 (2%)		
Hyperplasia, cystic, mild, endometrium	22 (46%)	24 (51%)	22 (46%)	15 (33%)
Hyperplasia, cystic, minimal, endometrium	4 (8%)	2 (4%)	4 (8%)	4 (9%)
Hyperplasia, cystic, moderate, endometrium	19 (40%)	12 (26%)	8 (17%)	9 (20%)
Infiltration cellular, histiocytic, mild			1 (2%)	
Infiltration cellular, polymorphonuclear, mild		1 (2%)		
Inflammation, mild			1 (2%)	
Inflammation, moderate		1 (2%)	1 (2%)	
Mineralization, mild			1 (2%)	
Pigmentation, moderate			1 (2%)	
Thrombosis, marked		1 (2%)	1 (2%)	3 (7%)
Thrombosis, moderate			3 (6%)	1 (2%)
Vacuolization cytoplasmic, minimal	1 (2%)			
Vagina	(48)	(47)	(46)	(43)
Autolysis, marked				1 (2%)
Exudate, minimal		2 (4%)		
Inflammation, mild	1 (2%)	1 (2%)		
Hematopoietic System				
Bone marrow	(48)	(47)	(46)	(47)
Angiectasis, mild				1 (2%)
Angiectasis, moderate				1 (2%)
Autolysis, marked				3 (6%)
Autolysis, moderate				1 (2%)
Hyperplasia, mild, myeloid cell	6 (13%)	3 (6%)	2 (4%)	3 (6%)
Hyperplasia, minimal, myeloid cell				1 (2%)
Hyperplasia, moderate, myeloid cell	2 (4%)	1 (2%)	3 (7%)	3 (6%)
Pigmentation, minimal			1 (2%)	
Lymph node	(48)	(47)	(47)	(46)
Autolysis, moderate, lumbar				1 (2%)
Hemorrhage, mild, lumbar			1 (2%)	
Hyperplasia, mild, lumbar				1 (2%)
Hyperplasia, mild, renal			1 (2%)	1 (2%)
Hyperplasia, moderate, mediastinal			1 (2%)	
Infiltration cellular, histiocytic, moderate, lumbar				1 (2%)
Infiltration cellular, polymorphonuclear, moderate, renal		1 (2%)		
Inflammation, mild, lumbar			1 (2%)	

Table D4
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Drinking Water Study of Urethane and 0% Ethanol

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
Hematopoietic System (continued)				
Lymph node, mandibular	(45)	(47)	(45)	(42)
Atrophy, mild	1 (2%)			
Atrophy, minimal				1 (2%)
Autolysis, marked				3 (7%)
Hematopoietic cell proliferation, moderate		1 (2%)		
Hemorrhage, marked	1 (2%)			
Hemorrhage, minimal				2 (5%)
Hemorrhage, moderate				1 (2%)
Hyperplasia, lymphoid, marked			1 (2%)	
Hyperplasia, lymphoid, mild	1 (2%)	4 (9%)	3 (7%)	2 (5%)
Hyperplasia, lymphoid, moderate		1 (2%)		
Hyperplasia, plasma cell, moderate		1 (2%)		
Infiltration cellular, histiocytic, mild	1 (2%)			2 (5%)
Lymph node, mesenteric	(47)	(45)	(42)	(39)
Angiectasis, mild			2 (5%)	1 (3%)
Angiectasis, moderate	1 (2%)			
Atrophy, mild	1 (2%)			3 (8%)
Autolysis, moderate	1 (2%)			1 (3%)
Cyst		1 (2%)		
Hematopoietic cell proliferation, mild	1 (2%)			2 (5%)
Hemorrhage, mild			1 (2%)	1 (3%)
Hemorrhage, moderate	1 (2%)			
Hyperplasia, lymphoid, marked		2 (4%)		
Hyperplasia, lymphoid, mild	2 (4%)	2 (4%)	1 (2%)	1 (3%)
Infiltration cellular, histiocytic, mild			1 (2%)	
Infiltration cellular, histiocytic, moderate				1 (3%)
Infiltration cellular, polymorphonuclear, marked		1 (2%)		
Spleen	(48)	(45)	(47)	(46)
Angiectasis, mild		1 (2%)		
Angiectasis, moderate				1 (2%)
Autolysis, marked				3 (7%)
Autolysis, moderate				4 (9%)
Hematopoietic cell proliferation, marked	1 (2%)		3 (6%)	3 (7%)
Hematopoietic cell proliferation, mild	3 (6%)	4 (9%)	5 (11%)	3 (7%)
Hematopoietic cell proliferation, moderate		4 (9%)	7 (15%)	15 (33%)
Hyperplasia, marked, lymphoid follicle		1 (2%)	1 (2%)	
Hyperplasia, mild, lymphoid follicle	11 (23%)	17 (38%)	10 (21%)	
Hyperplasia, minimal, lymphoid follicle	1 (2%)	3 (7%)	2 (4%)	
Hyperplasia, moderate, lymphoid follicle	3 (6%)	5 (11%)	1 (2%)	1 (2%)
Infiltration cellular, histiocytic, mild				1 (2%)
Pigmentation, mild		1 (2%)		
Pigmentation, moderate				1 (2%)
Polyarteritis, minimal				1 (2%)
Thrombosis, moderate				1 (2%)
Thymus	(40)	(37)	(32)	(38)
Atrophy, mild	6 (15%)	3 (8%)	5 (16%)	8 (21%)
Atrophy, moderate	3 (8%)			1 (3%)
Autolysis, marked				1 (3%)
Autolysis, moderate	2 (5%)			2 (5%)
Hyperplasia, mild	1 (3%)	4 (11%)	2 (6%)	
Hyperplasia, minimal			1 (3%)	
Hyperplasia, moderate	2 (5%)			

Table D4
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Drinking Water Study of Urethane and 0% Ethanol

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
Integumentary System				
Mammary gland	(47)	(46)	(46)	(48)
Autolysis, moderate			1 (2%)	
Ectasia, mild, duct	1 (2%)		1 (2%)	
Ectasia, moderate, duct	1 (2%)			
Hyperplasia, mild	1 (2%)	2 (4%)		1 (2%)
Hyperplasia, minimal	1 (2%)			
Hyperplasia, moderate		1 (2%)		
Infiltration cellular, lymphocytic, minimal		1 (2%)	1 (2%)	1 (2%)
Lactation, mild	1 (2%)	2 (4%)	2 (4%)	
Lactation, minimal	2 (4%)			
Lactation, moderate		1 (2%)		
Skin	(48)	(48)	(46)	(48)
Autolysis, marked				1 (2%)
Autolysis, moderate			1 (2%)	
Fibrosis, moderate		1 (2%)		
Hemorrhage, mild				1 (2%)
Inflammation, marked	1 (2%)			1 (2%)
Inflammation, mild				1 (2%)
Neovascularization, moderate				1 (2%)
Thrombosis				1 (2%)
Ulcer			1 (2%)	
Ulcer, mild		1 (2%)		
Musculoskeletal System				
Bone	(48)	(48)	(48)	(48)
Angiectasis, moderate, sternum		1 (2%)		
Degeneration, mild, cartilage, sternum	1 (2%)			1 (2%)
Fibrous osteodystrophy, mild, sternum	19 (40%)	14 (29%)	12 (25%)	3 (6%)
Fibrous osteodystrophy, minimal, sternum	9 (19%)	3 (6%)	4 (8%)	2 (4%)
Fibrous osteodystrophy, moderate, sternum	2 (4%)	5 (10%)	6 (13%)	1 (2%)
Bone, femur	(48)	(48)	(48)	(48)
Angiectasis, moderate		1 (2%)		
Fibrous osteodystrophy, mild	2 (4%)	1 (2%)	3 (6%)	2 (4%)
Fibrous osteodystrophy, minimal	5 (10%)	4 (8%)	1 (2%)	
Fibrous osteodystrophy, moderate	2 (4%)	3 (6%)	1 (2%)	1 (2%)
Skeletal muscle	(48)	(48)	(48)	(48)
Autolysis, moderate				1 (2%)
Hyperplasia, lymphoid, diaphragm		1 (2%)		
Nervous System				
Brain, cerebellum	(48)	(48)	(48)	(48)
Autolysis, moderate				1 (2%)
Inflammation, chronic active, mild, meninges		1 (2%)		
Mineralization, minimal, thalamus	1 (2%)			

Table D4
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Drinking Water Study of Urethane and 0% Ethanol

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
Nervous System (continued)				
Brain, cerebrum	(48)	(48)	(48)	(48)
Autolysis, moderate				1 (2%)
Compression, moderate, hypothalamus	1 (2%)			
Granuloma, minimal				2 (4%)
Hemorrhage, mild				1 (2%)
Hemorrhage, minimal			1 (2%)	1 (2%)
Inflammation, chronic active, mild, meninges		1 (2%)		
Mineralization, mild, thalamus	2 (4%)	1 (2%)	2 (4%)	3 (6%)
Mineralization, minimal, thalamus	19 (40%)	25 (52%)	24 (50%)	23 (48%)
Necrosis, mild				1 (2%)
Peripheral nerve	(48)	(47)	(48)	(48)
Autolysis, moderate				1 (2%)
Spinal cord, thoracic	(48)	(48)	(48)	(48)
Autolysis, marked				1 (2%)
Autolysis, moderate				1 (2%)
Hemorrhage, minimal			1 (2%)	
Respiratory System				
Larynx	(48)	(46)	(46)	(45)
Autolysis, marked				1 (2%)
Autolysis, moderate				1 (2%)
Lung	(48)	(48)	(48)	(47)
Congestion, moderate				1 (2%)
Hemorrhage, mild		1 (2%)	2 (4%)	
Hemorrhage, minimal	2 (4%)	4 (8%)	7 (15%)	
Hemorrhage, moderate				2 (4%)
Hyperplasia, mild, alveolar epithelium		1 (2%)	3 (6%)	5 (11%)
Hyperplasia, minimal, alveolar epithelium		1 (2%)	1 (2%)	1 (2%)
Hyperplasia, moderate, alveolar epithelium				1 (2%)
Infiltration cellular, histiocytic, mild		2 (4%)	2 (4%)	1 (2%)
Infiltration cellular, histiocytic, minimal			1 (2%)	
Infiltration cellular, histiocytic, moderate			3 (6%)	5 (11%)
Infiltration cellular, lymphocytic, mild	10 (21%)	8 (17%)	7 (15%)	5 (11%)
Infiltration cellular, lymphocytic, minimal	24 (50%)	19 (40%)	10 (21%)	6 (13%)
Infiltration cellular, lymphocytic, moderate		1 (2%)	1 (2%)	
Inflammation, chronic active, mild	1 (2%)			
Inflammation, chronic active, minimal			1 (2%)	
Nose	(48)	(48)	(48)	(46)
Autolysis, moderate				2 (4%)
Fibrous osteodystrophy, mild	2 (4%)			
Fibrous osteodystrophy, minimal	6 (13%)			
Inflammation, marked	1 (2%)			
Trachea	(48)	(47)	(47)	(46)
Autolysis, marked				1 (2%)
Autolysis, moderate				1 (2%)

Table D4
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Drinking Water Study of Urethane and 0% Ethanol

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
Special Senses System				
Eye	(48)	(47)	(46)	(48)
Atrophy, mild			1 (2%)	
Atrophy, moderate				2 (4%)
Autolysis, marked				1 (2%)
Autolysis, moderate	1 (2%)	1 (2%)		
Cataract, mild, lens				1 (2%)
Cataract, minimal, lens			1 (2%)	
Inflammation, marked, cornea		1 (2%)		1 (2%)
Inflammation, mild, cornea			4 (9%)	8 (17%)
Inflammation, minimal, cornea		2 (4%)	1 (2%)	1 (2%)
Inflammation, moderate, cornea			1 (2%)	
Phthisis bulbi		1 (2%)	2 (4%)	3 (6%)
Phthisis bulbi, bilateral				1 (2%)
Harderian gland	(48)	(48)	(48)	(48)
Autolysis, marked				1 (2%)
Dilatation, mild			1 (2%)	
Infiltration cellular, lymphocytic, mild	1 (2%)	1 (2%)		2 (4%)
Infiltration cellular, lymphocytic, minimal	17 (35%)	9 (19%)	8 (17%)	2 (4%)
Infiltration cellular, lymphocytic, moderate		1 (2%)		
Lacrimal gland	(45)	(47)	(43)	(40)
Atrophy, mild			1 (2%)	
Atrophy, minimal		4 (9%)	1 (2%)	
Autolysis, marked				1 (3%)
Cyst	1 (2%)			
Dilatation, minimal, duct		2 (4%)	1 (2%)	
Hemorrhage, moderate				1 (3%)
Hypertrophy, minimal, parenchymal cell	1 (2%)			
Infiltration cellular, lymphocytic, mild	8 (18%)	15 (32%)	1 (2%)	3 (8%)
Infiltration cellular, lymphocytic, minimal	18 (40%)	15 (32%)	17 (40%)	13 (33%)
Infiltration cellular, lymphocytic, moderate		2 (4%)	2 (5%)	
Vacuolization cytoplasmic, minimal			1 (2%)	
Zymbal's gland	(46)	(43)	(46)	(46)
Atrophy, minimal				1 (2%)
Autolysis, moderate				1 (2%)
Hyperplasia, mild			1 (2%)	
Urinary System				
Kidney	(48)	(48)	(48)	(48)
Accumulation, hyaline droplet, mild			1 (2%)	
Accumulation, hyaline droplet, moderate		1 (2%)		2 (4%)
Amyloid deposition, marked			1 (2%)	
Atrophy, minimal, renal tubule				1 (2%)
Autolysis, marked				1 (2%)
Autolysis, mild	1 (2%)			
Autolysis, moderate		1 (2%)	1 (2%)	3 (6%)
Casts, mild	1 (2%)			
Casts, minimal				2 (4%)
Congestion, mild			1 (2%)	
Cyst	1 (2%)			

Table D4
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Drinking Water Study of Urethane and 0% Ethanol

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
Urinary System (continued)				
Kidney (continued)	(48)	(48)	(48)	(48)
Degeneration, focal, minimal, renal tubule	1 (2%)			
Glomerulosclerosis, mild			1 (2%)	1 (2%)
Glomerulosclerosis, minimal				1 (2%)
Hydronephrosis, mild		1 (2%)		
Hydronephrosis, moderate		1 (2%)		1 (2%)
Infarct, minimal	3 (6%)			1 (2%)
Infiltration cellular, lymphocytic, mild	3 (6%)	8 (17%)	3 (6%)	3 (6%)
Infiltration cellular, lymphocytic, minimal	12 (25%)	10 (21%)	12 (25%)	13 (27%)
Infiltration cellular, lymphocytic, moderate	1 (2%)	2 (4%)		
Infiltration cellular, polymorphonuclear, mild			1 (2%)	
Metaplasia, osseous, minimal	1 (2%)		1 (2%)	1 (2%)
Mineralization, mild				1 (2%)
Mineralization, minimal		1 (2%)	1 (2%)	1 (2%)
Pigmentation, moderate, renal tubule			1 (2%)	
Polyarteritis				1 (2%)
Urinary bladder	(48)	(46)	(45)	(41)
Autolysis, marked				1 (2%)
Autolysis, moderate	3 (6%)	2 (4%)	1 (2%)	
Distended	1 (2%)			
Infiltration cellular, lymphocytic, mild	8 (17%)	7 (15%)	3 (7%)	5 (12%)
Infiltration cellular, lymphocytic, minimal	17 (35%)	20 (43%)	20 (44%)	7 (17%)
Infiltration cellular, lymphocytic, moderate		1 (2%)		1 (2%)

APPENDIX E
SUMMARY OF LESIONS IN FEMALE MICE IN THE 2-YEAR DRINKING WATER STUDY OF URETHANE AND 2.5% ETHANOL

Table E1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Drinking Water Study of Urethane and 2.5% Ethanol[a]

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
Disposition Summary				
Animals initially in study	48	47	48	48
Early deaths				
Accidental deaths	4	3		
Moribund	1	4	11	9
Natural deaths	4	7	18	31
Survivors				
Terminal sacrifice	39	33	19	8
Animals examined microscopically	47	47	48	48
Alimentary System				
Esophagus	(47)	(47)	(47)	(47)
Sarcoma, metastatic, kidney				1 (2%)
Gallbladder	(47)	(45)	(46)	(43)
Lymphoma malignant			1 (2%)	
Intestine large, cecum	(47)	(45)	(47)	(41)
Lymphoma malignant		1 (2%)	1 (2%)	1 (2%)
Intestine large, colon	(47)	(45)	(47)	(43)
Lymphoma malignant		1 (2%)		1 (2%)
Intestine large, rectum	(47)	(44)	(47)	(46)
Lymphoma malignant	1 (2%)			1 (2%)
Sarcoma, metastatic, uterus				1 (2%)
Squamous cell carcinoma				1 (2%)
Intestine small, duodenum	(47)	(45)	(47)	(39)
Lymphoma malignant	1 (2%)			
Intestine small, ileum	(47)	(45)	(47)	(40)
Lymphoma malignant		1 (2%)	1 (2%)	
Intestine small, jejunum	(47)	(45)	(47)	(39)
Lymphoma malignant			1 (2%)	
Sarcoma stromal, metastatic, uterus			1 (2%)	
Sarcoma, metastatic, skin			1 (2%)	
Liver	(47)	(47)	(47)	(46)
Hemangiosarcoma	1 (2%)	2 (4%)		7 (15%)
Hepatocellular adenoma	4 (9%)		6 (13%)	9 (20%)
Hepatocellular adenoma, multiple	2 (4%)	5 (11%)	9 (19%)	14 (30%)
Hepatocellular carcinoma	1 (2%)		3 (6%)	1 (2%)
Histiocytic sarcoma		2 (4%)	2 (4%)	1 (2%)
Ito cell tumor malignant	1 (2%)			
Lymphoma malignant	2 (4%)	7 (15%)	5 (11%)	3 (7%)
Osteosarcoma, metastatic, bone		1 (2%)	1 (2%)	
Sarcoma stromal, metastatic, uterus			1 (2%)	
Sarcoma, metastatic, skin			1 (2%)	
Mesentery	(2)	(5)	(6)	(6)
Hemangiosarcoma				1 (17%)
Lymphoma malignant		1 (20%)	1 (17%)	
Sarcoma		1 (20%)		
Sarcoma, metastatic, kidney				1 (17%)
Pancreas	(47)	(45)	(46)	(44)
Histiocytic sarcoma				1 (2%)
Lymphoma malignant	1 (2%)	3 (7%)	3 (7%)	1 (2%)
Sarcoma		1 (2%)		
Sarcoma stromal, metastatic, uterus			1 (2%)	
Sarcoma, metastatic, kidney				1 (2%)
Sarcoma, metastatic, skin			1 (2%)	

Table E1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Drinking Water Study of Urethane and 2.5% Ethanol

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
Alimentary System (continued)				
Salivary glands	(47)	(47)	(46)	(48)
Lymphoma malignant	2 (4%)	4 (9%)	3 (7%)	1 (2%)
Stomach, forestomach	(47)	(46)	(47)	(46)
Lymphoma malignant		1 (2%)		
Sarcoma stromal, metastatic, uterus			1 (2%)	
Sarcoma, metastatic, kidney				1 (2%)
Squamous cell carcinoma				1 (2%)
Squamous cell papilloma		4 (9%)		
Stomach, glandular	(47)	(46)	(47)	(45)
Lymphoma malignant		2 (4%)		
Tongue	(47)	(47)	(48)	(48)
Lymphoma malignant		1 (2%)		
Cardiovascular System				
Blood vessel	(47)	(47)	(48)	(48)
Lymphoma malignant				2 (4%)
Heart	(47)	(47)	(48)	(48)
Alveolar/bronchiolar carcinoma, metastatic, lung				1 (2%)
Hemangiosarcoma				3 (6%)
Histiocytic sarcoma		1 (2%)		
Lymphoma malignant		1 (2%)	1 (2%)	3 (6%)
Squamous cell carcinoma, metastatic, intestine large				1 (2%)
Endocrine System				
Adrenal gland	(46)	(47)	(46)	(44)
Adenoma, bilateral, subcapsular				1 (2%)
Adrenal gland, cortex	(46)	(47)	(46)	(44)
Adenocarcinoma, metastatic, mammary gland	1 (2%)			
Adenoma	1 (2%)			
Adenoma, subcapsular		1 (2%)		
Carcinoma, subcapsular				1 (2%)
Lymphoma malignant		3 (6%)	1 (2%)	1 (2%)
Osteosarcoma, metastatic, bone			1 (2%)	
Sarcoma stromal, metastatic, uterus			1 (2%)	
Sarcoma, metastatic, kidney				1 (2%)
Sarcoma, metastatic, skin				1 (2%)
Adrenal gland, medulla	(45)	(47)	(45)	(41)
Lymphoma malignant		1 (2%)		1 (2%)
Pheochromocytoma benign	1 (2%)	1 (2%)		
Pheochromocytoma malignant			1 (2%)	
Islets, pancreatic	(47)	(45)	(46)	(44)
Adenoma	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Lymphoma malignant			2 (4%)	1 (2%)
Parathyroid gland	(34)	(37)	(37)	(31)
Lymphoma malignant			1 (3%)	
Pituitary gland	(44)	(41)	(41)	(38)
Adenoma, pars distalis	7 (16%)	2 (5%)	3 (7%)	1 (3%)
Lymphoma malignant		1 (2%)		1 (3%)
Meningioma malignant, metastatic, brain			1 (2%)	
Thyroid gland	(46)	(47)	(45)	(46)
Adenoma, follicular cell	1 (2%)		1 (2%)	
Lymphoma malignant		1 (2%)		

Table E1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Drinking Water Study of Urethane and 2.5% Ethanol

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
General Body System				
Tissue NOS		(1)	(1)	
Sarcoma, abdominal		1 (100%)		
Genital System				
Clitoral gland	(40)	(40)	(34)	(40)
Lymphoma malignant	1 (3%)	1 (3%)		
Ovary	(47)	(46)	(47)	(48)
Adenoma, tubular	1 (2%)			1 (2%)
Cystadenoma	1 (2%)	2 (4%)		2 (4%)
Granulosa cell tumor benign			3 (6%)	3 (6%)
Hemangioma				1 (2%)
Hemangiosarcoma			1 (2%)	2 (4%)
Histiocytic sarcoma		1 (2%)	1 (2%)	
Lymphoma malignant	1 (2%)	4 (9%)	4 (9%)	3 (6%)
Thecoma benign				1 (2%)
Uterus	(47)	(47)	(48)	(48)
Hemangioma			1 (2%)	3 (6%)
Hemangiosarcoma			1 (2%)	1 (2%)
Histiocytic sarcoma		1 (2%)	2 (4%)	
Leiomyoma	1 (2%)			
Leiomyosarcoma				1 (2%)
Lymphoma malignant	1 (2%)	1 (2%)	2 (4%)	1 (2%)
Polyp stromal			1 (2%)	
Sarcoma				1 (2%)
Sarcoma stromal			1 (2%)	1 (2%)
Sarcoma, metastatic, skin				1 (2%)
Vagina	(47)	(47)	(47)	(47)
Hemangioma				1 (2%)
Histiocytic sarcoma		1 (2%)		
Lymphoma malignant	1 (2%)	1 (2%)		1 (2%)
Sarcoma stromal, metastatic, uterus			1 (2%)	
Sarcoma, metastatic, uterus				1 (2%)
Hematopoietic System				
Bone marrow	(47)	(46)	(48)	(48)
Hemangiosarcoma				1 (2%)
Histiocytic sarcoma		1 (2%)	1 (2%)	
Lymphoma malignant				1 (2%)
Lymph node	(47)	(47)	(47)	(47)
Histiocytic sarcoma, iliac				1 (2%)
Histiocytic sarcoma, lumbar		1 (2%)	1 (2%)	1 (2%)
Histiocytic sarcoma, pancreatic				1 (2%)
Histiocytic sarcoma, renal				1 (2%)
Lymphoma malignant, axillary		1 (2%)		1 (2%)
Lymphoma malignant, hemal			1 (2%)	
Lymphoma malignant, lumbar		2 (4%)	2 (4%)	2 (4%)
Lymphoma malignant, renal		2 (4%)	3 (6%)	2 (4%)
Lymphoma malignant, thoracic		3 (6%)	2 (4%)	
Sarcoma stromal, metastatic, lumbar, uterus			1 (2%)	
Sarcoma stromal, metastatic, renal, uterus			1 (2%)	
Sarcoma stromal, metastatic, thoracic, uterus			1 (2%)	
Sarcoma, metastatic, inguinal, skin				1 (2%)
Sarcoma, metastatic, lumbar, skin				1 (2%)

Table E1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Drinking Water Study of Urethane and 2.5% Ethanol

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
Hematopoietic System (continued)				
Lymph node, mandibular	(47)	(44)	(43)	(46)
Histiocytic sarcoma		2 (5%)	1 (2%)	1 (2%)
Lymphoma malignant	4 (9%)	4 (9%)	6 (14%)	4 (9%)
Lymph node, mesenteric	(43)	(42)	(42)	(38)
Histiocytic sarcoma		1 (2%)	1 (2%)	2 (5%)
Lymphoma malignant	5 (12%)	6 (14%)	8 (19%)	2 (5%)
Sarcoma stromal, metastatic, uterus			1 (2%)	
Sarcoma, metastatic, kidney				1 (3%)
Spleen	(47)	(46)	(46)	(46)
Hemangioma		1 (2%)		
Hemangiosarcoma				3 (7%)
Histiocytic sarcoma		2 (4%)	1 (2%)	2 (4%)
Lymphoma malignant	6 (13%)	8 (17%)	8 (17%)	3 (7%)
Sarcoma stromal, metastatic, uterus			1 (2%)	
Thymus	(41)	(40)	(34)	(36)
Alveolar/bronchiolar carcinoma, metastatic, lung			1 (3%)	2 (6%)
Histiocytic sarcoma			1 (3%)	
Lymphoma malignant	3 (7%)	5 (13%)	7 (21%)	5 (14%)
Sarcoma, metastatic, kidney				1 (3%)
Integumentary System				
Mammary gland	(47)	(45)	(48)	(47)
Adenoacanthoma			2 (4%)	3 (6%)
Adenocarcinoma	4 (9%)	3 (7%)	11 (23%)	14 (30%)
Lymphoma malignant	1 (2%)	1 (2%)		1 (2%)
Skin	(47)	(47)	(48)	(47)
Fibroma				1 (2%)
Hemangioma	1 (2%)		1 (2%)	
Hemangiosarcoma				2 (4%)
Osteosarcoma			1 (2%)	
Sarcoma	2 (4%)	1 (2%)	6 (13%)	5 (11%)
Squamous cell carcinoma, metastatic, intestine large				1 (2%)
Musculoskeletal System				
Bone	(47)	(47)	(48)	(48)
Lymphoma malignant, sternum				1 (2%)
Osteosarcoma, humerus			1 (2%)	
Osteosarcoma, rib			1 (2%)	
Osteosarcoma, right		1 (2%)		
Osteosarcoma, vertebra			1 (2%)	
Bone, femur	(46)	(47)	(48)	(48)
Hemangiosarcoma				1 (2%)
Lymphoma malignant				1 (2%)
Sarcoma, metastatic, skin			1 (2%)	
Skeletal muscle	(47)	(47)	(48)	(48)
Alveolar/bronchiolar carcinoma, metastatic, lung				1 (2%)
Hemangiosarcoma				1 (2%)
Lymphoma malignant	2 (4%)	2 (4%)	1 (2%)	1 (2%)
Sarcoma, metastatic, skin				1 (2%)

Table E1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Drinking Water Study of Urethane and 2.5% Ethanol

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
Nervous System				
Brain, cerebellum	(47)	(46)	(47)	(48)
Lymphoma malignant				1 (2%)
Brain, cerebrum	(47)	(47)	(47)	(48)
Lymphoma malignant				1 (2%)
Meningioma malignant			1 (2%)	
Peripheral nerve	(47)	(46)	(48)	(48)
Lymphoma malignant	1 (2%)			
Spinal cord, thoracic	(47)	(47)	(47)	(48)
Lymphoma malignant				1 (2%)
Respiratory System				
Lung	(47)	(47)	(48)	(48)
Adenocarcinoma, metastatic, mammary gland			1 (2%)	
Adenocarcinoma, metastatic, multiple, mammary gland	1 (2%)			
Alveolar/bronchiolar adenoma	5 (11%)	7 (15%)	12 (25%)	10 (21%)
Alveolar/bronchiolar adenoma, multiple		3 (6%)	4 (8%)	18 (38%)
Alveolar/bronchiolar carcinoma		2 (4%)	4 (8%)	11 (23%)
Alveolar/bronchiolar carcinoma, multiple			2 (4%)	12 (25%)
Carcinoma, metastatic, mammary gland			1 (2%)	
Carcinoma, metastatic, Zymbal's gland		1 (2%)		
Hepatocellular carcinoma, metastatic, liver			1 (2%)	
Histiocytic sarcoma		2 (4%)	1 (2%)	1 (2%)
Lymphoma malignant	1 (2%)	6 (13%)	3 (6%)	5 (10%)
Osteosarcoma, metastatic, bone		1 (2%)	1 (2%)	
Sarcoma stromal, metastatic, uterus				1 (2%)
Sarcoma, metastatic, skin			1 (2%)	3 (6%)
Squamous cell carcinoma, metastatic, intestine large				1 (2%)
Nose	(47)	(47)	(48)	(48)
Lymphoma malignant				1 (2%)
Special Senses System				
Eye	(47)	(45)	(48)	(46)
Lymphoma malignant				1 (2%)
Harderian gland	(47)	(47)	(46)	(47)
Adenoma	2 (4%)	3 (6%)	9 (20%)	16 (34%)
Adenoma, bilateral				3 (6%)
Carcinoma	1 (2%)	3 (6%)	6 (13%)	12 (26%)
Carcinoma, bilateral				4 (9%)
Lymphoma malignant	1 (2%)		1 (2%)	1 (2%)
Lacrimal gland	(45)	(45)	(44)	(43)
Lymphoma malignant	2 (4%)	3 (7%)	1 (2%)	1 (2%)
Zymbal's gland	(46)	(43)	(41)	(44)
Carcinoma		1 (2%)		
Lymphoma malignant				1 (2%)

Table E1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Drinking Water Study of Urethane and 2.5% Ethanol

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
Urinary System				
Kidney	(47)	(47)	(48)	(48)
Hemangiosarcoma				2 (4%)
Hemangiosarcoma, perirenal tissue				1 (2%)
Histiocytic sarcoma		1 (2%)		
Lymphoma malignant	1 (2%)	6 (13%)	3 (6%)	3 (6%)
Osteosarcoma, metastatic, bone			1 (2%)	
Sarcoma		1 (2%)		1 (2%)
Sarcoma, metastatic, skin			1 (2%)	
Urinary bladder	(45)	(43)	(47)	(45)
Lymphoma malignant	1 (2%)	1 (2%)	3 (6%)	1 (2%)
Neoplasm Summary				
Total animals with primary neoplasms[b]	29	32	45	48
Total primary neoplasms	77	148	182	255
Total animals with benign neoplasms	21	20	31	39
Total benign neoplasms	28	29	51	86
Total animals with malignant neoplasms	14	22	38	45
Total malignant neoplasms	49	119	131	169
Total animals with metastatic neoplasms	1	2	10	10
Total metastatic neoplasms	2	3	26	25

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

Table E2
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Drinking Water Study of Urethane and 2.5% Ethanol

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
Harderian Gland: Adenoma				
Overall rate[a]	2/47 (4.3%)	3/47 (6.4%)	9/46 (19.6%)	19/47 (40.4%)
Adjusted rate[b]	2/44.5 (4.5%)	3/42.5 (7.1%)	9/36.3 (24.8%)	19/37.9 (50.1%)
Terminal rate[c]	2/39 (5.1%)	3/33 (9.1%)	3/19 (15.8%)	2/8 (25.0%)
First incidence (days)	765 (T)	765 (T)	594	542
Poly-3 test[d]	P=0.001	P=0.461	P=0.007	P=0.001
Harderian Gland: Carcinoma				
Overall rate	1/47 (2.1%)	3/47 (6.4%)	6/46 (13.0%)	16/47 (34.0%)
Adjusted rate	1/44.5 (2.2%)	3/42.5 (7.1%)	6/35.6 (16.8%)	16/36.1 (44.4%)
Terminal rate	1/39 (2.6%)	3/33 (9.1%)	4/19 (21.1%)	3/8 (37.5%)
First incidence (days)	765 (T)	765 (T)	584	599
Poly-3 test	P=0.001	P=0.276	P=0.024	P=0.001
Harderian Gland: Adenoma or Carcinoma				
Overall rate	3/47 (6.4%)	5/47 (10.6%)	15/46 (32.6%)	35/47 (74.5%)
Adjusted rate	3/44.5 (6.7%)	5/42.5 (11.8%)	15/37.1 (40.4%)	35/41.5 (84.3%)
Terminal rate	3/39 (7.7%)	5/33 (15.2%)	7/19 (36.8%)	5/8 (62.5%)
First incidence (days)	765 (T)	765 (T)	584	542
Poly-3 test	P=0.001	P=0.311	P=0.001	P=0.001
Heart: Hemangiosarcoma				
Overall rate	0/47 (0.0%)	0/47 (0.0%)	0/48 (0.0%)	3/48 (6.3%)
Adjusted rate	0/44.5 (0.0%)	0/42.5 (0.0%)	0/36.2 (0.0%)	3/34.2 (8.8%)
Terminal rate	0/39 (0.0%)	0/33 (0.0%)	0/19 (0.0%)	0/8 (0.0%)
First incidence (days)	—[e]	—	—	565
Poly-3 test	P=0.005	—[f]	—	P=0.074
Kidney: Hemangiosarcoma				
Overall rate	0/47 (0.0%)	0/47 (0.0%)	0/48 (0.0%)	3/48 (6.3%)
Adjusted rate	0/44.5 (0.0%)	0/42.5 (0.0%)	0/36.2 (0.0%)	3/34.6 (8.7%)
Terminal rate	0/39 (0.0%)	0/33 (0.0%)	0/19 (0.0%)	0/8 (0.0%)
First incidence (days)	—	—	—	508
Poly-3 test	P=0.005	—	—	P=0.075
Liver: Hemangiosarcoma				
Overall rate	1/47 (2.1%)	2/47 (4.3%)	0/47 (0.0%)	7/46 (15.2%)
Adjusted rate	1/44.5 (2.2%)	2/42.5 (4.7%)	0/35.4 (0.0%)	7/32.6 (21.5%)
Terminal rate	1/39 (2.6%)	2/33 (6.1%)	0/19 (0.0%)	1/8 (12.5%)
First incidence (days)	765 (T)	765 (T)	—	677
Poly-3 test	P=0.001	P=0.470	P=0.553N	P=0.007
Liver: Hepatocellular Adenoma				
Overall rate	6/47 (12.8%)	5/47 (10.6%)	15/47 (31.9%)	23/46 (50.0%)
Adjusted rate	6/44.5 (13.5%)	5/42.5 (11.8%)	15/36.2 (41.4%)	23/36.4 (63.2%)
Terminal rate	6/39 (15.4%)	5/33 (15.2%)	13/19 (68.4%)	8/8 (100.0%)
First incidence (days)	765 (T)	765 (T)	600	608
Poly-3 test	P=0.001	P=0.559N	P=0.003	P=0.001
Liver: Hepatocellular Carcinoma				
Overall rate	1/47 (2.1%)	0/47 (0.0%)	3/47 (6.4%)	1/46 (2.2%)
Adjusted rate	1/44.5 (2.2%)	0/42.5 (0.0%)	3/36.0 (8.3%)	1/32.2 (3.1%)
Terminal rate	0/39 (0.0%)	0/33 (0.0%)	2/19 (10.5%)	0/8 (0.0%)
First incidence (days)	752	—	584	646
Poly-3 test	P=0.397	P=0.517N	P=0.221	P=0.672

Table E2
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Drinking Water Study of Urethane and 2.5% Ethanol

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rate	7/47 (14.9%)	5/47 (10.6%)	16/47 (34.0%)	23/46 (50.0%)
Adjusted rate	7/44.5 (15.7%)	5/42.5 (11.8%)	16/36.8 (43.5%)	23/36.4 (63.2%)
Terminal rate	6/39 (15.4%)	5/33 (15.2%)	13/19 (68.4%)	8/8 (100.0%)
First incidence (days)	752	765 (T)	584	608
Poly-3 test	P=0.001	P=0.441N	P=0.003	P=0.001
Lung: Alveolar/bronchiolar Adenoma				
Overall rate	5/47 (10.6%)	10/47 (21.3%)	16/48 (33.3%)	28/48 (58.3%)
Adjusted rate	5/44.5 (11.2%)	10/43.6 (22.9%)	16/39.2 (40.8%)	28/39.4 (71.1%)
Terminal rate	5/39 (12.8%)	6/33 (18.2%)	7/19 (36.8%)	6/8 (75.0%)
First incidence (days)	765 (T)	611	306	593
Poly-3 test	P=0.001	P=0.103	P=0.001	P=0.001
Lung: Alveolar/bronchiolar Carcinoma				
Overall rate	0/47 (0.0%)	2/47 (4.3%)	6/48 (12.5%)	23/48 (47.9%)
Adjusted rate	0/44.5 (0.0%)	2/42.5 (4.7%)	6/37.0 (16.2%)	23/37.3 (61.7%)
Terminal rate	0/39 (0.0%)	2/33 (6.1%)	3/19 (15.8%)	6/8 (75.0%)
First incidence (days)	—	765 (T)	640	499
Poly-3 test	P=0.001	P=0.219	P=0.007	P=0.001
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rate	5/47 (10.6%)	11/47 (23.4%)	21/48 (43.8%)	38/48 (79.2%)
Adjusted rate	5/44.5 (11.2%)	11/43.6 (25.2%)	21/39.7 (52.9%)	38/42.0 (90.6%)
Terminal rate	5/39 (12.8%)	7/33 (21.2%)	10/19 (52.6%)	8/8 (100.0%)
First incidence (days)	765 (T)	611	306	499
Poly-3 test	P=0.001	P=0.064	P=0.001	P=0.001
Lymph Node (Mandibular): Histiocytic Sarcoma				
Overall rate	0/47 (0.0%)	2/44 (4.5%)	1/43 (2.3%)	1/46 (2.2%)
Adjusted rate	0/44.5 (0.0%)	2/41.1 (4.9%)	1/32.6 (3.1%)	1/31.7 (3.2%)
Terminal rate	0/39 (0.0%)	1/33 (3.0%)	0/19 (0.0%)	0/8 (0.0%)
First incidence (days)	—	698	738	762
Poly-3 test	P=0.465	P=0.211	P=0.431	P=0.426
Lymph Node (Mesenteric): Histiocytic Sarcoma				
Overall rate	0/43 (0.0%)	1/42 (2.4%)	1/42 (2.4%)	2/38 (5.3%)
Adjusted rate	0/41.0 (0.0%)	1/38.8 (2.6%)	1/31.5 (3.2%)	2/27.0 (7.4%)
Terminal rate	0/36 (0.0%)	0/31 (0.0%)	0/17 (0.0%)	1/8 (12.5%)
First incidence (days)	—	698	738	762
Poly-3 test	P=0.101	P=0.482	P=0.442	P=0.150
Mammary Gland: Adenoacanthoma				
Overall rate	0/47 (0.0%)	0/45 (0.0%)	2/48 (4.2%)	3/47 (6.4%)
Adjusted rate	0/44.5 (0.0%)	0/41.0 (0.0%)	2/36.4 (5.5%)	3/33.4 (9.0%)
Terminal rate	0/39 (0.0%)	0/32 (0.0%)	1/19 (5.3%)	0/8 (0.0%)
First incidence (days)	—	—	690	599
Poly-3 test	P=0.017	—	P=0.188	P=0.071
Mammary Gland: Adenocarcinoma				
Overall rate	4/47 (8.5%)	3/45 (6.7%)	11/48 (22.9%)	14/47 (29.8%)
Adjusted rate	4/44.7 (9.0%)	3/41.0 (7.3%)	11/38.2 (28.8%)	14/35.6 (39.3%)
Terminal rate	2/39 (5.1%)	3/32 (9.4%)	4/19 (21.1%)	2/8 (25.0%)
First incidence (days)	718	765 (T)	607	648
Poly-3 test	P=0.001	P=0.568N	P=0.015	P=0.001

Table E2
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Drinking Water Study of Urethane and 2.5% Ethanol

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
Mammary Gland: Adenoacanthoma or Adenocarcinoma				
Overall rate	4/47 (8.5%)	3/45 (6.7%)	12/48 (25.0%)	16/47 (34.0%)
Adjusted rate	4/44.7 (9.0%)	3/41.0 (7.3%)	12/38.2 (31.2%)	16/36.3 (44.1%)
Terminal rate	2/39 (5.1%)	3/32 (9.4%)	4/19 (21.1%)	2/8 (25.0%)
First incidence (days)	718	765 (T)	607	599
Poly-3 test	P=0.001	P=0.568N	P=0.007	P=0.001
Ovary: Hemangioma or Hemangiosarcoma				
Overall rate	0/47 (0.0%)	0/46 (0.0%)	1/47 (2.1%)	3/48 (6.3%)
Adjusted rate	0/44.5 (0.0%)	0/41.5 (0.0%)	1/36.0 (2.8%)	3/33.8 (8.9%)
Terminal rate	0/39 (0.0%)	0/33 (0.0%)	0/19 (0.0%)	0/8 (0.0%)
First incidence (days)	—	—	696	611
Poly-3 test	P=0.011	—	P=0.450	P=0.073
Ovary: Benign Granulosa Cell Tumor				
Overall rate	0/47 (0.0%)	0/46 (0.0%)	3/47 (6.4%)	3/48 (6.3%)
Adjusted rate	0/44.5 (0.0%)	0/41.5 (0.0%)	3/36.0 (8.3%)	3/33.9 (8.9%)
Terminal rate	0/39 (0.0%)	0/33 (0.0%)	2/19 (10.5%)	1/8 (12.5%)
First incidence (days)	—	—	696	614
Poly-3 test	P=0.023	—	P=0.080	P=0.073
Pituitary Gland (Pars Distalis): Adenoma or Carcinoma				
Overall rate	7/44 (15.9%)	2/41 (4.9%)	3/41 (7.3%)	1/38 (2.6%)
Adjusted rate	7/42.5 (16.5%)	2/37.3 (5.4%)	3/30.9 (9.7%)	1/26.5 (3.8%)
Terminal rate	5/37 (13.5%)	2/30 (6.7%)	1/15 (6.7%)	0/8 (0.0%)
First incidence (days)	677	765 (T)	594	646
Poly-3 test	P=0.142N	P=0.123N	P=0.336N	P=0.130N
Skin: Sarcoma				
Overall rate	2/47 (4.3%)	1/47 (2.1%)	6/48 (12.5%)	5/47 (10.6%)
Adjusted rate	2/44.5 (4.5%)	1/42.5 (2.4%)	6/37.2 (16.1%)	5/33.5 (14.9%)
Terminal rate	2/39 (5.1%)	1/33 (3.0%)	2/19 (10.5%)	0/8 (0.0%)
First incidence (days)	765 (T)	765 (T)	636	626
Poly-3 test	P=0.035	P=0.530N	P=0.074	P=0.108
Skin: Fibroma or Sarcoma				
Overall rate	2/47 (4.3%)	1/47 (2.1%)	6/48 (12.5%)	6/47 (12.8%)
Adjusted rate	2/44.5 (4.7%)	1/42.5 (2.4%)	6/37.2 (16.1%)	6/33.7 (17.8%)
Terminal rate	2/39 (5.1%)	1/33 (3.0%)	2/19 (10.5%)	0/8 (0.0%)
First incidence (days)	765 (T)	765 (T)	636	626
Poly-3 test	P=0.013	P=0.530N	P=0.074	P=0.055
Spleen: Hemangiosarcoma				
Overall rate	0/47 (0.0%)	0/46 (0.0%)	0/46 (0.0%)	3/46 (6.5%)
Adjusted rate	0/44.5 (0.0%)	0/42.0 (0.0%)	0/35.1 (0.0%)	3/32.7 (9.2%)
Terminal rate	0/39 (0.0%)	0/33 (0.0%)	0/19 (0.0%)	0/8 (0.0%)
First incidence (days)	—	—	—	626
Poly-3 test	P=0.005	—	—	P=0.069
Spleen: Hemangioma or Hemangiosarcoma				
Overall rate	0/47 (0.0%)	1/46 (2.2%)	0/46 (0.0%)	3/46 (6.5%)
Adjusted rate	0/44.5 (0.0%)	1/42.0 (2.4%)	0/35.1 (0.0%)	3/32.7 (9.2%)
Terminal rate	0/39 (0.0%)	1/33 (3.0%)	0/19 (0.0%)	0/8 (0.0%)
First incidence (days)	—	765 (T)	—	626
Poly-3 test	P=0.023	P=0.481	—	P=0.069

Table E2
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Drinking Water Study of Urethane and 2.5% Ethanol

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
Stomach (Forestomach): Squamous Cell Papilloma				
Overall rate	0/47 (0.0%)	4/46 (8.7%)	0/47 (0.0%)	0/46 (0.0%)
Adjusted rate	0/44.5 (0.0%)	4/42.0 (9.5%)	0/35.4 (0.0%)	0/31.7 (0.0%)
Terminal rate	0/39 (0.0%)	3/33 (9.1%)	0/19 (0.0%)	0/8 (0.0%)
First incidence (days)	—	736	—	—
Poly-3 test	P=0.280N	P=0.049	—	—
Stomach (Forestomach): Squamous Cell Papilloma or Squamous Cell Carcinoma				
Overall rate	0/47 (0.0%)	4/46 (8.7%)	0/47 (0.0%)	1/46 (2.2%)
Adjusted rate	0/44.5 (0.0%)	4/42.1 (9.5%)	0/35.4 (0.0%)	1/32.1 (3.1%)
Terminal rate	0/39 (0.0%)	3/33 (9.1%)	0/19 (0.0%)	0/8 (0.0%)
First incidence (days)	—	736	—	659
Poly-3 test	P=0.606N	P=0.049	—	P=0.428
Uterus: Hemangioma				
Overall rate	0/47 (0.0%)	0/47 (0.0%)	1/48 (2.1%)	3/48 (6.3%)
Adjusted rate	0/44.5 (0.0%)	0/42.5 (0.0%)	1/36.2 (2.8%)	3/34.3 (8.7%)
Terminal rate	0/39 (0.0%)	0/33 (0.0%)	1/19 (5.3%)	0/8 (0.0%)
First incidence (days)	—	—	765 (T)	608
Poly-3 test	P=0.011	—	P=0.451	P=0.074
Uterus: Hemangioma or Hemangiosarcoma				
Overall rate	0/47 (0.0%)	0/44 (0.0%)	2/48 (4.2%)	4/48 (8.3%)
Adjusted rate	0/44.5 (0.0%)	0/42.5 (0.0%)	2/36.4 (5.5%)	4/34.3 (11.7%)
Terminal rate	0/39 (0.0%)	0/33 (0.0%)	1/19 (5.3%)	1/8 (12.5%)
First incidence (days)	—	—	696	608
Poly-3 test	P=0.004	—	P=0.188	P=0.031
All Organs: Hemangioma				
Overall rate	1/47 (2.1%)	1/47 (2.1%)	2/48 (4.2%)	4/48 (8.3%)
Adjusted rate	1/44.5 (2.2%)	1/42.5 (2.4%)	2/36.2 (5.5%)	4/34.5 (11.6%)
Terminal rate	1/39 (2.6%)	1/33 (3.0%)	2/19 (10.5%)	0/8 (0.0%)
First incidence (days)	765 (T)	765 (T)	765 (T)	608
Poly-3 test	P=0.038	P=0.741	P=0.414	P=0.104
All Organs: Hemangiosarcoma				
Overall rate	1/47 (2.1%)	2/47 (4.3%)	1/48 (2.1%)	17/48 (35.4%)
Adjusted rate	1/44.5 (2.2%)	2/42.5 (4.7%)	1/36.4 (2.7%)	17/37.8 (45.0%)
Terminal rate	1/39 (2.6%)	2/33 (6.1%)	0/19 (0.0%)	2/8 (25.0%)
First incidence (days)	765 (T)	765 (T)	696	508
Poly-3 test	P=0.001	P=0.470	P=0.703	P=0.001
All Organs: Hemangioma or Hemangiosarcoma				
Overall rate	2/47 (4.3%)	3/47 (6.4%)	3/48 (6.3%)	21/48 (43.8%)
Adjusted rate	2/44.5 (4.5%)	3/42.5 (7.1%)	3/36.4 (8.2%)	21/39.3 (53.5%)
Terminal rate	2/39 (5.1%)	3/33 (9.1%)	2/19 (10.5%)	2/8 (25.0%)
First incidence (days)	765 (T)	765 (T)	696	508
Poly-3 test	P=0.001	P=0.461	P=0.391	P=0.001
All Organs: Histiocytic Sarcoma				
Overall rate	0/47 (0.0%)	2/47 (4.3%)	3/48 (6.3%)	2/48 (4.2%)
Adjusted rate	0/44.5 (0.0%)	2/42.7 (4.7%)	3/37.0 (8.1%)	2/33.0 (6.1%)
Terminal rate	0/39 (0.0%)	1/33 (3.0%)	0/19 (0.0%)	1/8 (12.5%)
First incidence (days)	—	698	607	762
Poly-3 test	P=0.199	P=0.220	P=0.084	P=0.171

Table E2
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Drinking Water Study of Urethane and 2.5% Ethanol

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
All Organs: Malignant Lymphoma				
Overall rate	9/47 (19.1%)	10/47 (21.3%)	11/48 (22.9%)	6/48 (12.5%)
Adjusted rate	9/44.8 (20.1%)	10/43.6 (22.9%)	11/38.7 (28.4%)	6/35.4 (17.0%)
Terminal rate	7/39 (17.9%)	7/33 (21.2%)	5/19 (26.3%)	0/8 (0.0%)
First incidence (days)	677	611	593	360
Poly-3 test	P=0.429N	P=0.437	P=0.230	P=0.509N
All Organs: Benign Neoplasms				
Overall rate	21/47 (44.7%)	21/47 (44.7%)	31/48 (64.6%)	39/48 (81.3%)
Adjusted rate	21/45.0 (46.7%)	21/44.4 (47.3%)	31/40.5 (76.6%)	39/42.7 (91.4%)
Terminal rate	18/39 (46.2%)	15/33 (45.5%)	18/19 (94.7%)	8/8 (100.0%)
First incidence (days)	677	529	306	542
Poly-3 test	P=0.001	P=0.490N	P=0.001	P=0.001
All Organs: Malignant Neoplasms				
Overall rate	14/47 (29.8%)	22/47 (46.8%)	38/48 (79.2%)	45/48 (93.8%)
Adjusted rate	14/45.0 (31.1%)	22/44.4 (49.6%)	38/44.5 (85.4%)	45/46.3 (97.1%)
Terminal rate	10/39 (25.6%)	16/33 (48.5%)	15/19 (78.9%)	8/8 (100.0%)
First incidence (days)	677	611	468	360
Poly-3 test	P=0.001	P=0.042	P=0.001	P=0.001
All Organs: Benign or Malignant Neoplasms				
Overall rate	29/47 (61.7%)	33/47 (70.2%)	45/48 (93.8%)	48/48 (100.0%)
Adjusted rate	29/45.0 (67.4%)	33/45.2 (73.0%)	45/46.5 (96.8%)	48/48.0 (100.0%)
Terminal rate	25/39 (64.1%)	24/33 (72.7%)	18/19 (94.7%)	8/8 (100.0%)
First incidence (days)	677	529	306	360
Poly-3 test	P=0.001	P=0.180	P=0.001	P=0.001

(T) Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals with tissue examined microscopically
[b] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the control incidence (0 ppm urethane) is the P value associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and that exposed group. The Poly-3 test accounts for the differential mortality in animals that do not reach terminal sacrifice. A negative trend or a lower incidence in an exposed group is indicated by **N**.
[e] Not applicable; no neoplasms in animal group
[f] Value of statistic cannot be computed.

Table E3
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Drinking Water Study of Urethane and 2.5% Ethanol[a]

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
Disposition Summary				
Animals initially in study	48	47	48	48
Early deaths				
Accidental deaths	4	3		
Moribund	1	4	11	9
Natural deaths	4	7	18	31
Survivors				
Terminal sacrifice	39	33	19	8
Animals examined microscopically	47	47	48	48
Alimentary System				
Esophagus	(47)	(47)	(47)	(47)
Autolysis, marked			1 (2%)	
Gallbladder	(47)	(45)	(46)	(43)
Autolysis, marked				1 (2%)
Autolysis, moderate		2 (4%)	2 (4%)	3 (7%)
Infiltration cellular, lymphocytic, mild			1 (2%)	
Infiltration cellular, lymphocytic, minimal	1 (2%)			
Intestine large, cecum	(47)	(45)	(47)	(41)
Autolysis, marked			1 (2%)	2 (5%)
Autolysis, mild	1 (2%)			
Autolysis, moderate		1 (2%)	2 (4%)	8 (20%)
Hyperplasia, mild, lymphoid tissue	1 (2%)	1 (2%)		
Hyperplasia, minimal, lymphoid tissue			1 (2%)	
Intestine large, colon	(47)	(45)	(47)	(43)
Autolysis, marked			1 (2%)	2 (5%)
Autolysis, mild	1 (2%)			
Autolysis, moderate		1 (2%)	2 (4%)	8 (19%)
Hyperplasia, mild, lymphoid tissue		1 (2%)		
Hyperplasia, minimal, lymphoid tissue			1 (2%)	
Inflammation, chronic active, marked			1 (2%)	
Inflammation, chronic, moderate		1 (2%)		
Intestine large, rectum	(47)	(44)	(47)	(46)
Autolysis, marked			1 (2%)	
Autolysis, mild	1 (2%)			1 (2%)
Autolysis, moderate		1 (2%)	1 (2%)	6 (13%)
Intestine small, duodenum	(47)	(45)	(47)	(39)
Autolysis, marked			1 (2%)	2 (5%)
Autolysis, mild	1 (2%)			
Autolysis, moderate	1 (2%)	1 (2%)	3 (6%)	6 (15%)
Hyperplasia, moderate, lymphoid tissue		1 (2%)		
Intestine small, ileum	(47)	(45)	(47)	(40)
Autolysis, marked			1 (2%)	2 (5%)
Autolysis, mild	1 (2%)			
Autolysis, moderate	1 (2%)	1 (2%)	3 (6%)	7 (18%)
Hyperplasia, mild, lymphoid tissue	2 (4%)	1 (2%)	1 (2%)	
Intestine small, jejunum	(47)	(45)	(47)	(39)
Angiectasis, minimal				1 (3%)
Autolysis, marked			1 (2%)	2 (5%)
Autolysis, mild	1 (2%)			
Autolysis, moderate	1 (2%)	1 (2%)	2 (4%)	6 (15%)
Hyperplasia, marked, lymphoid tissue			1 (2%)	
Hyperplasia, mild, lymphoid tissue	1 (2%)	1 (2%)		

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

Table E3
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Drinking Water Study of Urethane and 2.5% Ethanol

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
Alimentary System (continued)				
Liver	(47)	(47)	(47)	(46)
Accessory spleen	1 (2%)			
Angiectasis	2 (4%)	5 (11%)	7 (15%)	20 (43%)
Autolysis, marked			1 (2%)	
Autolysis, mild	1 (2%)			
Autolysis, moderate	2 (4%)	1 (2%)		
Basophilic focus	2 (4%)			
Clear cell focus			1 (2%)	
Clear cell focus, multiple			1 (2%)	
Eosinophilic focus	2 (4%)	10 (21%)	1 (2%)	6 (13%)
Eosinophilic focus, multiple		10 (21%)	20 (43%)	22 (48%)
Fatty change, focal, minimal		1 (2%)		
Fatty change, moderate				1 (2%)
Fibrosis, mild		1 (2%)		
Granuloma, focal, mild			1 (2%)	
Granuloma, focal, minimal	2 (4%)		1 (2%)	
Hematopoietic cell proliferation, marked				1 (2%)
Hematopoietic cell proliferation, mild		12 (26%)	6 (13%)	18 (39%)
Hematopoietic cell proliferation, minimal	2 (4%)	3 (6%)		
Hematopoietic cell proliferation, moderate	1 (2%)	1 (2%)	7 (15%)	7 (15%)
Hyperplasia, mild, kupffer cell		1 (2%)		
Infarct, caudate lobe	1 (2%)		1 (2%)	
Infarct, median lobe				1 (2%)
Infiltration cellular, lymphocytic, mild	3 (6%)	2 (4%)	2 (4%)	2 (4%)
Infiltration cellular, lymphocytic, minimal	11 (23%)	9 (19%)	3 (6%)	1 (2%)
Infiltration cellular, lymphocytic, moderate	1 (2%)	1 (2%)		
Inflammation, chronic active, mild	1 (2%)			
Inflammation, chronic active, minimal	1 (2%)			
Inflammation, chronic active, moderate		1 (2%)		1 (2%)
Inflammation, granulomatous, marked	1 (2%)			
Inflammation, mild		1 (2%)		
Mixed cell focus		1 (2%)		
Mixed cell focus, multiple		5 (11%)	5 (11%)	3 (7%)
Necrosis, marked				1 (2%)
Necrosis, mild	2 (4%)		2 (4%)	9 (20%)
Necrosis, mild, hepatocyte		1 (2%)		
Necrosis, minimal	3 (6%)	2 (4%)	1 (2%)	2 (4%)
Necrosis, moderate			1 (2%)	6 (13%)
Necrosis, moderate, hepatocyte			1 (2%)	
Pigmentation, mild		1 (2%)		
Regeneration				2 (4%)
Thrombosis	1 (2%)		4 (9%)	9 (20%)
Vacuolization cytoplasmic, marked, hepatocyte			1 (2%)	
Vacuolization cytoplasmic, mild, hepatocyte	7 (15%)	7 (15%)	3 (6%)	
Vacuolization cytoplasmic, minimal, hepatocyte	2 (4%)	1 (2%)	1 (2%)	
Vacuolization cytoplasmic, moderate, hepatocyte	2 (4%)		2 (4%)	5 (11%)
Mesentery	(2)	(5)	(6)	(6)
Necrosis, fat	2 (100%)	3 (60%)	5 (83%)	4 (67%)
Pancreas	(47)	(45)	(46)	(44)
Angiectasis, mild	1 (2%)		1 (2%)	
Angiectasis, minimal			1 (2%)	
Atrophy, moderate, acinar cell			1 (2%)	
Autolysis, moderate			2 (4%)	6 (14%)
Cyst	1 (2%)			
Cyst, duct		1 (2%)		

Table E3
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Drinking Water Study of Urethane and 2.5% Ethanol

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
Alimentary System (continued)				
Pancreas (continued)	(47)	(45)	(46)	(44)
Hemorrhage, mild			1 (2%)	
Infiltration cellular, lymphocytic, mild	2 (4%)	1 (2%)	1 (2%)	
Infiltration cellular, lymphocytic, minimal	12 (26%)	17 (38%)	7 (15%)	2 (5%)
Inflammation, chronic, moderate		1 (2%)		
Salivary glands	(47)	(47)	(46)	(48)
Fibrosis, minimal		1 (2%)		
Infiltration cellular, lymphocytic, mild	11 (23%)	12 (26%)	15 (33%)	10 (21%)
Infiltration cellular, lymphocytic, minimal	31 (66%)	25 (53%)	17 (37%)	21 (44%)
Infiltration cellular, lymphocytic, moderate	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Inflammation, mild			1 (2%)	
Stomach, forestomach	(47)	(46)	(47)	(46)
Autolysis, marked			1 (2%)	
Autolysis, mild	1 (2%)			1 (2%)
Autolysis, moderate		1 (2%)	1 (2%)	4 (9%)
Foreign body			2 (4%)	
Hyperkeratosis, mild				2 (4%)
Hyperplasia, marked, epithelium	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Hyperplasia, mild, epithelium	2 (4%)	1 (2%)	6 (13%)	3 (7%)
Hyperplasia, minimal, epithelium		1 (2%)	1 (2%)	3 (7%)
Hyperplasia, moderate, epithelium	1 (2%)	1 (2%)		2 (4%)
Infiltration cellular, lymphocytic, mild		1 (2%)		
Inflammation, mild	1 (2%)	1 (2%)	2 (4%)	1 (2%)
Inflammation, minimal				1 (2%)
Ulcer, mild	1 (2%)			
Ulcer, minimal		1 (2%)		
Stomach, glandular	(47)	(46)	(47)	(45)
Autolysis, marked			1 (2%)	
Autolysis, mild	1 (2%)			1 (2%)
Autolysis, moderate		1 (2%)	1 (2%)	4 (9%)
Infiltration cellular, lymphocytic, mild		1 (2%)		
Infiltration cellular, lymphocytic, minimal			1 (2%)	
Inflammation, mild			1 (2%)	
Mineralization, minimal				1 (2%)
Tongue	(47)	(47)	(48)	(48)
Polyarteritis, mild	1 (2%)			
Cardiovascular System				
Heart	(47)	(47)	(48)	(48)
Abscess		1 (2%)		
Angiectasis, mild				2 (4%)
Angiectasis, minimal			1 (2%)	2 (4%)
Cardiomyopathy, mild		1 (2%)	2 (4%)	1 (2%)
Cardiomyopathy, minimal	2 (4%)	3 (6%)	1 (2%)	1 (2%)
Hyperplasia, mild, endothelium				3 (6%)
Hyperplasia, minimal, endothelium			3 (6%)	4 (8%)
Hyperplasia, moderate, endothelium				1 (2%)
Hypertrophy, minimal, artery	1 (2%)			
Inflammation, chronic, mild, epicardium	1 (2%)			
Inflammation, chronic, minimal, epicardium				1 (2%)
Inflammation, mild, myocardium			2 (4%)	
Inflammation, minimal, myocardium				1 (2%)
Inflammation, moderate, atrium			1 (2%)	

Table E3
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Drinking Water Study of Urethane and 2.5% Ethanol

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
Cardiovascular System (continued)				
Heart (continued)	(47)	(47)	(48)	(48)
Mineralization, minimal		1 (2%)	2 (4%)	
Necrosis, mild			1 (2%)	
Thrombosis, mild, atrium			1 (2%)	
Thrombosis, minimal, myocardium			1 (2%)	
Thrombosis, moderate, atrium		1 (2%)		
Endocrine System				
Adrenal gland, cortex	(46)	(47)	(46)	(44)
Angiectasis, mild		1 (2%)	3 (7%)	1 (2%)
Angiectasis, moderate	1 (2%)		1 (2%)	1 (2%)
Atrophy, moderate			1 (2%)	
Cyst		1 (2%)		1 (2%)
Hematopoietic cell proliferation, mild			1 (2%)	
Hematopoietic cell proliferation, minimal				1 (2%)
Hyperplasia, mild, subcapsular	26 (57%)	20 (43%)	22 (48%)	23 (52%)
Hyperplasia, minimal, subcapsular	15 (33%)	13 (28%)	7 (15%)	5 (11%)
Hyperplasia, moderate, subcapsular	1 (2%)	4 (9%)	6 (13%)	2 (5%)
Infarct, mild		1 (2%)		
Infiltration cellular, lymphocytic, minimal				1 (2%)
Inflammation, mild			1 (2%)	
Thrombosis, moderate	1 (2%)			
Adrenal gland, medulla	(45)	(47)	(45)	(41)
Hyperplasia, mild			1 (2%)	
Hyperplasia, minimal		1 (2%)		
Islets, pancreatic	(47)	(45)	(46)	(44)
Autolysis, moderate			2 (4%)	4 (9%)
Hyperplasia, mild	1 (2%)	2 (4%)		
Hyperplasia, minimal	6 (13%)		3 (7%)	4 (9%)
Infiltration cellular, lymphocytic, minimal	2 (4%)	2 (4%)		
Inflammation, minimal		1 (2%)		
Parathyroid gland	(34)	(37)	(37)	(31)
Autolysis, marked			1 (3%)	
Cyst				1 (3%)
Pituitary gland	(44)	(41)	(41)	(38)
Angiectasis, mild			2 (5%)	
Angiectasis, minimal	1 (2%)			
Angiectasis, moderate		1 (2%)		
Cyst		2 (5%)		
Hemorrhage, mild				1 (3%)
Hyperplasia, mild, pars distalis	1 (2%)	2 (5%)	1 (2%)	1 (3%)
Hyperplasia, minimal, pars distalis			1 (2%)	
Hyperplasia, moderate, pars distalis			1 (2%)	
Thyroid gland	(46)	(47)	(45)	(46)
Autolysis, marked			1 (2%)	
Cyst multilocular	2 (4%)		1 (2%)	1 (2%)
Depletion secretory				1 (2%)
Hyperplasia, minimal, C-cell	1 (2%)		1 (2%)	
Hyperplasia, minimal, follicular cell	1 (2%)			
Infiltration cellular, lymphocytic, mild		1 (2%)		
Infiltration cellular, lymphocytic, minimal	1 (2%)	1 (2%)	1 (2%)	1 (2%)

Table E3
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Drinking Water Study of Urethane and 2.5% Ethanol

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
General Body System				
Tissue NOS		(1)	(1)	
Cyst, abdominal			1 (100%)	
Inflammation, moderate, abdominal			1 (100%)	
Genital System				
Clitoral gland	(40)	(40)	(34)	(40)
Atrophy, mild	37 (93%)	35 (88%)	26 (76%)	34 (85%)
Atrophy, minimal			3 (9%)	2 (5%)
Atrophy, moderate		3 (8%)	1 (3%)	1 (3%)
Autolysis, moderate				1 (3%)
Pigmentation		1 (3%)		
Ovary	(47)	(46)	(47)	(48)
Angiectasis, mild		1 (2%)	3 (6%)	3 (6%)
Angiectasis, moderate		1 (2%)	1 (2%)	3 (6%)
Atrophy, marked	20 (43%)	34 (74%)	33 (70%)	36 (75%)
Atrophy, mild	6 (13%)	2 (4%)	2 (4%)	1 (2%)
Atrophy, minimal	4 (9%)			
Atrophy, moderate	15 (32%)	4 (9%)	2 (4%)	5 (10%)
Cyst	14 (30%)	12 (26%)	7 (15%)	4 (8%)
Cyst, periovarian tissue	1 (2%)			1 (2%)
Hematocyst	6 (13%)	6 (13%)		2 (4%)
Hemorrhage, marked		1 (2%)		
Hemorrhage, mild			2 (4%)	
Hyperplasia, tubular, mild				2 (4%)
Hyperplasia, tubular, minimal				1 (2%)
Hyperplasia, tubular, moderate		1 (2%)		2 (4%)
Infiltration cellular, histiocytic, moderate		1 (2%)	1 (2%)	
Infiltration cellular, lymphocytic, moderate, periovarian tissue			1 (2%)	
Metaplasia, osseous, mild	1 (2%)			
Mineralization, moderate		1 (2%)	1 (2%)	
Pigmentation, moderate		1 (2%)	1 (2%)	
Thrombosis, marked		2 (4%)		
Uterus	(47)	(47)	(48)	(48)
Angiectasis, marked			1 (2%)	1 (2%)
Angiectasis, mild	1 (2%)	2 (4%)	2 (4%)	5 (10%)
Angiectasis, moderate			4 (8%)	3 (6%)
Atrophy, mild			1 (2%)	
Autolysis, marked			1 (2%)	
Hemorrhage, mild			1 (2%)	
Hemorrhage, moderate			2 (4%)	1 (2%)
Hemorrhage, moderate, cervix			1 (2%)	
Hyperplasia, cystic, marked, endometrium	2 (4%)		1 (2%)	
Hyperplasia, cystic, mild, endometrium	24 (51%)	26 (55%)	14 (29%)	21 (44%)
Hyperplasia, cystic, minimal, endometrium	1 (2%)	4 (9%)	8 (17%)	6 (13%)
Hyperplasia, cystic, moderate, endometrium	15 (32%)	10 (21%)	15 (31%)	6 (13%)
Inflammation, moderate		1 (2%)		
Inflammation, suppurative, marked				1 (2%)
Thrombosis, marked			1 (2%)	2 (4%)
Thrombosis, mild			2 (4%)	
Thrombosis, moderate			2 (4%)	4 (8%)

Table E3
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Drinking Water Study of Urethane and 2.5% Ethanol

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
Genital System (continued)				
Vagina	(47)	(47)	(47)	(47)
Exudate, mild		2 (4%)		1 (2%)
Exudate, minimal	1 (2%)			
Exudate, moderate	1 (2%)			
Hemorrhage, moderate				1 (2%)
Inflammation, mild	1 (2%)	1 (2%)		
Hematopoietic System				
Bone marrow	(47)	(46)	(48)	(48)
Angiectasis, mild				2 (4%)
Autolysis, marked			1 (2%)	
Autolysis, moderate				1 (2%)
Hyperplasia, mild, myeloid cell		1 (2%)	1 (2%)	5 (10%)
Hyperplasia, moderate, myeloid cell		1 (2%)	2 (4%)	1 (2%)
Infiltration cellular, histiocytic, mild			1 (2%)	
Pigmentation, mild	1 (2%)			
Lymph node	(47)	(47)	(47)	(47)
Autolysis, marked, thoracic			1 (2%)	
Hemorrhage, mild, lumbar	1 (2%)			
Hemorrhage, moderate, lumbar			1 (2%)	1 (2%)
Hyperplasia, mild, lumbar	1 (2%)		1 (2%)	1 (2%)
Hyperplasia, mild, renal		1 (2%)		
Hyperplasia, moderate, lumbar			1 (2%)	1 (2%)
Hyperplasia, moderate, renal				1 (2%)
Hyperplasia, moderate, thoracic			2 (4%)	
Infiltration cellular, plasma cell, moderate, lumbar			1 (2%)	
Infiltration cellular, polymorphonuclear, moderate, lumbar			1 (2%)	1 (2%)
Lymph node, mandibular	(47)	(44)	(43)	(46)
Hemorrhage, mild	1 (2%)		1 (2%)	
Hyperplasia, lymphoid, marked		1 (2%)		
Hyperplasia, lymphoid, mild	3 (6%)	1 (2%)	1 (2%)	4 (9%)
Hyperplasia, lymphoid, minimal	1 (2%)		1 (2%)	
Hyperplasia, lymphoid, moderate		3 (7%)	2 (5%)	2 (4%)
Infiltration cellular, histiocytic, mild				1 (2%)
Infiltration cellular, histiocytic, minimal				1 (2%)
Infiltration cellular, plasma cell, moderate				1 (2%)
Inflammation, mild			1 (2%)	
Lymph node, mesenteric	(43)	(42)	(42)	(38)
Angiectasis, mild		1 (2%)	1 (2%)	2 (5%)
Angiectasis, minimal	1 (2%)			
Atrophy, mild			1 (2%)	1 (3%)
Autolysis, marked			1 (2%)	1 (3%)
Autolysis, moderate				1 (3%)
Hematopoietic cell proliferation, mild				1 (3%)
Hemorrhage, marked				1 (3%)
Hemorrhage, mild			1 (2%)	1 (3%)
Hyperplasia, lymphoid, marked		1 (2%)		
Hyperplasia, lymphoid, mild	4 (9%)		1 (2%)	
Hyperplasia, lymphoid, moderate	1 (2%)	1 (2%)		
Infiltration cellular, polymorphonuclear, mild				1 (3%)
Inflammation, granulomatous, moderate	1 (2%)			
Pigmentation, mild			1 (2%)	

Table E3
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Drinking Water Study of Urethane and 2.5% Ethanol

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
Hematopoietic System (continued)				
Spleen	(47)	(46)	(46)	(46)
Angiectasis, mild	1 (2%)			2 (4%)
Angiectasis, moderate	1 (2%)	1 (2%)		
Atrophy, mild, red pulp			1 (2%)	
Autolysis, moderate			1 (2%)	4 (9%)
Hematopoietic cell proliferation granulocytic, moderate		1 (2%)		
Hematopoietic cell proliferation, marked			1 (2%)	2 (4%)
Hematopoietic cell proliferation, mild	1 (2%)	3 (7%)	7 (15%)	6 (13%)
Hematopoietic cell proliferation, moderate	1 (2%)	5 (11%)	7 (15%)	17 (37%)
Hemorrhage, mild				1 (2%)
Hyperplasia, marked, lymphoid follicle	2 (4%)	1 (2%)	1 (2%)	
Hyperplasia, mild, lymphoid follicle	14 (30%)	11 (24%)	8 (17%)	4 (9%)
Hyperplasia, minimal, lymphoid follicle	3 (6%)		1 (2%)	
Hyperplasia, moderate, lymphoid follicle	6 (13%)	4 (9%)	2 (4%)	1 (2%)
Inflammation, mild, capsule		1 (2%)		
Pigmentation, mild	2 (4%)		1 (2%)	1 (2%)
Pigmentation, minimal	1 (2%)	1 (2%)		
Thrombosis, marked				1 (2%)
Thymus	(41)	(40)	(34)	(36)
Atrophy, mild	2 (5%)	6 (15%)	8 (24%)	11 (31%)
Atrophy, minimal			1 (3%)	1 (3%)
Atrophy, moderate				3 (8%)
Autolysis, marked			1 (3%)	
Autolysis, moderate			1 (3%)	2 (6%)
Hyperplasia, mild	3 (7%)	6 (15%)	3 (9%)	2 (6%)
Hyperplasia, minimal	1 (2%)			
Integumentary System				
Mammary gland	(47)	(45)	(48)	(47)
Autolysis, marked			1 (2%)	
Ectasia, mild, duct			1 (2%)	
Ectasia, moderate, duct	1 (2%)			
Hyperplasia, mild	2 (4%)		1 (2%)	1 (2%)
Hyperplasia, minimal			1 (2%)	1 (2%)
Infiltration cellular, lymphocytic, minimal				1 (2%)
Lactation, mild	2 (4%)	1 (2%)	2 (4%)	
Lactation, minimal	1 (2%)	1 (2%)	4 (8%)	3 (6%)
Skin	(47)	(47)	(48)	(47)
Autolysis, marked			1 (2%)	
Cyst epithelial inclusion				1 (2%)
Inflammation, mild				1 (2%)
Ulcer, moderate			1 (2%)	
Musculoskeletal System				
Bone	(47)	(47)	(48)	(48)
Autolysis, marked, sternum			1 (2%)	
Fibrous osteodystrophy, mild, sternum	8 (17%)	10 (21%)	8 (17%)	1 (2%)
Fibrous osteodystrophy, minimal, sternum	9 (19%)	10 (21%)	6 (13%)	3 (6%)
Fibrous osteodystrophy, moderate, sternum	2 (4%)		1 (2%)	

Table E3
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Drinking Water Study of Urethane and 2.5% Ethanol

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
Musculoskeletal System (continued)				
Bone, femur	(46)	(47)	(48)	(48)
Fibrous osteodystrophy, mild	2 (4%)	2 (4%)		1 (2%)
Fibrous osteodystrophy, minimal	3 (7%)	3 (6%)	1 (2%)	
Fibrous osteodystrophy, moderate	2 (4%)		2 (4%)	
Skeletal muscle	(47)	(47)	(48)	(48)
Degeneration, moderate				1 (2%)
Mineralization, moderate				1 (2%)
Nervous System				
Brain, cerebellum	(47)	(46)	(47)	(48)
Abscess, moderate				1 (2%)
Autolysis, moderate			1 (2%)	
Hemorrhage, mild		1 (2%)		
Brain, cerebrum	(47)	(47)	(47)	(48)
Autolysis, moderate			1 (2%)	
Hemorrhage, moderate			1 (2%)	
Mineralization, mild, thalamus		1 (2%)	1 (2%)	1 (2%)
Mineralization, minimal, thalamus	29 (62%)	28 (60%)	22 (47%)	17 (35%)
Spinal cord, thoracic	(47)	(47)	(47)	(48)
Autolysis, moderate			1 (2%)	
Hemorrhage, mild				1 (2%)
Respiratory System				
Larynx	(47)	(46)	(47)	(46)
Autolysis, marked			1 (2%)	
Hemorrhage, mild			1 (2%)	
Inflammation, mild			1 (2%)	
Lung	(47)	(47)	(48)	(48)
Autolysis, mild	2 (4%)			
Autolysis, moderate	1 (2%)			
Congestion, moderate		3 (6%)		
Crystals, mild		1 (2%)		
Exudate, mild, alveolus				1 (2%)
Hemorrhage, mild	4 (9%)	6 (13%)	1 (2%)	1 (2%)
Hemorrhage, minimal	3 (6%)	6 (13%)	1 (2%)	
Hyperplasia, mild, alveolar epithelium	1 (2%)		2 (4%)	2 (4%)
Hyperplasia, minimal, alveolar epithelium			3 (6%)	1 (2%)
Infiltration cellular, histiocytic, mild		1 (2%)		6 (13%)
Infiltration cellular, histiocytic, minimal			1 (2%)	
Infiltration cellular, histiocytic, moderate	1 (2%)		1 (2%)	3 (6%)
Infiltration cellular, lymphocytic, mild	4 (9%)	5 (11%)	4 (8%)	6 (13%)
Infiltration cellular, lymphocytic, minimal	18 (38%)	21 (45%)	19 (40%)	10 (21%)
Infiltration cellular, lymphocytic, moderate	2 (4%)		2 (4%)	
Inflammation, chronic active, minimal		1 (2%)		
Inflammation, suppurative, moderate			1 (2%)	
Pigmentation, mild	1 (2%)			
Nose	(47)	(47)	(48)	(48)
Hemorrhage, moderate			1 (2%)	
Inflammation, moderate				1 (2%)
Trachea	(47)	(47)	(46)	(47)
Autolysis, marked			1 (2%)	

Table E3
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Drinking Water Study of Urethane and 2.5% Ethanol

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
Special Senses System				
Eye	(47)	(45)	(48)	(46)
Atrophy, mild				2 (4%)
Atrophy, moderate				1 (2%)
Cataract, mild, lens				2 (4%)
Cataract, minimal, lens				1 (2%)
Hemorrhage, moderate			1 (2%)	
Infiltration cellular, lymphocytic, mild			1 (2%)	
Inflammation, marked, cornea				1 (2%)
Inflammation, mild, cornea		1 (2%)	2 (4%)	5 (11%)
Inflammation, minimal, cornea	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Inflammation, moderate, cornea		1 (2%)	1 (2%)	1 (2%)
Phthisis bulbi	1 (2%)			1 (2%)
Harderian gland	(47)	(47)	(46)	(47)
Atrophy, mild		1 (2%)		
Hyperplasia, mild	2 (4%)		1 (2%)	
Hyperplasia, minimal				2 (4%)
Infiltration cellular, lymphocytic, mild	1 (2%)		1 (2%)	
Infiltration cellular, lymphocytic, minimal	9 (19%)	10 (21%)	8 (17%)	1 (2%)
Inflammation, mild		1 (2%)		
Inflammation, moderate				1 (2%)
Necrosis, marked		1 (2%)		
Lacrimal gland	(45)	(45)	(44)	(43)
Atrophy, mild		1 (2%)	1 (2%)	1 (2%)
Atrophy, minimal	4 (9%)	3 (7%)	2 (5%)	1 (2%)
Cyst		1 (2%)		
Dilatation, minimal, duct	1 (2%)	4 (9%)	1 (2%)	1 (2%)
Infiltration cellular, lymphocytic, mild	6 (13%)	8 (18%)	11 (25%)	5 (12%)
Infiltration cellular, lymphocytic, minimal	19 (42%)	19 (42%)	15 (34%)	15 (35%)
Infiltration cellular, lymphocytic, moderate		1 (2%)	1 (2%)	
Inflammation, mild			1 (2%)	
Zymbal's gland	(46)	(43)	(41)	(44)
Infiltration cellular, lymphocytic, minimal		1 (2%)		
Inflammation, chronic, minimal		1 (2%)		
Urinary System				
Kidney	(47)	(47)	(48)	(48)
Accumulation, hyaline droplet, moderate		1 (2%)		1 (2%)
Amyloid deposition, moderate	1 (2%)			1 (2%)
Autolysis, marked			2 (4%)	
Autolysis, mild	2 (4%)			
Embolus bacterial, moderate		1 (2%)		
Glomerulosclerosis, mild	1 (2%)		1 (2%)	3 (6%)
Glomerulosclerosis, minimal	1 (2%)		1 (2%)	
Hydronephrosis, mild				2 (4%)
Infarct, minimal			1 (2%)	
Infarct, moderate		1 (2%)		
Infiltration cellular, lymphocytic, mild	3 (6%)	2 (4%)	2 (4%)	1 (2%)
Infiltration cellular, lymphocytic, minimal	15 (32%)	12 (26%)	17 (35%)	9 (19%)
Infiltration cellular, lymphocytic, moderate			1 (2%)	1 (2%)
Infiltration cellular, plasma cell, mild			1 (2%)	
Infiltration cellular, plasma cell, moderate				1 (2%)
Inflammation, minimal		1 (2%)		

Table E3
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Drinking Water Study of Urethane and 2.5% Ethanol

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
Urinary System (continued)				
Kidney (continued)	(47)	(47)	(48)	(48)
Metaplasia, osseous, minimal	1 (2%)			1 (2%)
Mineralization, mild				1 (2%)
Nephropathy, mild		1 (2%)		1 (2%)
Regeneration, minimal				1 (2%)
Urinary bladder	(45)	(43)	(47)	(45)
Autolysis, marked			1 (2%)	
Autolysis, moderate				3 (7%)
Infiltration cellular, lymphocytic, mild	4 (9%)	3 (7%)	4 (9%)	4 (9%)
Infiltration cellular, lymphocytic, minimal	25 (56%)	17 (40%)	23 (49%)	15 (33%)

APPENDIX F
SUMMARY OF LESIONS IN FEMALE MICE IN THE 2-YEAR DRINKING WATER STUDY OF URETHANE AND 5% ETHANOL

Table F1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Drinking Water Study of Urethane and 5% Ethanol[a]

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
Disposition Summary				
Animals initially in study	48	48	48	48
Early deaths				
Accidental deaths	4			
Moribund	6	4	4	11
Natural deaths	7	12	17	33
Survivors				
Terminal sacrifice	31	32	27	4
Animals examined microscopically	48	48	48	48
Alimentary System				
Esophagus	(47)	(48)	(47)	(46)
Lymphoma malignant			1 (2%)	
Gallbladder	(47)	(44)	(47)	(45)
Lymphoma malignant	1 (2%)		2 (4%)	1 (2%)
Intestine large, cecum	(47)	(44)	(48)	(42)
Lymphoma malignant			1 (2%)	
Mast cell tumor malignant		1 (2%)		
Intestine large, colon	(47)	(45)	(48)	(42)
Sarcoma, metastatic, skin				1 (2%)
Intestine large, rectum	(48)	(47)	(46)	(44)
Lymphoma malignant			1 (2%)	
Sarcoma, metastatic, skin		1 (2%)		
Intestine small, duodenum	(47)	(44)	(46)	(40)
Adenoma	1 (2%)			
Lymphoma malignant		1 (2%)	1 (2%)	
Intestine small, ileum	(47)	(44)	(47)	(40)
Lymphoma malignant	1 (2%)		1 (2%)	1 (3%)
Intestine small, jejunum	(47)	(44)	(47)	(40)
Hemangioma				1 (3%)
Liver	(48)	(47)	(48)	(48)
Hemangiosarcoma				6 (13%)
Hepatocellular adenoma	3 (6%)	4 (9%)	5 (10%)	2 (4%)
Hepatocellular adenoma, multiple		2 (4%)	11 (23%)	14 (29%)
Hepatocellular carcinoma		1 (2%)		
Hepatocellular carcinoma, multiple				1 (2%)
Histiocytic sarcoma	4 (8%)		3 (6%)	2 (4%)
Lymphoma malignant	4 (8%)	3 (6%)	9 (19%)	6 (13%)
Mast cell tumor malignant		1 (2%)		
Sarcoma stromal, metastatic, uterus			1 (2%)	1 (2%)
Sarcoma, metastatic, skin		1 (2%)		1 (2%)
Mesentery	(3)	(3)	(5)	(4)
Hemangiosarcoma				2 (50%)
Lymphoma malignant	1 (33%)			
Pancreas	(47)	(45)	(48)	(44)
Histiocytic sarcoma	3 (6%)		1 (2%)	1 (2%)
Lymphoma malignant			5 (10%)	1 (2%)
Sarcoma stromal, metastatic, uterus			1 (2%)	1 (2%)
Sarcoma, metastatic, skin		1 (2%)		1 (2%)
Teratoma malignant, metastatic, ovary		1 (2%)		

Table F1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Drinking Water Study of Urethane and 5% Ethanol

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
Alimentary System (continued)				
Salivary glands	(48)	(47)	(48)	(47)
Histiocytic sarcoma	1 (2%)			
Lymphoma malignant	1 (2%)		5 (10%)	1 (2%)
Mast cell tumor malignant		1 (2%)		
Stomach, forestomach	(48)	(47)	(48)	(45)
Lymphoma malignant				1 (2%)
Mast cell tumor malignant				1 (2%)
Squamous cell papilloma	2 (4%)	3 (6%)	2 (4%)	
Stomach, glandular	(48)	(46)	(48)	(45)
Lymphoma malignant				1 (2%)
Mast cell tumor malignant		1 (2%)		
Sarcoma, metastatic, skin				1 (2%)
Cardiovascular System				
Blood vessel	(47)	(48)	(46)	(45)
Lymphoma malignant			1 (2%)	1 (2%)
Heart	(47)	(48)	(48)	(47)
Alveolar/bronchiolar carcinoma, metastatic, lung			1 (2%)	1 (2%)
Hemangioma			2 (4%)	
Hemangiosarcoma				6 (13%)
Lymphoma malignant		1 (2%)	2 (4%)	2 (4%)
Endocrine System				
Adrenal gland, cortex	(46)	(46)	(47)	(46)
Adenoma			1 (2%)	
Adenoma, subcapsular			2 (4%)	3 (7%)
Carcinoma, subcapsular		1 (2%)		
Histiocytic sarcoma	1 (2%)			
Lymphoma malignant	1 (2%)			2 (4%)
Sarcoma, metastatic, skin				1 (2%)
Adrenal gland, medulla	(44)	(44)	(46)	(46)
Alveolar/bronchiolar carcinoma, metastatic, lung			1 (2%)	
Pheochromocytoma malignant		1 (2%)		
Islets, pancreatic	(47)	(45)	(48)	(44)
Adenoma		1 (2%)	3 (6%)	
Histiocytic sarcoma			1 (2%)	
Lymphoma malignant			2 (4%)	1 (2%)
Sarcoma, metastatic, skin		1 (2%)		
Parathyroid gland	(35)	(41)	(41)	(36)
Lymphoma malignant				1 (3%)
Pituitary gland	(40)	(41)	(40)	(38)
Adenoma, pars distalis	6 (15%)	6 (15%)	5 (13%)	1 (3%)
Carcinoma, pars distalis	1 (3%)			
Histiocytic sarcoma	1 (3%)			
Lymphoma malignant	1 (3%)			
Thyroid gland	(45)	(48)	(45)	(46)
Adenoma, follicular cell	2 (4%)		1 (2%)	1 (2%)

Table F1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Drinking Water Study of Urethane and 5% Ethanol

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
General Body System				
Tissue NOS		(1)		(2)
Alveolar/bronchiolar carcinoma, metastatic, thoracic, lung		1 (100%)		
Histiocytic sarcoma, abdominal				1 (50%)
Genital System				
Ovary	(46)	(47)	(46)	(45)
Adenoma, tubular			1 (2%)	2 (4%)
Cystadenoma	2 (4%)	1 (2%)	3 (7%)	2 (4%)
Granulosa cell tumor benign			5 (11%)	3 (7%)
Granulosa cell tumor malignant			1 (2%)	
Hemangioma			1 (2%)	
Histiocytic sarcoma	4 (9%)		2 (4%)	2 (4%)
Lymphoma malignant		1 (2%)	5 (11%)	2 (4%)
Sarcoma stromal, metastatic, uterus				1 (2%)
Sarcoma, metastatic, skin		1 (2%)		1 (2%)
Teratoma malignant		1 (2%)		
Uterus	(48)	(48)	(47)	(45)
Adenoma, endometrium		1 (2%)		
Alveolar/bronchiolar carcinoma, metastatic, lung			1 (2%)	
Hemangioma		1 (2%)	2 (4%)	1 (2%)
Hemangiosarcoma		2 (4%)	1 (2%)	1 (2%)
Histiocytic sarcoma	3 (6%)		1 (2%)	1 (2%)
Leiomyoma			2 (4%)	
Lymphoma malignant			1 (2%)	
Polyp stromal	2 (4%)	1 (2%)		
Sarcoma stromal			1 (2%)	2 (4%)
Sarcoma, metastatic, skin				1 (2%)
Vagina	(48)	(48)	(46)	(44)
Histiocytic sarcoma	1 (2%)			
Lymphoma malignant			2 (4%)	1 (2%)
Sarcoma stromal, metastatic, uterus			1 (2%)	
Sarcoma, metastatic, skin		1 (2%)		
Squamous cell carcinoma			1 (2%)	
Hematopoietic System				
Bone marrow	(48)	(46)	(48)	(47)
Histiocytic sarcoma	2 (4%)		1 (2%)	1 (2%)
Lymphoma malignant			1 (2%)	1 (2%)
Lymph node	(48)	(47)	(48)	(47)
Alveolar/bronchiolar carcinoma, metastatic, lumbar, lung			1 (2%)	
Histiocytic sarcoma, lumbar	1 (2%)			1 (2%)
Histiocytic sarcoma, renal				1 (2%)
Lymphoma malignant, axillary			1 (2%)	
Lymphoma malignant, iliac			1 (2%)	
Lymphoma malignant, inguinal			4 (8%)	
Lymphoma malignant, lumbar	1 (2%)	1 (2%)	5 (10%)	1 (2%)
Lymphoma malignant, renal	1 (2%)	1 (2%)	4 (8%)	1 (2%)
Lymphoma malignant, thoracic			1 (2%)	1 (2%)
Sarcoma stromal, metastatic, renal, uterus			1 (2%)	1 (2%)

Table F1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Drinking Water Study of Urethane and 5% Ethanol

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
Hematopoietic System (continued)				
Lymph node (continued)	(48)	(47)	(48)	(47)
Sarcoma, metastatic, axillary, skin	1 (2%)	1 (2%)		
Sarcoma, metastatic, lumbar, skin		1 (2%)		
Sarcoma, metastatic, renal, skin		1 (2%)		
Lymph node, mandibular	(48)	(46)	(45)	(47)
Histiocytic sarcoma	2 (4%)			
Lymphoma malignant	2 (4%)	3 (7%)	9 (20%)	2 (4%)
Mast cell tumor malignant		1 (2%)		1 (2%)
Lymph node, mesenteric	(45)	(42)	(46)	(38)
Alveolar/bronchiolar carcinoma, metastatic, lung				1 (3%)
Histiocytic sarcoma	4 (9%)		3 (7%)	2 (5%)
Lymphoma malignant	4 (9%)	5 (12%)	10 (22%)	4 (11%)
Mast cell tumor malignant		1 (2%)		
Sarcoma stromal, metastatic, uterus			1 (2%)	1 (3%)
Sarcoma, metastatic, skin				1 (3%)
Spleen	(48)	(47)	(48)	(45)
Hemangioma			1 (2%)	
Hemangiosarcoma		1 (2%)		1 (2%)
Histiocytic sarcoma	4 (8%)		3 (6%)	2 (4%)
Lymphoma malignant	3 (6%)	4 (9%)	9 (19%)	6 (13%)
Mast cell tumor malignant		1 (2%)		
Sarcoma stromal, metastatic, uterus			1 (2%)	
Sarcoma, metastatic, skin		2 (4%)		1 (2%)
Thymus	(39)	(38)	(43)	(39)
Adenocarcinoma, metastatic, mammary gland				1 (3%)
Alveolar/bronchiolar carcinoma, metastatic, lung			1 (2%)	3 (8%)
Histiocytic sarcoma	2 (5%)			2 (5%)
Lymphoma malignant	2 (5%)	1 (3%)	11 (26%)	6 (15%)
Sarcoma, metastatic, skin		1 (3%)		1 (3%)
Integumentary System				
Mammary gland	(47)	(48)	(48)	(45)
Adenoacanthoma			1 (2%)	9 (20%)
Adenocarcinoma	3 (6%)	4 (8%)	6 (13%)	15 (33%)
Lymphoma malignant			1 (2%)	1 (2%)
Mast cell tumor malignant, lymphatic				1 (2%)
Skin	(48)	(48)	(48)	(47)
Lymphoma malignant			1 (2%)	
Osteosarcoma	1 (2%)			
Sarcoma	3 (6%)	7 (15%)	4 (8%)	7 (15%)
Musculoskeletal System				
Bone	(48)	(48)	(48)	(47)
Alveolar/bronchiolar carcinoma, metastatic, lung				1 (2%)
Lymphoma malignant, sternum				1 (2%)
Bone, femur	(48)	(48)	(48)	(47)
Lymphoma malignant				1 (2%)

Table F1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Drinking Water Study of Urethane and 5% Ethanol

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
Musculoskeletal System (continued)				
Skeletal muscle	(48)	(48)	(48)	(47)
Adenocarcinoma, metastatic, diaphragm, mammary gland				1 (2%)
Alveolar/bronchiolar carcinoma, metastatic, diaphragm, lung				1 (2%)
Lymphoma malignant			4 (8%)	
Mast cell tumor malignant		1 (2%)		
Sarcoma				2 (4%)
Sarcoma, metastatic, skin		1 (2%)		1 (2%)
Teratoma malignant, metastatic, diaphragm, ovary		1 (2%)		
Nervous System				
Brain, cerebrum	(48)	(48)	(48)	(47)
Carcinoma, deep invasion	1 (2%)			
Lymphoma malignant				2 (4%)
Respiratory System				
Lung	(48)	(48)	(48)	(48)
Adenoacanthoma, metastatic, mammary gland				1 (2%)
Adenocarcinoma, metastatic, mammary gland		1 (2%)		1 (2%)
Alveolar/bronchiolar adenoma	4 (8%)	8 (17%)	15 (31%)	8 (17%)
Alveolar/bronchiolar adenoma, multiple	1 (2%)	2 (4%)	3 (6%)	22 (46%)
Alveolar/bronchiolar carcinoma	1 (2%)	5 (10%)	7 (15%)	8 (17%)
Alveolar/bronchiolar carcinoma, multiple		2 (4%)	2 (4%)	15 (31%)
Carcinoma, metastatic, mammary gland				1 (2%)
Granulosa cell tumor malignant, metastatic, ovary			1 (2%)	
Hepatocellular carcinoma, metastatic, liver			1 (2%)	
Histiocytic sarcoma	4 (8%)		3 (6%)	1 (2%)
Leukemia		1 (2%)		
Lymphoma malignant	1 (2%)	1 (2%)	5 (10%)	4 (8%)
Osteosarcoma, metastatic, skin	1 (2%)			
Sarcoma, metastatic, skin	1 (2%)	4 (8%)		3 (6%)
Sarcoma, metastatic, uncertain primary site				1 (2%)
Nose	(47)	(48)	(48)	(47)
Carcinoma, metastatic, harderian gland				1 (2%)
Special Senses System				
Ear			(1)	
Squamous cell papilloma			1 (100%)	
Eye	(48)	(48)	(47)	(45)
Alveolar/bronchiolar carcinoma, metastatic, lung				1 (2%)
Harderian gland	(48)	(48)	(46)	(46)
Adenoma	4 (8%)	7 (15%)	6 (13%)	14 (30%)
Adenoma, bilateral				6 (13%)
Carcinoma	1 (2%)	10 (21%)	6 (13%)	10 (22%)
Carcinoma, bilateral		1 (2%)	1 (2%)	
Histiocytic sarcoma	1 (2%)			
Lymphoma malignant			3 (7%)	

Table F1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Drinking Water Study of Urethane and 5% Ethanol

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
Special Senses System (continued)				
Lacrimal gland	(45)	(45)	(45)	(43)
Histiocytic sarcoma	1 (2%)			
Lymphoma malignant			3 (7%)	1 (2%)
Mast cell tumor malignant		1 (2%)		
Zymbal's gland	(48)	(46)	(43)	(40)
Atrophy, minimal			1 (2%)	
Infiltration cellular, lymphocytic, minimal				1 (3%)
Urinary System				
Kidney	(48)	(48)	(48)	(47)
Alveolar/bronchiolar carcinoma, metastatic, lung				1 (2%)
Hemangiosarcoma				1 (2%)
Histiocytic sarcoma	1 (2%)			1 (2%)
Lymphoma malignant	2 (4%)		5 (10%)	3 (6%)
Mast cell tumor malignant		1 (2%)		1 (2%)
Osteosarcoma, metastatic, skin	1 (2%)			
Sarcoma, metastatic, skin		2 (4%)		
Urinary bladder	(46)	(46)	(47)	(45)
Histiocytic sarcoma	1 (2%)			
Lymphoma malignant	1 (2%)		4 (9%)	
Neoplasm Summary				
Total animals with primary neoplasms[b]	32	43	47	47
Total primary neoplasms	106	106	242	245
Total animals with benign neoplasms	22	26	37	41
Total benign neoplasms	27	37	72	80
Total animals with malignant neoplasms	17	35	37	46
Total malignant neoplasms	79	69	170	165
Total animals with metastatic neoplasms	3	8	4	12
Total metastatic neoplasms	4	23	13	35

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

Table F2
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Drinking Water Study of Urethane and 5% Ethanol

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
Adrenal Cortex: Adenoma				
Overall rate[a]	0/46 (0.0%)	0/46 (0.0%)	3/47 (6.4%)	3/46 (6.5%)
Adjusted rate[b]	0/38.9 (0.0%)	0/40.0 (0.0%)	3/39.6 (7.6%)	3/29.7 (10.1%)
Terminal rate[c]	0/31 (0.0%)	0/32 (0.0%)	3/27 (11.1%)	1/4 (25.0%)
First incidence (days)	—[e]	—	765 (T)	700
Poly-3 test[d]	P=0.018	—[f]	P=0.105	P=0.067
Adrenal Cortex: Adenoma or Carcinoma				
Overall rate	0/46 (0.0%)	1/46 (2.2%)	3/47 (6.4%)	3/46 (6.5%)
Adjusted rate	0/38.9 (0.0%)	1/40.0 (2.5%)	3/39.6 (7.6%)	3/29.7 (10.1%)
Terminal rate	0/31 (0.0%)	1/32 (3.1%)	3/27 (11.1%)	1/4 (25.0%)
First incidence (days)	—	765 (T)	765 (T)	700
Poly-3 test	P=0.041	P=0.486	P=0.105	P=0.067
Harderian Gland: Adenoma				
Overall rate	4/48 (8.3%)	7/48 (14.6%)	6/46 (13.0%)	20/46 (43.5%)
Adjusted rate	4/40.8 (9.8%)	7/42.0 (16.7%)	6/39.5 (15.2%)	20/36.5 (54.7%)
Terminal rate	3/31 (9.7%)	5/32 (15.6%)	3/26 (11.5%)	2/4 (50.0%)
First incidence (days)	718	721	663	433
Poly-3 test	P=0.001	P=0.226	P=0.294	P=0.001
Harderian Gland: Carcinoma				
Overall rate	1/48 (2.1%)	11/48 (22.9%)	7/46 (15.2%)	10/46 (21.7%)
Adjusted rate	1/40.6 (2.5%)	11/41.9 (26.2%)	7/38.8 (18.0%)	10/32.7 (30.5%)
Terminal rate	1/31 (3.2%)	10/32 (31.3%)	7/26 (26.9%)	0/4 (0.0%)
First incidence (days)	765 (T)	738	765 (T)	559
Poly-3 test	P=0.011	P=0.001	P=0.017	P=0.001
Harderian Gland: Adenoma or Carcinoma				
Overall rate	5/48 (10.4%)	18/48 (37.5%)	13/46 (28.3%)	29/46 (63.0%)
Adjusted rate	5/40.8 (12.3%)	18/42.1 (42.7%)	13/39.5 (32.9%)	29/39.7 (73.0%)
Terminal rate	4/31 (12.9%)	15/32 (46.9%)	10/26 (38.5%)	2/4 (50.0%)
First incidence (days)	718	721	663	433
Poly-3 test	P=0.001	P=0.001	P=0.013	P=0.001
Heart: Hemangiosarcoma				
Overall rate	0/47 (0.0%)	0/48 (0.0%)	0/48 (0.0%)	6/47 (12.8%)
Adjusted rate	0/39.8 (0.0%)	0/41.8 (0.0%)	0/40.6 (0.0%)	6/31.5 (19.1%)
Terminal rate	0/31 (0.0%)	0/32 (0.0%)	0/27 (0.0%)	1/4 (25.0%)
First incidence (days)	—	—	—	603
Poly-3 test	P=0.001	—	—	P=0.004
Liver: Hemangiosarcoma				
Overall rate	0/48 (0.0%)	0/47 (0.0%)	0/48 (0.0%)	6/48 (12.5%)
Adjusted rate	0/40.6 (0.0%)	0/41.1 (0.0%)	0/40.6 (0.0%)	6/32.1 (18.7%)
Terminal rate	0/31 (0.0%)	0/32 (0.0%)	0/27 (0.0%)	0/4 (0.0%)
First incidence (days)	—	—	—	485
Poly-3 test	P=0.001	—	—	P=0.004
Liver: Histiocytic Sarcoma				
Overall rate	4/48 (8.3%)	0/47 (0.0%)	3/48 (6.3%)	2/48 (4.2%)
Adjusted rate	4/41.7 (9.6%)	0/41.1 (0.0%)	3/41.0 (7.3%)	2/31.1 (6.4%)
Terminal rate	0/31 (0.0%)	0/32 (0.0%)	0/27 (0.0%)	0/4 (0.0%)
First incidence (days)	515	—	687	674
Poly-3 test	P=0.548	P=0.074N	P=0.558N	P=0.523N

Table F2
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Drinking Water Study of Urethane and 5% Ethanol

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
Liver: Hepatocellular Adenoma				
Overall rate	3/48 (6.3%)	6/47 (12.8%)	16/48 (33.3%)	16/48 (33.3%)
Adjusted rate	3/40.6 (7.4%)	6/41.2 (14.6%)	16/41.1 (38.9%)	16/35.5 (45.0%)
Terminal rate	3/31 (9.7%)	4/32 (12.5%)	12/27 (44.4%)	3/4 (75.0%)
First incidence (days)	765 (T)	738	685	559
Poly-3 test	P=0.001	P=0.205	P=0.001	P=0.001
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rate	3/48 (6.3%)	7/47 (14.9%)	16/48 (33.3%)	17/48 (35.4%)
Adjusted rate	3/40.6 (7.4%)	7/41.2 (17.0%)	16/41.1 (38.9%)	17/35.7 (47.6%)
Terminal rate	3/31 (9.7%)	5/32 (15.6%)	12/27 (44.4%)	3/4 (75.0%)
First incidence (days)	765 (T)	738	685	559
Poly-3 test	P=0.001	P=0.127	P=0.001	P=0.001
Lung: Histiocytic Sarcoma				
Overall rate	4/48 (8.3%)	0/48 (0.0%)	3/48 (6.3%)	1/48 (2.1%)
Adjusted rate	4/41.7 (9.6%)	0/41.8 (0.0%)	3/41.0 (7.3%)	1/31.0 (3.2%)
Terminal rate	0/31 (0.0%)	0/32 (0.0%)	0/27 (0.0%)	0/4 (0.0%)
First incidence (days)	515	—	687	674
Poly-3 test	P=0.422N	P=0.072N	P=0.558N	P=0.317N
Lung: Alveolar/bronchiolar Adenoma				
Overall rate	5/48 (10.4%)	10/48 (20.8%)	18/48 (37.5%)	30/48 (62.5%)
Adjusted rate	5/40.6 (12.3%)	10/42.1 (23.8%)	18/42.2 (42.7%)	30/38.9 (77.1%)
Terminal rate	5/31 (16.1%)	7/32 (21.9%)	14/27 (51.9%)	4/4 (100.0%)
First incidence (days)	765 (T)	721	380	433
Poly-3 test	P=0.001	P=0.103	P=0.001	P=0.001
Lung: Alveolar/bronchiolar Carcinoma				
Overall rate	1/48 (2.1%)	7/48 (14.6%)	9/48 (18.8%)	23/48 (47.9%)
Adjusted rate	1/40.6 (2.5%)	7/42.1 (16.6%)	9/40.9 (22.0%)	23/37.7 (61.1%)
Terminal rate	1/31 (3.2%)	5/32 (15.6%)	8/27 (29.6%)	3/4 (75.0%)
First incidence (days)	765 (T)	703	670	485
Poly-3 test	P=0.001	P=0.024	P=0.005	P=0.001
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rate	5/48 (10.4%)	17/48 (35.4%)	24/48 (50.0%)	37/48 (77.1%)
Adjusted rate	5/40.6 (12.3%)	17/42.3 (40.2%)	24/42.5 (56.5%)	37/41.8 (88.5%)
Terminal rate	5/31 (16.1%)	12/32 (37.5%)	19/27 (70.4%)	4/4 (100.0%)
First incidence (days)	765 (T)	703	380	433
Poly-3 test	P=0.001	P=0.001	P=0.001	P=0.001
Lymph Node (Mesenteric): Histiocytic Sarcoma				
Overall rate	4/45 (8.9%)	0/42 (0.0%)	3/46 (6.5%)	2/38 (5.3%)
Adjusted rate	4/38.8 (10.3%)	0/37.3 (0.0%)	3/39.6 (7.6%)	2/25.2 (7.9%)
Terminal rate	0/29 (0.0%)	0/31 (0.0%)	0/26 (0.0%)	0/4 (0.0%)
First incidence (days)	515	—	687	674
Poly-3 test	P=0.496	P=0.078N	P=0.541N	P=0.591N
Mammary Gland: Adenoacanthoma				
Overall rate	0/47 (0.0%)	0/48 (0.0%)	1/48 (2.1%)	9/45 (20.0%)
Adjusted rate	0/40.2 (0.0%)	0/41.8 (0.0%)	1/40.6 (2.5%)	9/32.0 (28.1%)
Terminal rate	0/31 (0.0%)	0/32 (0.0%)	1/27 (3.7%)	2/4 (50.0%)
First incidence (days)	—	—	765 (T)	459
Poly-3 test	P=0.001	—	P=0.483	P=0.001

Table F2
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Drinking Water Study of Urethane and 5% Ethanol

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
Mammary Gland: Adenocarcinoma				
Overall rate	3/47 (6.4%)	4/48 (8.3%)	6/48 (12.5%)	15/45 (33.3%)
Adjusted rate	3/40.2 (7.5%)	4/42.2 (9.5%)	6/41.7 (14.4%)	15/33.8 (44.3%)
Terminal rate	2/31 (6.5%)	3/32 (9.4%)	2/27 (7.4%)	1/4 (25.0%)
First incidence (days)	754	644	642	559
Poly-3 test	P=0.001	P=0.476	P=0.214	P=0.001
Mammary Gland: Adenoacanthoma or Adenocarcinoma				
Overall rate	3/47 (6.4%)	4/48 (8.3%)	7/48 (14.6%)	23/45 (51.1%)
Adjusted rate	3/40.2 (7.5%)	4/42.2 (9.5%)	7/41.7 (16.8%)	23/36.9 (62.4%)
Terminal rate	2/31 (6.5%)	3/32 (9.4%)	3/27 (11.1%)	2/4 (50.0%)
First incidence (days)	754	644	642	459
Poly-3 test	P=0.001	P=0.476	P=0.134	P=0.001
Ovary: Histiocytic Sarcoma				
Overall rate	4/46 (8.7%)	0/47 (0.0%)	2/46 (4.3%)	2/45 (4.4%)
Adjusted rate	4/39.9 (10.0%)	0/41.1 (0.0%)	2/38.9 (5.1%)	2/29.3 (6.8%)
Terminal rate	0/31 (0.0%)	0/32 (0.0%)	0/26 (0.0%)	0/4 (0.0%)
First incidence (days)	515	—	745	674
Poly-3 test	P=0.567	P=0.068N	P=0.393N	P=0.532N
Ovary: Cystadenoma				
Overall rate	2/46 (4.3%)	1/47 (2.1%)	3/46 (6.5%)	2/45 (4.4%)
Adjusted rate	2/38.8 (5.2%)	1/41.1 (2.4%)	3/38.8 (7.7%)	2/29.5 (6.8%)
Terminal rate	2/31 (6.5%)	1/32 (3.1%)	3/26 (11.5%)	0/4 (0.0%)
First incidence (days)	765 (T)	765 (T)	765 (T)	661
Poly-3 test	P=0.359	P=0.513N	P=0.456	P=0.553
Ovary: Benign Granulosa Cell Tumor				
Overall rate	0/46 (0.0%)	0/47 (0.0%)	5/46 (10.9%)	3/45 (6.7%)
Adjusted rate	0/38.8 (0.0%)	0/41.1 (0.0%)	5/39.3 (12.7%)	3/28.9 (10.4%)
Terminal rate	0/31 (0.0%)	0/32 (0.0%)	3/26 (11.5%)	3/4 (75.0%)
First incidence (days)	—	—	685	765 (T)
Poly-3 test	P=0.021	—	P=0.023	P=0.064
Ovary: Benign or Malignant Granulosa Cell Tumor				
Overall rate	0/46 (0.0%)	0/47 (0.0%)	6/46 (13.0%)	3/45 (6.7%)
Adjusted rate	0/38.8 (0.0%)	0/41.1 (0.0%)	6/39.5 (15.2%)	3/28.9 (10.4%)
Terminal rate	0/31 (0.0%)	0/32 (0.0%)	3/26 (11.5%)	3/4 (75.0%)
First incidence (days)	—	—	685	765 (T)
Poly-3 test	P=0.022	—	P=0.011	P=0.064
Pancreas: Histocytic Sarcoma				
Overall rate	3/47 (6.4%)	0/45 (0.0%)	1/48 (2.1%)	1/44 (2.3%)
Adjusted rate	3/40.1 (7.5%)	0/39.8 (0.0%)	1/40.6 (2.5%)	1/28.5 (3.5%)
Terminal rate	0/31 (0.0%)	0/32 (0.0%)	0/27 (0.0%)	0/4 (0.0%)
First incidence (days)	706	—	746	762
Poly-3 test	P=0.508N	P=0.138N	P=0.334N	P=0.471N
Pancreatic Islets: Adenoma				
Overall rate	0/47 (0.0%)	1/45 (2.2%)	3/48 (6.3%)	0/44 (0.0%)
Adjusted rate	0/39.7 (0.0%)	1/40.1 (2.5%)	3/40.6 (7.4%)	0/28.5 (0.0%)
Terminal rate	0/31 (0.0%)	0/32 (0.0%)	2/27 (7.4%)	0/4 (0.0%)
First incidence (days)	—	662	745	—
Poly-3 test	P=0.619	P=0.483	P=0.106	—

Table F2
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Drinking Water Study of Urethane and 5% Ethanol

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
Pituitary Gland (Pars Distalis): Adenoma or Carcinoma				
Overall rate	7/40 (17.5%)	6/41 (14.6%)	5/40 (12.5%)	1/38 (2.6%)
Adjusted rate	7/33.8 (20.7%)	6/35.5 (16.9%)	5/34.4 (14.5%)	1/25.1 (4.0%)
Terminal rate	6/25 (24.0%)	6/27 (22.2%)	5/25 (20.0%)	0/4 (0.0%)
First incidence (days)	718	765 (T)	765 (T)	726
Poly-3 test	P=0.076N	P=0.527N	P=0.424N	P=0.092N
Skin: Sarcoma				
Overall rate	3/48 (6.3%)	7/48 (14.6%)	4/48 (8.3%)	7/47 (14.9%)
Adjusted rate	3/41.4 (7.2%)	7/42.2 (16.6%)	4/41.1 (9.7%)	7/32.2 (21.7%)
Terminal rate	0/31 (0.0%)	3/32 (9.4%)	2/27 (7.4%)	0/4 (0.0%)
First incidence (days)	571	721	685	573
Poly-3 test	P=0.090	P=0.129	P=0.446	P=0.055
Spleen: Histiocytic Sarcoma				
Overall rate	4/48 (8.3%)	0/47 (0.0%)	3/48 (6.3%)	2/45 (4.4%)
Adjusted rate	4/41.7 (9.6%)	0/41.1 (0.0%)	3/41.0 (7.3%)	2/29.3 (6.8%)
Terminal rate	0/31 (0.0%)	0/32 (0.0%)	0/27 (0.0%)	0/4 (0.0%)
First incidence (days)	515	—	687	674
Poly-3 test	P=0.524	P=0.074N	P=0.558N	P=0.551N
Stomach (Forestomach): Squamous Cell Papilloma				
Overall rate	2/48 (4.2%)	3/47 (6.4%)	2/48 (4.2%)	0/45 (0.0%)
Adjusted rate	2/40.7 (4.9%)	3/41.1 (7.3%)	2/40.8 (4.9%)	0/28.8 (0.0%)
Terminal rate	1/31 (3.2%)	3/32 (9.4%)	1/27 (3.7%)	0/4 (0.0%)
First incidence (days)	737	765 (T)	702	—
Poly-3 test	P=0.219N	P=0.463	P=0.661N	P=0.344N
Thymus: Histiocytic Sarcoma				
Overall rate	2/39 (5.1%)	0/38 (0.0%)	0/43 (0.0%)	2/39 (5.1%)
Adjusted rate	2/33.1 (6.0%)	0/32.1 (0.0%)	0/36.1 (0.0%)	2/24.3 (8.2%)
Terminal rate	0/24 (0.0%)	0/24 (0.0%)	0/24 (0.0%)	0/2 (0.0%)
First incidence (days)	515	—	—	674
Poly-3 test	P=0.337	P=0.270N	P=0.243N	P=0.534
Uterus: Histiocytic Sarcoma				
Overall rate	3/48 (6.3%)	0/48 (0.0%)	1/47 (2.1%)	1/45 (2.2%)
Adjusted rate	3/41.5 (7.2%)	0/41.8 (0.0%)	1/39.6 (2.5%)	1/29.0 (3.5%)
Terminal rate	0/31 (0.0%)	0/32 (0.0%)	0/26 (0.0%)	0/4 (0.0%)
First incidence (days)	515	—	746	762
Poly-3 test	P=0.512N	P=0.134N	P=0.355N	P=0.477N
Uterus: Hemangioma or Hemangiosarcoma				
Overall rate	0/48 (0.0%)	3/48 (6.3%)	3/47 (6.4%)	2/45 (4.4%)
Adjusted rate	0/40.6 (0.0%)	3/41.9 (7.2%)	3/40.0 (7.5%)	2/29.1 (6.9%)
Terminal rate	0/31 (0.0%)	2/32 (6.3%)	1/26 (3.8%)	0/4 (0.0%)
First incidence (days)	—	754	675	749
Poly-3 test	P=0.238	P=0.108	P=0.100	P=0.156

Table F2
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Drinking Water Study of Urethane and 5% Ethanol

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
All Organs: Hemangioma				
Overall rate	0/48 (0.0%)	1/48 (2.1%)	6/48 (12.5%)	2/48 (4.2%)
Adjusted rate	0/40.6 (0.0%)	1/41.8 (2.4%)	6/41.0 (14.6%)	2/31.2 (6.4%)
Terminal rate	0/31 (0.0%)	1/32 (3.1%)	4/27 (14.8%)	0/4 (0.0%)
First incidence (days)	—	765 (T)	675	643
Poly-3 test	P=0.123	P=0.488	P=0.011	P=0.168
All Organs: Hemangiosarcoma				
Overall rate	0/48 (0.0%)	3/48 (6.3%)	1/48 (2.1%)	13/48 (27.1%)
Adjusted rate	0/40.6 (0.0%)	3/41.9 (7.2%)	1/40.6 (2.5%)	13/33.8 (38.5%)
Terminal rate	0/31 (0.0%)	2/32 (6.3%)	1/27 (3.7%)	2/4 (50.0%)
First incidence (days)	—	754	765 (T)	485
Poly-3 test	P=0.001	P=0.108	P=0.481	P=0.001
All Organs: Hemangioma or Hemangiosarcoma				
Overall rate	0/48 (0.0%)	4/48 (8.3%)	7/48 (14.6%)	14/48 (29.2%)
Adjusted rate	0/40.6 (0.0%)	4/41.9 (9.6%)	7/41.0 (17.1%)	14/34.2 (40.9%)
Terminal rate	0/31 (0.0%)	3/32 (9.4%)	5/27 (18.5%)	2/4 (50.0%)
First incidence (days)	—	754	675	485
Poly-3 test	P=0.001	P=0.052	P=0.005	P=0.001
All Organs: Histiocytic Sarcoma				
Overall rate	4/48 (8.3%)	0/48 (0.0%)	3/48 (6.3%)	2/48 (4.2%)
Adjusted rate	4/41.7 (9.6%)	0/41.8 (0.0%)	3/41.0 (7.3%)	2/31.1 (6.4%)
Terminal rate	0/31 (0.0%)	0/32 (0.0%)	0/27 (0.0%)	0/4 (0.0%)
First incidence (days)	515	—	687	674
Poly-3 test	P=0.546	P=0.072N	P=0.558N	P=0.523N
All Organs: Malignant Lymphoma				
Overall rate	5/48 (10.4%)	6/48 (12.5%)	15/48 (31.3%)	10/48 (20.8%)
Adjusted rate	5/40.8 (12.2%)	6/42.8 (14.0%)	15/43.8 (34.3%)	10/35.2 (28.4%)
Terminal rate	3/31 (9.7%)	4/32 (12.5%)	6/27 (22.2%)	1/4 (25.0%)
First incidence (days)	718	553	285	433
Poly-3 test	P=0.028	P=0.468	P=0.008	P=0.046
All Organs: Benign Neoplasms				
Overall rate	22/48 (45.8%)	26/48 (54.2%)	37/48 (77.1%)	41/48 (85.4%)
Adjusted rate	22/41.1 (53.5%)	26/42.6 (61.1%)	37/44.0 (84.2%)	41/44.0 (93.2%)
Terminal rate	18/31 (58.1%)	20/32 (62.5%)	25/27 (92.6%)	4/4 (100.0%)
First incidence (days)	718	662	380	433
Poly-3 test	P=0.001	P=0.171	P=0.001	P=0.001
All Organs: Malignant Neoplasms				
Overall rate	17/48 (35.4%)	35/48 (72.9%)	37/48 (77.1%)	46/48 (95.8%)
Adjusted rate	17/43.1 (39.5%)	35/44.8 (78.2%)	37/46.2 (80.1%)	46/47.0 (97.8%)
Terminal rate	8/31 (25.8%)	24/32 (75.0%)	20/27 (74.1%)	3/4 (75.0%)
First incidence (days)	515	531	285	433
Poly-3 test	P=0.001	P=0.001	P=0.001	P=0.001

TABLE F2
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Drinking Water Study of Urethane and 5% Ethanol

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
All Organs: Benign or Malignant Neoplasms				
Overall rate	32/48 (66.7%)	43/48 (89.6%)	47/48 (97.9%)	47/48 (97.9%)
Adjusted rate	32/43.3 (73.8%)	43/45.1 (95.2%)	47/47.5 (98.9%)	47/47.0 (99.9%)
Terminal rate	21/31 (67.7%)	30/32 (93.8%)	27/27 (100.0%)	4/4 (100.0%)
First incidence (days)	515	531	285	433
Poly-3 test	P=0.001	P=0.001	P=0.001	P=0.001

(T) Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals with tissue examined microscopically
[b] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the control incidence (0 ppm urethane) is the P value associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and that exposed group. The Poly-3 test accounts for the differential mortality in animals that do not reach terminal sacrifice. A negative trend or a lower incidence in an exposed group is indicated by **N**.
[e] Not applicable; no neoplasms in animal group
[f] Value of statistic cannot be computed.

TABLE F3
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Drinking Water Study of Urethane and 5% Ethanol[a]

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
Disposition Summary				
Animals initially in study	48	48	48	48
Early deaths				
Accidental deaths	4			
Moribund	6	4	4	11
Natural deaths	7	12	17	33
Survivors				
Terminal sacrifice	31	32	27	4
Animals examined microscopically	48	48	48	48
Alimentary System				
Esophagus	(47)	(48)	(47)	(46)
Autolysis, moderate		1 (2%)		
Gallbladder	(47)	(44)	(47)	(45)
Autolysis, marked				1 (2%)
Autolysis, mild			1 (2%)	
Autolysis, moderate	2 (4%)	1 (2%)	1 (2%)	3 (7%)
Infiltration cellular, lymphocytic, minimal	1 (2%)	1 (2%)		
Intestine large	(48)	(47)	(48)	(44)
Inflammation, mild	1 (2%)			
Intestine large, cecum	(47)	(44)	(48)	(42)
Autolysis, marked	1 (2%)	1 (2%)		
Autolysis, moderate	2 (4%)	1 (2%)	5 (10%)	4 (10%)
Intestine large, colon	(47)	(45)	(48)	(42)
Autolysis, marked	1 (2%)	1 (2%)		
Autolysis, moderate	2 (4%)	1 (2%)	4 (8%)	4 (10%)
Intestine large, rectum	(48)	(47)	(46)	(44)
Autolysis, marked	1 (2%)	1 (2%)		
Autolysis, moderate	2 (4%)	2 (4%)	3 (7%)	3 (7%)
Inflammation, mild			1 (2%)	
Polyarteritis, moderate		1 (2%)		
Intestine small, duodenum	(47)	(44)	(46)	(40)
Autolysis, marked	1 (2%)	1 (2%)		
Autolysis, moderate	4 (9%)	1 (2%)	6 (13%)	5 (13%)
Intestine small, ileum	(47)	(44)	(47)	(40)
Autolysis, marked	1 (2%)	1 (2%)		
Autolysis, moderate	4 (9%)	1 (2%)	6 (13%)	6 (15%)
Hyperplasia, mild, lymphoid tissue			1 (2%)	
Hyperplasia, moderate, lymphoid tissue			1 (2%)	
Intussusception		1 (2%)		
Intestine small, jejunum	(47)	(44)	(47)	(40)
Autolysis, marked	1 (2%)	1 (2%)		
Autolysis, moderate	4 (9%)	1 (2%)	6 (13%)	6 (15%)
Hyperplasia, mild, lymphoid tissue			1 (2%)	1 (3%)
Hyperplasia, moderate, lymphoid tissue		2 (5%)		
Liver	(48)	(47)	(48)	(48)
Angiectasis	2 (4%)	1 (2%)	5 (10%)	22 (46%)
Autolysis, marked		1 (2%)		
Autolysis, moderate	1 (2%)		2 (4%)	1 (2%)
Basophilic focus	1 (2%)			
Eosinophilic focus	2 (4%)	12 (26%)	4 (8%)	1 (2%)
Eosinophilic focus, multiple		14 (30%)	21 (44%)	20 (42%)

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

Table F3
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Drinking Water Study of Urethane and 5% Ethanol

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
Alimentary System (continued)				
Liver (continued)	(48)	(47)	(48)	(48)
Granuloma, focal, minimal	2 (4%)	1 (2%)		
Hematopoietic cell proliferation, marked			1 (2%)	3 (6%)
Hematopoietic cell proliferation, mild	2 (4%)	6 (13%)	11 (23%)	14 (29%)
Hematopoietic cell proliferation, minimal		3 (6%)	3 (6%)	
Hematopoietic cell proliferation, moderate	1 (2%)	2 (4%)	3 (6%)	10 (21%)
Hepatodiaphragmatic nodule	1 (2%)			
Hyperplasia, moderate, Kupffer cell		1 (2%)		
Infarct, caudate lobe			1 (2%)	
Infiltration cellular, lymphocytic, mild	3 (6%)	3 (6%)	3 (6%)	2 (4%)
Infiltration cellular, lymphocytic, minimal	10 (21%)	5 (11%)	1 (2%)	2 (4%)
Infiltration cellular, lymphocytic, moderate	1 (2%)			
Inflammation, chronic active, mild				1 (2%)
Inflammation, chronic, mild		1 (2%)		
Inflammation, mild			1 (2%)	
Leukocytosis, moderate				1 (2%)
Mixed cell focus	1 (2%)	1 (2%)		
Mixed cell focus, multiple		4 (9%)	9 (19%)	2 (4%)
Necrosis, marked				1 (2%)
Necrosis, mild			2 (4%)	7 (15%)
Necrosis, mild, centrilobular		1 (2%)		1 (2%)
Necrosis, minimal		1 (2%)	1 (2%)	2 (4%)
Necrosis, moderate				5 (10%)
Necrosis, moderate, centrilobular				1 (2%)
Pigmentation, mild	1 (2%)			
Pigmentation, moderate, centrilobular			1 (2%)	
Regeneration				3 (6%)
Thrombosis			1 (2%)	8 (17%)
Vacuolization cytoplasmic, mild, hepatocyte		5 (11%)	5 (10%)	2 (4%)
Vacuolization cytoplasmic, mild, hepatocyte, acanthosis		1 (2%)		
Vacuolization cytoplasmic, minimal, hepatocyte		1 (2%)	1 (2%)	
Vacuolization cytoplasmic, moderate, hepatocyte			4 (8%)	1 (2%)
Mesentery	(3)	(3)	(5)	(4)
Fibrosis, mild	1 (33%)			
Necrosis, fat	2 (67%)	3 (100%)	5 (100%)	3 (75%)
Pancreas	(47)	(45)	(48)	(44)
Atrophy, marked, acinar cell			1 (2%)	
Atrophy, minimal, acinar cell	1 (2%)			1 (2%)
Autolysis, moderate	2 (4%)	1 (2%)	1 (2%)	3 (7%)
Infiltration cellular, lymphocytic, mild	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Infiltration cellular, lymphocytic, minimal	10 (21%)	8 (18%)	6 (13%)	4 (9%)
Infiltration cellular, lymphocytic, moderate				1 (2%)
Salivary glands	(48)	(47)	(48)	(47)
Hypertrophy, minimal, parenchymal cell				1 (2%)
Infiltration cellular, lymphocytic, mild	15 (31%)	12 (26%)	12 (25%)	10 (21%)
Infiltration cellular, lymphocytic, minimal	18 (38%)	26 (55%)	25 (52%)	29 (62%)
Infiltration cellular, lymphocytic, moderate		1 (2%)		
Stomach, forestomach	(48)	(47)	(48)	(45)
Autolysis, marked	1 (2%)	1 (2%)		
Autolysis, moderate	1 (2%)	1 (2%)	1 (2%)	2 (4%)
Foreign body		1 (2%)	2 (4%)	
Hyperkeratosis, mild		1 (2%)	2 (4%)	5 (11%)
Hyperplasia, marked, epithelium	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Hyperplasia, mild, epithelium	1 (2%)		3 (6%)	4 (9%)

Table F3
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Drinking Water Study of Urethane and 5% Ethanol

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
Alimentary System (continued)				
Stomach, forestomach (continued)	(48)	(47)	(48)	(45)
Hyperplasia, minimal, epithelium	1 (2%)		2 (4%)	2 (4%)
Hyperplasia, moderate, epithelium	1 (2%)	1 (2%)	4 (8%)	
Inflammation, mild	2 (4%)	1 (2%)		
Inflammation, minimal		1 (2%)		
Ulcer, mild				1 (2%)
Ulcer, moderate			1 (2%)	
Stomach, glandular	(48)	(46)	(48)	(45)
Autolysis, marked	1 (2%)	1 (2%)		
Autolysis, moderate	1 (2%)	1 (2%)	1 (2%)	2 (4%)
Cyst			1 (2%)	
Metaplasia, squamous, mild				1 (2%)
Mineralization, mild				1 (2%)
Mineralization, minimal	1 (2%)		1 (2%)	1 (2%)
Cardiovascular System				
Blood vessel	(47)	(48)	(46)	(45)
Inflammation, minimal				1 (2%)
Mineralization, moderate	1 (2%)			
Heart	(47)	(48)	(48)	(47)
Angiectasis, mild			2 (4%)	3 (6%)
Angiectasis, minimal			1 (2%)	1 (2%)
Cardiomyopathy, mild			4 (8%)	2 (4%)
Cardiomyopathy, minimal			2 (4%)	
Embolus tumor			1 (2%)	
Hyperplasia, mild, endothelium			1 (2%)	7 (15%)
Hyperplasia, minimal, endothelium			2 (4%)	5 (11%)
Hyperplasia, moderate, endothelium		1 (2%)		2 (4%)
Inflammation, chronic, mild, epicardium			1 (2%)	
Inflammation, chronic, minimal, epicardium				2 (4%)
Inflammation, minimal, myocardium			1 (2%)	
Mineralization, mild			2 (4%)	1 (2%)
Mineralization, minimal	2 (4%)	1 (2%)		1 (2%)
Thrombosis, mild, myocardium			1 (2%)	1 (2%)
Endocrine System				
Adrenal gland, cortex	(46)	(46)	(47)	(46)
Accessory adrenal cortical nodule				1 (2%)
Angiectasis, mild			1 (2%)	
Angiectasis, minimal	1 (2%)			
Autolysis, moderate		1 (2%)		1 (2%)
Hematopoietic cell proliferation, mild				1 (2%)
Hematopoietic cell proliferation, minimal				1 (2%)
Hemorrhage, mild				1 (2%)
Hyperplasia, marked, subcapsular	1 (2%)			
Hyperplasia, mild, subcapsular	25 (54%)	27 (59%)	32 (68%)	25 (54%)
Hyperplasia, minimal, subcapsular	9 (20%)	3 (7%)	3 (6%)	4 (9%)
Hyperplasia, moderate, subcapsular	1 (2%)	3 (7%)	2 (4%)	4 (9%)
Infiltration cellular, lymphocytic, minimal				3 (7%)
Inflammation, acute, minimal				1 (2%)
Pigmentation, minimal				1 (2%)
Vacuolization cytoplasmic, minimal	1 (2%)			

Table F3
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Drinking Water Study of Urethane and 5% Ethanol

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
Endocrine System (continued)				
Adrenal gland, medulla	(44)	(44)	(46)	(46)
Autolysis, moderate		1 (2%)		1 (2%)
Hemorrhage, mild				1 (2%)
Hyperplasia, mild	1 (2%)	1 (2%)		
Hyperplasia, minimal		1 (2%)		
Islets, pancreatic	(47)	(45)	(48)	(44)
Autolysis, moderate	2 (4%)	1 (2%)	1 (2%)	2 (5%)
Hyperplasia, mild	3 (6%)	1 (2%)	3 (6%)	2 (5%)
Hyperplasia, minimal	5 (11%)	1 (2%)	2 (4%)	1 (2%)
Hyperplasia, moderate				1 (2%)
Infiltration cellular, lymphocytic, minimal	1 (2%)			
Parathyroid gland	(35)	(41)	(41)	(36)
Autolysis, moderate		1 (2%)		
Cyst			1 (2%)	
Infiltration cellular, lymphocytic, mild			1 (2%)	
Pituitary gland	(40)	(41)	(40)	(38)
Angiectasis, mild	1 (3%)	1 (2%)		1 (3%)
Angiectasis, minimal			1 (3%)	
Angiectasis, moderate	1 (3%)			
Hyperplasia, mild, pars distalis				1 (3%)
Hyperplasia, minimal, pars distalis		2 (5%)	1 (3%)	
Hyperplasia, moderate, pars distalis	1 (3%)	1 (2%)		
Thyroid gland	(45)	(48)	(45)	(46)
Autolysis, marked				1 (2%)
Autolysis, moderate		1 (2%)		
Cyst multilocular			1 (2%)	
Cyst, minimal				1 (2%)
Hyperplasia, minimal, C-cell			1 (2%)	
Infiltration cellular, lymphocytic, minimal		1 (2%)	1 (2%)	
General Body System				
Tissue NOS		(1)		(2)
Necrosis, moderate, abdominal, fat				1 (50%)
Genital System				
Clitoral gland	(38)	(41)	(41)	(35)
Atrophy, mild	27 (71%)	35 (85%)	33 (80%)	22 (63%)
Atrophy, minimal	2 (5%)			5 (14%)
Atrophy, moderate	2 (5%)	1 (2%)	4 (10%)	2 (6%)
Dilatation, mild			1 (2%)	
Infiltration cellular, lymphocytic, mild	1 (3%)			
Ovary	(46)	(47)	(46)	(45)
Angiectasis, mild		2 (4%)	2 (4%)	3 (7%)
Angiectasis, minimal		1 (2%)		1 (2%)
Angiectasis, moderate		1 (2%)	2 (4%)	2 (4%)
Atrophy, marked	11 (24%)	35 (74%)	36 (78%)	30 (67%)
Atrophy, mild	6 (13%)	2 (4%)		1 (2%)
Atrophy, minimal	3 (7%)			
Atrophy, moderate	13 (28%)	2 (4%)	1 (2%)	5 (11%)
Congestion, minimal		1 (2%)		
Cyst	12 (26%)	12 (26%)	7 (15%)	6 (13%)
Cyst, periovarian tissue				2 (4%)

TABLE F3
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Drinking Water Study of Urethane and 5% Ethanol

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
Genital System (continued)				
Ovary (continued)	(46)	(47)	(46)	(45)
Hematocyst	6 (13%)	1 (2%)		
Hemorrhage, marked			1 (2%)	
Hyperplasia, tubular, mild				1 (2%)
Hyperplasia, tubular, moderate			1 (2%)	3 (7%)
Infiltration cellular, histiocytic, moderate	1 (2%)	1 (2%)		
Infiltration cellular, lymphocytic, mild	1 (2%)		1 (2%)	
Infiltration cellular, lymphocytic, moderate, periovarian tissue		1 (2%)		
Inflammation, marked, periovarian tissue				1 (2%)
Mineralization, minimal	1 (2%)			
Mineralization, moderate	1 (2%)	1 (2%)	1 (2%)	
Pigmentation, mild	1 (2%)			
Pigmentation, moderate	1 (2%)	1 (2%)		
Polyarteritis, moderate		1 (2%)		
Thrombosis, marked	1 (2%)	1 (2%)	2 (4%)	1 (2%)
Thrombosis, mild			1 (2%)	
Thrombosis, moderate				2 (4%)
Uterus	(48)	(48)	(47)	(45)
Angiectasis, marked	2 (4%)	2 (4%)		1 (2%)
Angiectasis, mild	1 (2%)		6 (13%)	2 (4%)
Angiectasis, moderate	1 (2%)		2 (4%)	3 (7%)
Hemorrhage, marked			1 (2%)	
Hemorrhage, mild			1 (2%)	
Hyperplasia, cystic, mild, endometrium	18 (38%)	22 (46%)	19 (40%)	18 (40%)
Hyperplasia, cystic, minimal, endometrium		4 (8%)	5 (11%)	2 (4%)
Hyperplasia, cystic, moderate, endometrium	18 (38%)	12 (25%)	11 (23%)	11 (24%)
Thrombosis, marked	1 (2%)	2 (4%)		1 (2%)
Thrombosis, moderate			2 (4%)	3 (7%)
Vagina	(48)	(48)	(46)	(44)
Exudate, mild		1 (2%)		
Exudate, moderate			1 (2%)	
Inflammation, mild			1 (2%)	
Polyarteritis, moderate		1 (2%)		
Hematopoietic System				
Bone marrow	(48)	(46)	(48)	(47)
Autolysis, marked				1 (2%)
Autolysis, mild				1 (2%)
Autolysis, moderate				1 (2%)
Hyperplasia, marked, myeloid cell				2 (4%)
Hyperplasia, mild, myeloid cell		2 (4%)	4 (8%)	5 (11%)
Hyperplasia, moderate, myeloid cell	1 (2%)		1 (2%)	5 (11%)
Lymph node	(48)	(47)	(48)	(47)
Hematocyst, mild	1 (2%)			
Hematopoietic cell proliferation, marked, renal				1 (2%)
Hematopoietic cell proliferation, moderate, lumbar			1 (2%)	
Hemorrhage, moderate, lumbar				1 (2%)
Hyperplasia, lymphoid, mild, renal				1 (2%)
Hyperplasia, moderate, lumbar		1 (2%)		
Infiltration cellular, histiocytic, mild, lumbar			1 (2%)	
Inflammation, mild, lumbar			1 (2%)	
Pigmentation, moderate	1 (2%)			

Table F3
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Drinking Water Study of Urethane and 5% Ethanol

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
Hematopoietic System (continued)				
Lymph node, mandibular	(48)	(46)	(45)	(47)
Autolysis, moderate				1 (2%)
Hyperplasia, lymphoid, mild	5 (10%)	2 (4%)	4 (9%)	2 (4%)
Hyperplasia, lymphoid, minimal				1 (2%)
Hyperplasia, lymphoid, moderate		1 (2%)		3 (6%)
Infiltration cellular, histiocytic, minimal				3 (6%)
Lymph node, mesenteric	(45)	(42)	(46)	(38)
Angiectasis, mild				1 (3%)
Angiectasis, moderate	1 (2%)	1 (2%)		
Atrophy, moderate				1 (3%)
Autolysis, moderate	2 (4%)	1 (2%)		2 (5%)
Hematopoietic cell proliferation, mild				1 (3%)
Hematopoietic cell proliferation, moderate				1 (3%)
Hemorrhage, mild				1 (3%)
Hemorrhage, moderate	1 (2%)			
Hyperplasia, lymphoid, marked			2 (4%)	
Hyperplasia, lymphoid, mild	2 (4%)	3 (7%)	1 (2%)	3 (8%)
Hyperplasia, lymphoid, minimal			1 (2%)	
Hyperplasia, lymphoid, moderate				1 (3%)
Infiltration cellular, histiocytic, minimal	1 (2%)			
Infiltration cellular, polymorphonuclear, moderate				1 (3%)
Spleen	(48)	(47)	(48)	(45)
Angiectasis, mild			1 (2%)	1 (2%)
Autolysis, moderate		2 (4%)	1 (2%)	2 (4%)
Hematopoietic cell proliferation, marked				6 (13%)
Hematopoietic cell proliferation, mild		7 (15%)	2 (4%)	4 (9%)
Hematopoietic cell proliferation, moderate	3 (6%)	3 (6%)	7 (15%)	19 (42%)
Hemorrhage, moderate			1 (2%)	
Hyperplasia, marked, lymphoid follicle	3 (6%)	2 (4%)		
Hyperplasia, mild, lymphoid follicle	10 (21%)	11 (23%)	8 (17%)	3 (7%)
Hyperplasia, minimal, lymphoid follicle	5 (10%)		1 (2%)	
Hyperplasia, moderate, lymphoid follicle	5 (10%)	6 (13%)	4 (8%)	2 (4%)
Pigmentation, moderate			1 (2%)	
Thrombosis, mild				1 (2%)
Thrombosis, moderate	1 (2%)			
Thymus	(39)	(38)	(43)	(39)
Atrophy, mild	3 (8%)	8 (21%)	7 (16%)	13 (33%)
Atrophy, minimal				1 (3%)
Atrophy, moderate		2 (5%)	1 (2%)	
Autolysis, moderate	1 (3%)	1 (3%)		3 (8%)
Cyst, minimal		1 (3%)		
Hemorrhage, mild		1 (3%)		
Hyperplasia, mild	2 (5%)	3 (8%)	3 (7%)	1 (3%)
Hyperplasia, minimal	1 (3%)			
Hyperplasia, moderate	1 (3%)			
Integumentary System				
Mammary gland	(47)	(48)	(48)	(45)
Autolysis, marked	1 (2%)			
Autolysis, moderate		1 (2%)		
Hyperplasia, mild	1 (2%)	1 (2%)	2 (4%)	2 (4%)
Hyperplasia, minimal	1 (2%)	1 (2%)		
Hyperplasia, moderate	2 (4%)	1 (2%)		

Table F3
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Drinking Water Study of Urethane and 5% Ethanol

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
Integumentary System (continued)				
Mammary gland (continued)	(47)	(48)	(48)	(45)
Infiltration cellular, lymphocytic, mild				1 (2%)
Infiltration cellular, lymphocytic, minimal				1 (2%)
Lactation, mild	3 (6%)		2 (4%)	
Lactation, minimal	1 (2%)		2 (4%)	1 (2%)
Skin	(48)	(48)	(48)	(47)
Autolysis, marked	1 (2%)			2 (4%)
Autolysis, moderate		1 (2%)		
Distended, sebaceous gland			1 (2%)	
Inflammation, chronic, moderate			1 (2%)	
Necrosis, fat			1 (2%)	
Musculoskeletal System				
Bone	(48)	(48)	(48)	(47)
Fibrous osteodystrophy, mild, sternum	10 (21%)	7 (15%)	5 (10%)	1 (2%)
Fibrous osteodystrophy, minimal, sternum	5 (10%)	11 (23%)	6 (13%)	2 (4%)
Fibrous osteodystrophy, moderate, sternum			1 (2%)	
Bone, femur	(48)	(48)	(48)	(47)
Fibrous osteodystrophy, mild	1 (2%)	2 (4%)		
Fibrous osteodystrophy, minimal		4 (8%)	1 (2%)	
Fibrous osteodystrophy, moderate		1 (2%)	2 (4%)	
Skeletal muscle	(48)	(48)	(48)	(47)
Degeneration, minimal		1 (2%)		
Infiltration cellular, lymphocytic, mild			1 (2%)	
Infiltration cellular, lymphocytic, minimal				1 (2%)
Nervous System				
Brain	(48)	(48)	(48)	(47)
Hemorrhage, minimal, brain stem			1 (2%)	
Brain, cerebellum	(48)	(48)	(47)	(47)
Hemorrhage, mild			1 (2%)	1 (2%)
Hemorrhage, minimal		1 (2%)	1 (2%)	
Brain, cerebrum	(48)	(48)	(48)	(47)
Hemorrhage, mild			1 (2%)	1 (2%)
Hemorrhage, minimal		1 (2%)	1 (2%)	1 (2%)
Infiltration cellular, lymphocytic, minimal, perivascular			1 (2%)	
Inflammation, mild				1 (2%)
Inflammation, moderate, meninges			1 (2%)	
Mineralization, mild, thalamus		2 (4%)	1 (2%)	2 (4%)
Mineralization, minimal, thalamus	29 (60%)	26 (54%)	25 (52%)	26 (55%)
Necrosis, mild				1 (2%)
Spinal cord, thoracic	(48)	(48)	(48)	(47)
Hemorrhage, mild				1 (2%)
Hemorrhage, minimal		1 (2%)		
Respiratory System				
Larynx	(45)	(47)	(47)	(47)
Autolysis, moderate		1 (2%)		
Lung	(48)	(48)	(48)	(48)
Hemorrhage, marked			1 (2%)	
Hemorrhage, mild		2 (4%)	1 (2%)	1 (2%)

Table F3
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Drinking Water Study of Urethane and 5% Ethanol

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
Respiratory System (continued)				
Lung (continued)	(48)	(48)	(48)	(48)
Hemorrhage, minimal	3 (6%)	4 (8%)	2 (4%)	2 (4%)
Hemorrhage, moderate				1 (2%)
Hyperplasia, mild, alveolar epithelium		2 (4%)	1 (2%)	4 (8%)
Hyperplasia, minimal, alveolar epithelium		2 (4%)	2 (4%)	1 (2%)
Hyperplasia, moderate, alveolar epithelium				1 (2%)
Hypertrophy, mild, arteriole	1 (2%)			
Infiltration cellular, histiocytic, marked				1 (2%)
Infiltration cellular, histiocytic, mild	1 (2%)	1 (2%)	4 (8%)	3 (6%)
Infiltration cellular, histiocytic, moderate		2 (4%)	1 (2%)	2 (4%)
Infiltration cellular, lymphocytic, mild	8 (17%)	8 (17%)	2 (4%)	4 (8%)
Infiltration cellular, lymphocytic, minimal	19 (40%)	12 (25%)	15 (31%)	17 (35%)
Infiltration cellular, lymphocytic, moderate		2 (4%)	2 (4%)	
Inflammation, chronic active, minimal		1 (2%)		
Leukocytosis, marked				1 (2%)
Leukocytosis, moderate				1 (2%)
Trachea	(47)	(48)	(47)	(45)
Autolysis, moderate		1 (2%)		
Ectasia, mild, glands				1 (2%)
Special Senses System				
Eye	(48)	(48)	(47)	(45)
Atrophy, marked				2 (4%)
Atrophy, mild				1 (2%)
Atrophy, moderate				2 (4%)
Autolysis, moderate	2 (4%)			1 (2%)
Cataract, moderate, lens		1 (2%)	1 (2%)	1 (2%)
Inflammation, marked, cornea	1 (2%)			2 (4%)
Inflammation, mild, cornea		2 (4%)	2 (4%)	1 (2%)
Inflammation, minimal, cornea	1 (2%)	3 (6%)	1 (2%)	
Inflammation, moderate, cornea		1 (2%)		1 (2%)
Phthisis bulbi			1 (2%)	1 (2%)
Harderian gland	(48)	(48)	(46)	(46)
Autolysis, moderate				1 (2%)
Hyperplasia, mild				2 (4%)
Hyperplasia, moderate				1 (2%)
Infiltration cellular, lymphocytic, minimal	7 (15%)	3 (6%)	8 (17%)	3 (7%)
Inflammation, chronic, moderate				1 (2%)
Inflammation, moderate			1 (2%)	
Lacrimal gland	(45)	(45)	(45)	(43)
Atrophy, mild		2 (4%)	1 (2%)	
Atrophy, minimal	2 (4%)	4 (9%)	1 (2%)	
Atrophy, moderate	1 (2%)			
Dilatation, minimal, duct	2 (4%)	2 (4%)	1 (2%)	
Dilatation, moderate, duct	1 (2%)			
Infiltration cellular, lymphocytic, marked	1 (2%)			
Infiltration cellular, lymphocytic, mild	6 (13%)	11 (24%)	9 (20%)	2 (5%)
Infiltration cellular, lymphocytic, minimal	17 (38%)	14 (31%)	16 (36%)	24 (56%)
Infiltration cellular, lymphocytic, moderate	1 (2%)			
Zymbal's gland	(48)	(46)	(43)	(40)
Atrophy, minimal			1 (2%)	
Infiltration cellular, lymphocytic, minimal				1 (3%)

Table F3
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Drinking Water Study of Urethane and 5% Ethanol

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
Urinary System				
Kidney	(48)	(48)	(48)	(47)
Accumulation, hyaline droplet, mild		1 (2%)		1 (2%)
Accumulation, hyaline droplet, moderate	1 (2%)	1 (2%)	3 (6%)	2 (4%)
Amyloid deposition, moderate				1 (2%)
Autolysis, marked		1 (2%)		
Autolysis, moderate		1 (2%)	1 (2%)	
Casts, mild				1 (2%)
Casts, minimal			1 (2%)	
Cyst		1 (2%)		
Glomerulosclerosis, mild	1 (2%)	1 (2%)		2 (4%)
Glomerulosclerosis, minimal			1 (2%)	
Hematopoietic cell proliferation, mild				1 (2%)
Hydronephrosis, moderate	1 (2%)			
Infarct, mild	1 (2%)			
Infarct, minimal	2 (4%)			
Infiltration cellular, lymphocytic, mild	4 (8%)	1 (2%)	1 (2%)	4 (9%)
Infiltration cellular, lymphocytic, minimal	14 (29%)	20 (42%)	17 (35%)	18 (38%)
Infiltration cellular, lymphocytic, moderate	1 (2%)			2 (4%)
Metaplasia, osseous, minimal	1 (2%)			
Mineralization, mild	1 (2%)			
Mineralization, minimal			1 (2%)	2 (4%)
Necrosis, minimal, papilla			1 (2%)	
Nephropathy, mild			1 (2%)	
Nephropathy, moderate		1 (2%)		
Pigmentation, moderate, renal tubule		1 (2%)		
Urinary bladder	(46)	(46)	(47)	(45)
Autolysis, marked				2 (4%)
Autolysis, moderate	2 (4%)	3 (7%)		2 (4%)
Fibrosis, moderate				1 (2%)
Infiltration cellular, lymphocytic, mild	2 (4%)	6 (13%)	7 (15%)	1 (2%)
Infiltration cellular, lymphocytic, minimal	22 (48%)	16 (35%)	14 (30%)	16 (36%)
Infiltration cellular, lymphocytic, moderate	1 (2%)		2 (4%)	
Polyarteritis, moderate		1 (2%)		

APPENDIX G
4-WEEK STUDY RESULTS

Table G1
Body Weights of Mice in the 4-Week Drinking Water Study of Urethane, Ethanol, and Urethane/Ethanol[a]

	% Ethanol	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
n		8	8	8	8
Male					
Week 1	0	22.89 ± 0.57	22.01 ± 0.63	22.74 ± 0.57	23.53 ± 0.56
	2.5	22.17 ± 0.99	22.29 ± 0.65	22.91 ± 0.71	22.05 ± 0.70
	5	22.55 ± 0.69	23.05 ± 0.47	22.61 ± 0.78	21.99 ± 0.87
Week 2	0	25.43 ± 0.58	24.08 ± 0.64	24.71 ± 0.58	25.70 ± 0.43
	2.5	24.46 ± 1.05	24.44 ± 0.68	24.89 ± 0.70	24.21 ± 0.65
	5	24.90 ± 0.74	24.98 ± 0.43	25.16 ± 0.57	24.06 ± 0.77
Week 3	0	26.86 ± 0.41	25.74 ± 0.61	26.23 ± 0.51	27.15 ± 0.29
	2.5	26.24 ± 0.92	26.19 ± 0.64	26.88 ± 0.64	26.01 ± 0.63
	5	26.65 ± 0.63	26.68 ± 0.42	27.03 ± 0.49	26.46 ± 0.75
Week 4	0	27.94 ± 0.44	27.04 ± 0.68	27.31 ± 0.52	28.09 ± 0.26
	2.5	27.35 ± 0.80	27.19 ± 0.69	28.16 ± 0.59	26.81 ± 0.58
	5	27.14 ± 0.72	27.64 ± 0.28	28.20 ± 0.59	27.46 ± 0.85
Female					
Week 1	0	18.63 ± 0.49	17.81 ± 0.37	17.79 ± 0.37	18.53 ± 0.45
	2.5	18.69 ± 0.43	18.41 ± 0.43	18.74 ± 0.68	18.19 ± 0.51
	5	18.53 ± 0.35	18.15 ± 0.51	18.53 ± 0.49	17.56 ± 0.45
Week 2	0	18.94 ± 0.45	18.70 ± 0.52	18.30 ± 0.35	19.40 ± 0.45
	2.5	19.65 ± 0.48	18.76 ± 0.44	19.61 ± 0.45	18.66 ± 0.44
	5	18.90 ± 0.48	19.00 ± 0.51	19.15 ± 0.40	18.69 ± 0.42
Week 3	0	20.09 ± 0.32	19.10 ± 0.41	19.04 ± 0.33	19.76 ± 0.45
	2.5	20.75 ± 0.48	19.87 ± 0.41	20.25 ± 0.50	19.17 ± 0.53
	5	19.79 ± 0.43	19.99 ± 0.47	20.21 ± 0.40	19.81 ± 0.31
Week 4	0	20.29 ± 0.37	19.36 ± 0.48	19.78 ± 0.27	20.50 ± 0.46
	2.5	20.88 ± 0.49	20.19 ± 0.45	21.01 ± 0.56	19.74 ± 0.43
	5	20.29 ± 0.32	20.64 ± 0.86	20.50 ± 0.45	20.34 ± 0.37

[a] Data are given in grams (mean ± standard error). Neither urethane nor ethanol had any effect on body weights.

Table G2
Water Consumption by Mice in the 4-Week Drinking Water Study of Urethane, Ethanol, and Urethane/Ethanol[a]

	% Ethanol	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
n		8	8	8	8
Male					
Week 1	0	4.00 ± 0.08	3.87 ± 0.63	3.70 ± 0.03	4.08 ± 0.42
	2.5	2.64[b]	3.41[b]	3.43 ± 0.09	3.11 ± 0.13
	5	3.06 ± 0.12	3.02 ± 0.88	3.19[b]	3.00 ± 0.18
Week 2	0	4.71 ± 0.90	3.02 ± 0.02*	3.45 ± 0.20*	3.27 ± 1.25*
	2.5	2.99 ± 0.10*	3.58 ± 0.34	3.30 ± 0.23*	3.40[b]
	5	2.87 ± 0.16*	2.95 ± 0.16*	3.67 ± 0.04	3.12 ± 0.15*
Week 3	0	4.79 ± 0.47	3.81 ± 0.02	3.82 ± 0.17	4.17 ± 0.54
	2.5	3.23 ± 0.04*	4.08 ± 0.29	3.41 ± 0.27*	3.42 ± 0.29*
	5	3.04 ± 0.18*	3.25 ± 0.25*	4.18 ± 0.13	3.33 ± 0.07*
Week 4	0	4.77 ± 0.37	4.32 ± 0.11	4.04 ± 0.13	4.23 ± 0.70
	2.5	3.61 ± 0.18	4.42 ± 0.57	3.29 ± 0.01*	3.19 ± 0.33*
	5	3.18 ± 0.35*	3.67 ± 0.64	4.31 ± 0.15	3.51 ± 0.19*
Female					
Week 1	0	2.89 ± 0.33	2.42 ± 0.27	2.09 ± 0.08	2.41 ± 0.20
	2.5	2.44 ± 0.03	2.61 ± 0.25	2.54 ± 0.00	2.56 ± 0.05
	5	2.39 ± 0.02	2.38 ± 0.01	2.51 ± 0.08	2.21 ± 0.18
Week 2	0	3.23 ± 0.27	2.61 ± 0.08	2.41 ± 0.08	2.93 ± 0.03
	2.5	2.98 ± 0.54	2.66 ± 0.03	2.62 ± 0.00	2.82 ± 0.02
	5	2.70 ± 0.01	2.71 ± 0.02	2.74 ± 0.12	2.54 ± 0.20
Week 3	0	3.07 ± 0.51	2.73 ± 0.02	2.96 ± 0.13	3.02 ± 0.42
	2.5	2.77 ± 0.16	2.71 ± 0.15	2.79 ± 0.15	2.64 ± 0.02
	5	2.66 ± 0.24	2.75 ± 0.13	2.78 ± 0.22	2.71 ± 0.02
Week 4	0	2.81 ± 0.51	2.76 ± 0.02	2.78 ± 0.21	3.27 ± 0.53
	2.5	2.90 ± 0.18	2.72 ± 0.00	2.83 ± 0.05	2.99[b]
	5	2.58 ± 0.39	2.86 ± 0.09	2.67 ± 0.14	2.71 ± 0.09

* Significantly different ($P \leq 0.05$) from the control group (0 ppm urethane/0% ethanol) at the same time point by Dunnett's test

a Data are given in grams per animal per day (mean ± standard error). Increasing the urethane concentration had no effect on water consumption by males or females. Increasing the ethanol concentration caused a significant decrease in water consumption by males (P=0.009), but not females.

b Data are for one cage.

Table G3
Feed Consumption by Mice in the 4-Week Drinking Water Study of Urethane, Ethanol, and Urethane/Ethanol[a]

	% Ethanol	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
n		8	8	8	8
Male					
Week 1	0	3.76 ± 0.13	3.76 ± 0.41	3.75 ± 0.07	3.89 ± 0.38
	2.5	3.05 ± 0.33	3.05 ± 0.24	3.29 ± 0.22	3.12 ± 0.35
	5	2.85 ± 0.48	4.34[b]	2.54 ± 0.97	2.74 ± 0.34
Week 2	0	4.15 ± 0.32	3.19 ± 0.45	4.09 ± 0.22	3.23 ± 0.85
	2.5	3.53 ± 0.04	3.61 ± 0.37	3.63 ± 0.12	3.51 ± 0.22
	5	3.44 ± 0.11	2.88 ± 0.30	3.67 ± 0.08	3.28 ± 0.08
Week 3	0	4.65 ± 0.71	3.91 ± 0.03	4.94 ± 0.92	5.11 ± 0.46
	2.5	4.20 ± 0.37	3.92 ± 0.34	4.38 ± 0.44	3.98 ± 0.44
	5	4.01 ± 0.15	4.08 ± 0.75	4.41 ± 0.15	3.89 ± 0.05
Week 4	0	5.64[b]	3.93 ± 0.21	4.41 ± 0.47	4.48 ± 0.32
	2.5	4.35 ± 0.38	4.27 ± 0.45	4.66 ± 0.27	4.28 ± 0.58
	5	3.70 ± 0.06	3.90 ± 0.34	5.49 ± 0.69	3.84 ± 0.30
Female					
Week 1	0	2.79[b]	2.54 ± 0.25	2.70[b]	3.04[b]
	2.5	2.70 ± 0.07	2.65[b]	3.86[b]	2.86[b]
	5	2.71[b]	2.74[b]	2.68[b]	2.44 ± 0.21
Week 2	0	3.09 ± 0.17	3.01 ± 0.33	2.87 ± 0.08	3.06 ± 0.12
	2.5	2.95 ± 0.07	2.83 ± 0.01	2.91 ± 0.02	2.81 ± 0.04
	5	2.90 ± 0.16	2.88 ± 0.04	2.78 ± 0.03	2.63 ± 0.28
Week 3	0	3.26 ± 0.22	3.06 ± 0.16	3.08 ± 0.02	3.21 ± 0.10
	2.5	3.27 ± 0.09	3.10 ± 0.02	3.18 ± 0.11	2.91 ± 0.01
	5	3.08 ± 0.25	3.01 ± 0.12	3.02 ± 0.10	3.26 ± 0.33
Week 4	0	3.31 ± 0.22	3.06 ± 0.23	3.14 ± 0.10	3.39 ± 0.14
	2.5	3.33 ± 0.06	3.18 ± 0.12	3.47 ± 0.11	3.04 ± 0.02
	5	3.76 ± 0.40	3.21 ± 0.04	3.15 ± 0.08	3.03 ± 0.02

[a] Data are given in grams per animal per day (mean ± standard error). Increasing the urethane concentration had no effect on feed consumption by males or females. Increasing the ethanol concentration caused a significant exposure-related decrease in feed consumption by males (P=0.023) but not by females. Pairwise comparisons at each week (Dunnett's test) indicated no significant differences from the control groups (0 ppm urethane/0% ethanol).

[b] Data are for one cage.

Table G4
Serum Concentrations of Urethane in Mice in the 4-Week Drinking Water Study of Urethane, Ethanol, and Urethane/Ethanol[a]

	% Ethanol	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
n		4	4	4	4
Male					
	0	0.01 ± 0.002	0.01 ± 0.002	0.02 ± 0.01	0.02 ± 0.003
	2.5	0.01 ± 0.004	0.02 ± 0.004	0.03 ± 0.01	0.04 ± 0.02
	5	0.01 ± 0.003	0.05 ± 0.003	2.75 ± 0.95*	0.43 ± 0.38
Female					
	0	0.01 ± 0.002	0.01 ± 0.003	0.05 ± 0.007	0.07 ± 0.01
	2.5	0.01 ± 0.003	0.11 ± 0.03	0.12 ± 0.05	0.04 ± 0.007
	5	0.01 ± 0.005	0.17 ± 0.12	1.67 ± 0.86*	1.56 ± 1.05*

* Significantly different ($P \leq 0.05$) from the control group (0 ppm urethane/0% ethanol) by Dunnett's test
a Data are given in ppm (mean ± standard error).

Table G5
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 4-Week Drinking Water Study of Urethane, Ethanol, and Urethane/Ethanol[a]

	% Ethanol	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
n		4	4	4	4
Male					
Necropsy body wt	0	25.3 ± 0.41	23.3 ± 0.38	23.8 ± 0.28	24.9 ± 0.49
	2.5	24.0 ± 0.27	24.6 ± 0.72	24.7 ± 0.35	23.9 ± 0.21
	5	24.2 ± 1.10	24.5 ± 0.22	24.9 ± 0.76	23.7 ± 0.93
Liver					
Absolute	0	1.250 ± 0.035	1.135 ± 0.057	1.218 ± 0.022	1.309 ± 0.057
Relative	0	4.94 ± 0.082	4.87 ± 0.208	5.12 ± 0.046	5.26 ± 0.225
Absolute	2.5	1.187 ± 0.018	1.186 ± 0.030	1.188 ± 0.049	1.237 ± 0.042
Relative	2.5	4.95 ± 0.033	4.82 ± 0.123	4.81 ± 0.152	5.16 ± 0.136
Absolute	5	1.290 ± 0.087	1.316 ± 0.029	1.239 ± 0.036	1.188 ± 0.064
Relative	5	5.31 ± 0.170	5.36 ± 0.089	4.97 ± 0.014	5.01 ± 0.115
Lung					
Absolute	0	216 ± 23	210 ± 5	212 ± 24	229 ± 27
Relative	0	8.58 ± 1.03	9.00 ± 0.23	8.91 ± 0.99	9.16 ± 1.00
Absolute	2.5	209 ± 29	204 ± 11	224 ± 8	210 ± 26
Relative	2.5	8.75 ± 1.32	8.32 ± 0.62	9.05 ± 0.35	8.77 ± 1.06
Absolute	5	243 ± 26	254 ± 22	188 ± 10	190 ± 13
Relative	5	10.0 ± 1.03	10.3 ± 0.86	7.55 ± 0.40	8.02 ± 0.59

TABLE G5
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 4-Week Drinking Water Study of Urethane, Ethanol, and Urethane/Ethanol

	% Ethanol	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
n		4	4	4	4
Female					
Necropsy body wt	0	18.1 ± 0.56	16.5 ± 0.18	17.8 ± 0.53	18.2 ± 0.35
	2.5	19.2 ± 0.53	18.2 ± 0.68	19.3 ± 1.04	17.5 ± 0.28
	5	18.0 ± 0.27	17.7 ± 0.73	18.2 ± 0.79	18.0 ± 0.50
Liver					
Absolute	0	0.878 ± 0.017	0.747 ± 0.029	0.797 ± 0.016	0.911 ± 0.012
Relative	0	4.86 ± 0.10	4.51 ± 0.14	4.48 ± 0.14	5.01 ± 0.12
Absolute	2.5	0.851 ± 0.047	0.859 ± 0.053	0.875 ± 0.013	0.798 ± 0.037
Relative	2.5	4.42 ± 0.17	4.71 ± 0.15	4.56 ± 0.21	4.55 ± 0.17
Absolute	5	0.867 ± 0.029	0.879 ± 0.074	0.832 ± 0.049	0.781 ± 0.021
Relative	5	4.80 ± 0.10	4.93 ± 0.20	4.57 ± 0.12	4.33 ± 0.12
Lung					
Absolute	0	157 ± 16	158 ± 10	179 ± 16	178 ± 5
Relative	0	8.66 ± 0.78	9.53 ± 0.47	10.1 ± 1.09	9.81 ± 0.17
Absolute	2.5	192 ± 20	183 ± 12	197 ± 15	177 ± 10
Relative	2.5	9.92 ± 0.87	10.0 ± 0.42	10.1 ± 0.39	10.1 ± 0.41
Absolute	5	173 ± 8	208 ± 46	184 ± 13	164 ± 3
Relative	5	9.59 ± 0.36	11.5 ± 2.03	10.1 ± 0.48	9.12 ± 0.32

[a] Liver weights (absolute weights) and body weights are given in grams; lung weights (absolute weights) are given in milligrams; organ-weight-to-body-weight ratios (relative weights) are given as g liver weight/g body weight as a percent or mg lung weight/g body weight (mean ± standard error). Terminal body weights and liver and lung weights were not affected by either urethane or ethanol in male or female mice.

Table G6
Cell Cycle Distribution and Percent Apoptosis in the Liver of Mice in the 4-Week Drinking Water Study of Urethane, Ethanol, and Urethane/Ethanol[a]

	% Ethanol	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
n		4	4	4	4
Male					
Cell Cycle Phase					
G_0	0	99.47 ± 0.46	99.83 ± 0.08	99.84 ± 0.07	99.87 ± 0.06
	2.5	99.87 ± 0.06	99.83 ± 0.09	99.03 ± 0.15	99.69 ± 0.12
	5	99.55 ± 0.11	99.74 ± 0.05	99.93 ± 0.06	99.82 ± 0.08
G_1	0	0.13 ± 0.10	0.07 ± 0.04	0.05 ± 0.03	0.07 ± 0.04
	2.5	0.06 ± 0.04	0.01 ± 0.01	0.26 ± 0.06	0.05 ± 0.04
	5	0.14 ± 0.04	0.13 ± 0.03	0.05 ± 0.03	0.05 ± 0.03
G_2	0	0.06 ± 0.06	0.00 ± 0.00	0.02 ± 0.02	0.00 ± 0.00
	2.5	0.04 ± 0.04	0.02 ± 0.02	0.11 ± 0.04	0.07 ± 0.04
	5	0.14 ± 0.06	0.06 ± 0.01	0.00 ± 0.00	0.00 ± 0.00
S	0	0.22 ± 0.18	0.09 ± 0.04	0.05 ± 0.02	0.06 ± 0.02
	2.5	0.04 ± 0.04	0.10 ± 0.05	0.23 ± 0.08	0.15 ± 0.07
	5	0.12 ± 0.03	0.06 ± 0.04	0.02 ± 0.02	0.13 ± 0.07
M	0	0.12 ± 0.12	0.01 ± 0.01	0.04 ± 0.02	0.00 ± 0.00
	2.5	0.00 ± 0.00	0.04 ± 0.04	0.38 ± 0.04	0.04 ± 0.02
	5	0.05 ± 0.02	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Apoptosis	0	0.11 ± 0.04	0.65 ± 0.06	0.33 ± 0.07	0.31 ± 0.11
	2.5	0.25 ± 0.15	0.11 ± 0.04	0.36 ± 0.08	0.28 ± 0.08
	5	0.12 ± 0.01	0.33 ± 0.13	0.66 ± 0.13	0.12 ± 0.01

Table G6
Cell Cycle Distribution and Percent Apoptosis in the Liver of Mice in the 4-Week Drinking Water Study of Urethane, Ethanol, and Urethane/Ethanol

	% Ethanol	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
n		4	4	4	4
Female					
Cell Cycle Phase					
G_0	0	99.69 ± 0.09	99.33 ± 0.09	99.57 ± 0.51	99.29 ± 0.19
	2.5	99.30 ± 0.19	99.46 ± 0.19	99.12 ± 0.32	98.67 ± 0.22
	5	99.44 ± 0.14	99.54 ± 0.06	99.18 ± 0.11	98.93 ± 0.16
G_1	0	0.11 ± 0.02	0.22 ± 0.03	0.46 ± 0.11	0.40 ± 0.10
	2.5	0.29 ± 0.05	0.20 ± 0.05	0.40 ± 0.20	0.85 ± 0.20
	5	0.24 ± 0.08	0.22 ± 0.06	0.44 ± 0.11	0.71 ± 0.14
G_2	0	0.07 ± 0.14	0.20 ± 0.10	0.33 ± 0.23	0.21 ± 0.06
	2.5	0.24 ± 0.11	0.10 ± 0.02	0.08 ± 0.04	0.17 ± 0.08
	5	0.17 ± 0.06	0.10 ± 0.03	0.29 ± 0.07	0.07 ± 0.05
S	0	0.10 ± 0.07	0.22 ± 0.05	0.61 ± 0.21	0.10 ± 0.03
	2.5	0.16 ± 0.05	0.24 ± 0.04	0.30 ± 0.16	0.24 ± 0.06
	5	0.13 ± 0.03	0.13 ± 0.04	0.09 ± 0.02	0.26 ± 0.08
M	0	0.02 ± 0.01	0.02 ± 0.01	0.03 ± 0.02	0.00 ± 0.00
	2.5	0.00 ± 0.00	0.00 ± 0.00	0.09 ± 0.06	0.06 ± 0.01
	5	0.01 ± 0.01	0.00 ± 0.00	0.00 ± 0.00	0.02 ± 0.01
Apoptosis	0	0.16 ± 0.02	0.15 ± 0.06	0.11 ± 0.05	0.18 ± 0.09
	2.5	0.13 ± 0.01	0.31 ± 0.11	0.15 ± 0.05	0.41 ± 0.02
	5	0.39 ± 0.11	0.16 ± 0.10	0.06 ± 0.02	0.50 ± 0.08

[a] Data are given as percentage of cells in each cell cycle phase or apoptotic (mean ± standard error). Approximately 2,000 cells were counted per liver. Increasing the ethanol concentration had no effect on the cell cycle distribution in the liver of males or females. The percentage of G_0 cells was decreased and the percentage of G_1 cells was increased in females exposed to 30 or 90 ppm urethane ($P \leq 0.05$); the percentages were unchanged in males. The extent of apoptosis was affected by urethane in males, but not females, and the difference was significant in males exposed to 10 or 30 ppm urethane; the extent of apoptosis was not affected by ethanol in either sex.

Table G7
PCNA-Labeling Index in the Lung of Mice in the 4-Week Drinking Water Study of Urethane, Ethanol, and Urethane/Ethanol[a]

	% Ethanol	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
n		4	4	4	4
Male					
	0	10.7 ± 1.4	7.5 ± 1.0	5.7 ± 1.4	5.0 ± 0.9
	2.5	9.2 ± 0.6	8.7 ± 0.9	2.7 ± 1.2	6.2 ± 1.2
	5	10.5 ± 2.2	7.2 ± 2.1	7.2 ± 1.7	3.7 ± 0.6
Female					
	0	10.5 ± 1.6	9.5 ± 2.1	5.0 ± 1.5	6.5 ± 0.6
	2.5	12.0 ± 2.0	8.7 ± 1.5	4.0 ± 0.9	6.5 ± 1.8
	5	11.2 ± 1.7	11.0 ± 1.6	4.0 ± 0.9	7.7 ± 3.1

* Significantly different ($P \leq 0.05$) from the control group (0 ppm urethane/0% ethanol) by Dunnett's test

a Data are given as percentage of PCNA-labeled cells (mean ± standard error). Approximately 2,000 cells were counted per lung. The percentage of PCNA labeling was decreased in the lung of mice exposed to 30 or 90 ppm urethane ($P \leq 0.05$). Increasing the ethanol concentration had no effect on the extent of PCNA labeling in the lung of males or females.

Table G8
Total Cytochrome P450, Cytochrome P450 2E1 Activity, and Glutathione Content in the Liver of Mice in the 4-Week Drinking Water Study of Urethane, Ethanol, and Urethane/Ethanol[a]

	% Ethanol	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
n		4	4	4	4
Male					
Cytochrome P450 (nmol/g liver)					
	0	11.6 ± 0.3	ND	12.6 ± 0.2[b]	13.3 ± 0.5
	2.5	12.6 ± 0.8	11.0 ± 1.6	13.9 ± 1.1	11.1 ± 0.6
	5	12.3 ± 0.9[c]	13.0 ± 1.0	11.1 ± 2.3	14.7 ± 0.6
Cytochrome P450 2E1 (nmol 4-nitrocatechol/mg protein per minute)					
	0	4.5 ± 0.1	ND	4.9 ± 0.1[b]	4.0 ± 0.3
	2.5	4.0 ± 0.1	4.3 ± 0.3	3.7 ± 0.2	3.9 ± 0.3
	5	5.0 ± 0.2[c]	4.4 ± 0.3	5.0 ± 0.4	5.0 ± 0.2
Glutathione (absorbance; relative units)					
	0	0.31 ± 0.01	0.30 ± 0.02	0.28 ± 0.02	0.30 ± 0.02
	2.5	0.50 ± 0.05	0.33 ± 0.05	0.44 ± 0.04	0.32 ± 0.02
	5	0.24 ± 0.03	0.26 ± 0.01	0.23 ± 0.04	0.29 ± 0.02
Female					
Cytochrome P450 (nmol/g liver)					
	0	14.4 ± 0.6	13.8 ± 0.6[d]	12.7 ± 0.4	14.3 ± 0.2
	2.5	13.8 ± 0.1	12.9 ± 0.2	12.1 ± 1.0	14.6 ± 1.7
	5	14.2 ± 1.3	12.9 ± 0.6	11.2 ± 1.5	13.6 ± 0.9
Cytochrome P450 2E1 (nmol 4-nitrocatechol/mg protein per minute)					
	0	3.5 ± 0.3	3.5 ± 0.1	4.0 ± 0.3	3.5 ± 0.2
	2.5	4.4 ± 0.5	5.4 ± 0.2	4.8 ± 0.2	3.9 ± 0.2
	5	5.4 ± 0.2	6.1 ± 0.4	6.0 ± 0.4	5.8 ± 0.2
Glutathione (absorbance; relative units)					
	0	0.30 ± 0.02	0.28 ± 0.02[d]	0.23 ± 0.04	0.32 ± 0.003
	2.5	0.23 ± 0.003	0.20 ± 0.01	0.22 ± 0.01	0.28 ± 0.02
	5	0.21 ± 0.01	0.19 ± 0.02	0.17 ± 0.02	0.25 ± 0.03

[a] Data are given as mean ± standard error. Total cytochrome P450 content was not affected by either urethane or ethanol in males or females. Urethane did not affect the cytochrome P450 2E1 activity in males or females. Ethanol caused an exposure-related increase in cytochrome P450 2E1 activity in the liver of females, and the levels in females exposed to 2.5% or 5% ethanol were significantly increased ($P \le 0.05$); this trend did not occur in males. Ethanol caused an exposure-related decrease in glutathione content in the females, and the levels in the 2.5% and 5% ethanol groups were significantly less ($P \le 0.05$) than those of the controls; this trend did not occur in males. Urethane did not affect the glutathione content. ND=not determined

[b] n=2

[c] n=3

[d] n=8

TABLE G9
Etheno-DNA Adducts in the Liver and Lung of Male and Female Mice in the 4-Week Drinking Water Study of Urethane, Ethanol, and Urethane/Ethanol[a]

	% Ethanol	0 ppm Urethane	90 ppm Urethane
n		8	8
Liver			
Etheno-dA/10^8 nucleotides			
	0	1.19 ± 0.07	1.48 ± 0.14
	5	0.81 ± 0.06	1.10 ± 0.20
Lung			
Etheno-dA/10^8 nucleotides			
	0	0.97 ± 0.18	1.12 ± 0.13
	5	0.92 ± 0.15	1.06 ± 0.10
Etheno-dC/10^8 nucleotides			
	0	0.92 ± 0.21	0.97 ± 0.18
	5	1.16 ± 0.15	0.76 ± 0.16

[a] Data are given as mean ± standard error. The levels of hepatic DNA etheno-dA adducts were increased ($P<0.05$) by exposure to 90 ppm urethane and decreased ($P<0.05$) by exposure to 5% ethanol.

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

Table H1
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 2-Year Drinking Water Study of Urethane, Ethanol, and Urethane/Ethanol[a]

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
Male				
0% Ethanol				
n	26	26	24	8
Necropsy body wt	39.5 ± 1.2	39.3 ± 0.9	37.1 ± 1.3	34.8 ± 1.9*
Liver				
Absolute	2.33 ± 0.22	2.09 ± 0.12	2.38 ± 0.19	2.65 ± 0.58
Relative	61.43 ± 7.3	54.15 ± 3.92	65.6 ± 5.68	72.81 ± 12.4
Lung				
Absolute	0.36 ± 0.03	0.32 ± 0.01	0.39 ± 0.04	0.55 ± 0.19*
Relative	9.07 ± 0.72	8.28 ± 0.26	10.93 ± 1.46	16.83 ± 6.4**
2.5% Ethanol				
n	31	30	25	16
Necropsy body wt	37.7 ± 1.1	36.8 ± 0.9	37.8 ± 1.0	32.9 ± 0.7**
Liver				
Absolute	2.01 ± 0.15	2.16 ± 0.14[b]	2.29 ± 0.16	2.19 ± 0.25
Relative	55.95 ± 5.87	60.37 ± 5.03[b]	61.73 ± 4.95	65.9 ± 6.66
Lung				
Absolute	0.38 ± 0.03	0.37 ± 0.04	0.41 ± 0.04	0.42 ± 0.05
Relative	10.24 ± 0.93	10.33 ± 1.37	11.12 ± 1.23	13.1 ± 1.87
5% Ethanol				
n	36	29	21	12
Necropsy body wt	39.0 ± 0.5	37.9 ± 0.9	38.7 ± 1.0	31.5 ± 1.0**
Liver				
Absolute	2.24 ± 0.11	2.31 ± 0.19	2.02 ± 0.09	1.86 ± 0.16
Relative	58.04 ± 3.37	63.67 ± 6.78	52.46 ± 2.11	60.23 ± 5.93
Lung				
Absolute	0.37 ± 0.03	0.32 ± 0.02	0.36 ± 0.02	0.47 ± 0.09
Relative	9.58 ± 0.77	8.62 ± 0.49	9.34 ± 0.7	15.05 ± 2.97*

Table H1
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 2-Year Drinking Water Study of Urethane, Ethanol, and Urethane/Ethanol

	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
Female				
0% Ethanol				
n	37	36	27	0[c]
Necropsy body wt	47.3 ± 1.7	47.0 ± 1.4	43.7 ± 1.6	
Liver				
Absolute	2.19 ± 0.14	1.97 ± 0.07	2.13 ± 0.01[d]	
Relative	48.09 ± 4.05	42.67 ± 1.55	49.72 ± 2.69[d]	
Lung				
Absolute	0.28 ± 0.01	0.27 ± 0.01	0.36 ± 0.04	
Relative	6.33 ± 0.37	5.88 ± 0.23	8.86 ± 1.16	
2.5% Ethanol				
n	39	33	19	8
Necropsy body wt	46.9 ± 1.5	43.8 ± 1.6	39.6 ± 1.7**	30.4 ± 2.4**
Liver				
Absolute	1.98 ± 0.08	2.12 ± 0.1	2.06 ± 0.14	1.73 ± 0.21
Relative	42.65 ± 1.53	50.51 ± 3.22	52.45 ± 3.17	57.8 ± 7.04
Lung				
Absolute	0.27 ± 0.01	0.29 ± 0.01	0.33 ± 0.05	0.61 ± 0.18**
Relative	5.99 ± 0.24	6.97 ± 0.45	9.4 ± 2.32	23.36 ± 8.36**
5% Ethanol				
n	31	32	26	4
Necropsy body wt	44.2 ± 1.2	42.4 ± 1.2	41.2 ± 1.6	34.2 ± 4.7
Liver				
Absolute	1.95 ± 0.09	2.01 ± 0.08	2.21 ± 0.16*	1.95 ± 0.38
Relative	44.37 ± 1.92	48.5 ± 2.55	56.25 ± 5.96	55.81 ± 4.2
Lung				
Absolute	0.27 ± 0.01[e]	0.3 ± 0.01	0.34 ± 0.03[f]	0.37 ± 0.09
Relative	6.27 ± 0.23[e]	7.12 ± 0.37	8.5 ± 0.69[f]	10.91 ± 2.23

* Significantly different ($P \leq 0.05$) from the control group (0 ppm urethane/0%, 2.5%, or 5% ethanol) by Dunnett's test
** $P \leq 0.01$
[a] Organ weights (absolute weights) and body weights are given in grams; organ-weight-to-body-weight ratios (relative weights) are given as mg organ weight/g body weight (mean ± standard error).
[b] n=29
[c] No data were available for the 90 ppm group because only one animal survived in this group.
[d] n=26
[e] n=30
[f] n=25

APPENDIX I
CHEMICAL CHARACTERIZATION AND DOSE FORMULATION STUDIES

CHEMICAL CHARACTERIZATION AND DOSE FORMULATION STUDIES

Procurement and Characterization of Urethane and Ethanol

Urethane was obtained from Aldrich Chemical Company (Milwaukee, WI) in one lot (09101PN), and ethanol was obtained from AAPER Alcohol (Shelbyville, KY) in one lot (961730BB); both lots were used during the 4-week and 2-year studies. Identity, purity, and stability analyses were conducted by the study laboratory.

Lot 09101PN, a white crystalline solid, was identified as urethane by ^{1}H- and ^{13}C-nuclear magnetic resonance (NMR) spectroscopy and mass spectrometry (MS). Lot 961730BB, a clear liquid, was identified as ethanol by ^{1}H- and ^{13}C-NMR spectroscopy. All spectra were consistent with the structures of urethane or ethanol. The NMR spectra are presented in Figures I1 to I4.

The purity of lots 09101PN and 961730BB were determined by ^{1}H- and ^{13}C-NMR spectroscopy and gas chromatography (GC)/MS (lot 09101PN). The water content of urethane and ethanol were determined by Karl Fischer titration. For urethane, the results of ^{1}H- and ^{13}C-NMR spectroscopy indicated a purity of 99% or greater, and GC/MS indicated a purity of greater than 95% with no minor impurity peaks detected. For ethanol, no impurities other than water were detected; ^{1}H-NMR spectroscopy indicated 92.6% ethanol and 7.4% water. Karl Fischer titration indicated 0.1% water in urethane and 7.4% water in ethanol.

The bulk urethane was stored in sealed plastic bags in glass dessicators under phosphorus pentoxide at ambient temperature. The bulk ethanol was stored in glass containers at ambient temperature. Stability of urethane and ethanol in aqueous solutions was monitored for 56 (urethane) or 35 (ethanol) days using GC with a flame ionization detector and a GP 60/80 Carbopak-B, 5% Carbowax 20M column (6 ft × 2 mm) (Supelco, Bellefonte, PA) with helium as the carrier gas at 57 mL/minute and an oven temperature of 80° C for 0.5 minutes, then 80° C to 180° C at 40° C per minute with a 5-minute hold. Concentrations of 10 ppm urethane and 0%, 2.5%, and 5% ethanol and 1% urethane were used to monitor the stability of urethane; concentrations of 2.5% ethanol and water and 2.5% ethanol and 90 ppm urethane were used to monitor the stability of ethanol. No degradation of the bulk chemical was detected.

Preparation and Analysis of Dose Formulations

The dose formulations were prepared once weekly during the 4-week study and approximately every 8 weeks during the 2-year study by mixing urethane with deionized water, ethanol with Millipore-filtered tap water, and then urethane with Millipore-filtered tap water or Millipore-filtered tap water containing ethanol (Table I1).

Stability studies of the dose formulations were performed by the study laboratory with GC using the methods and concentrations described for the bulk chemical analyses. Stability was confirmed for at least 56 (urethane) or 35 (ethanol) days.

Periodic analyses of the dose formulations were conducted by the study laboratory using GC as described above. The dose formulations were analyzed once weekly during the 4-week study (Table I2) and approximately every 8 weeks during the 2-year study (Table I3). During the 2-year study, animal room samples of the dose formulations were analyzed approximately every 6 months. Of the urethane dose formulations used during the 4-week study, 90 of 90 were within the target concentrations (± 20% for the 10 ppm or ± 10% for the 30 and 90 ppm dose formulations); of the ethanol dose formulations, 80 of 80 were within the target concentrations

(± 20% for the 2.5% or ± 10% for the 5% dose formulations). Of the urethane dose formulations used during the 2-year study, 223 of 228 were within the target concentrations; of the animal room samples analyzed, 35 of 36 were within the target concentrations. Of the ethanol dose formulations, 200 of 203 were within the target concentrations; of the animal room samples analyzed, 31 of 32 were within the target concentrations.

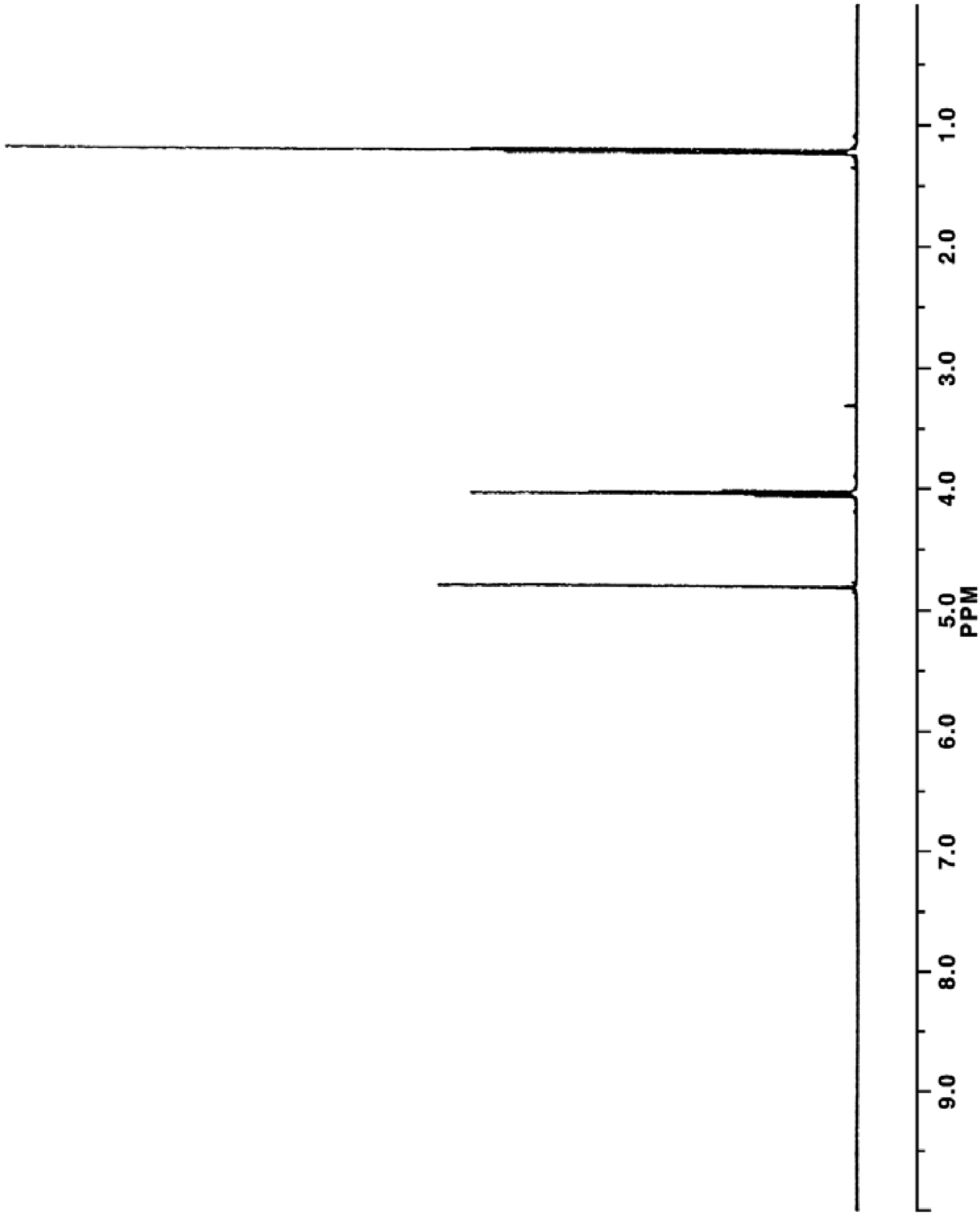

FIGURE I1
[1]H-Nuclear Magnetic Resonance Spectrum of Urethane

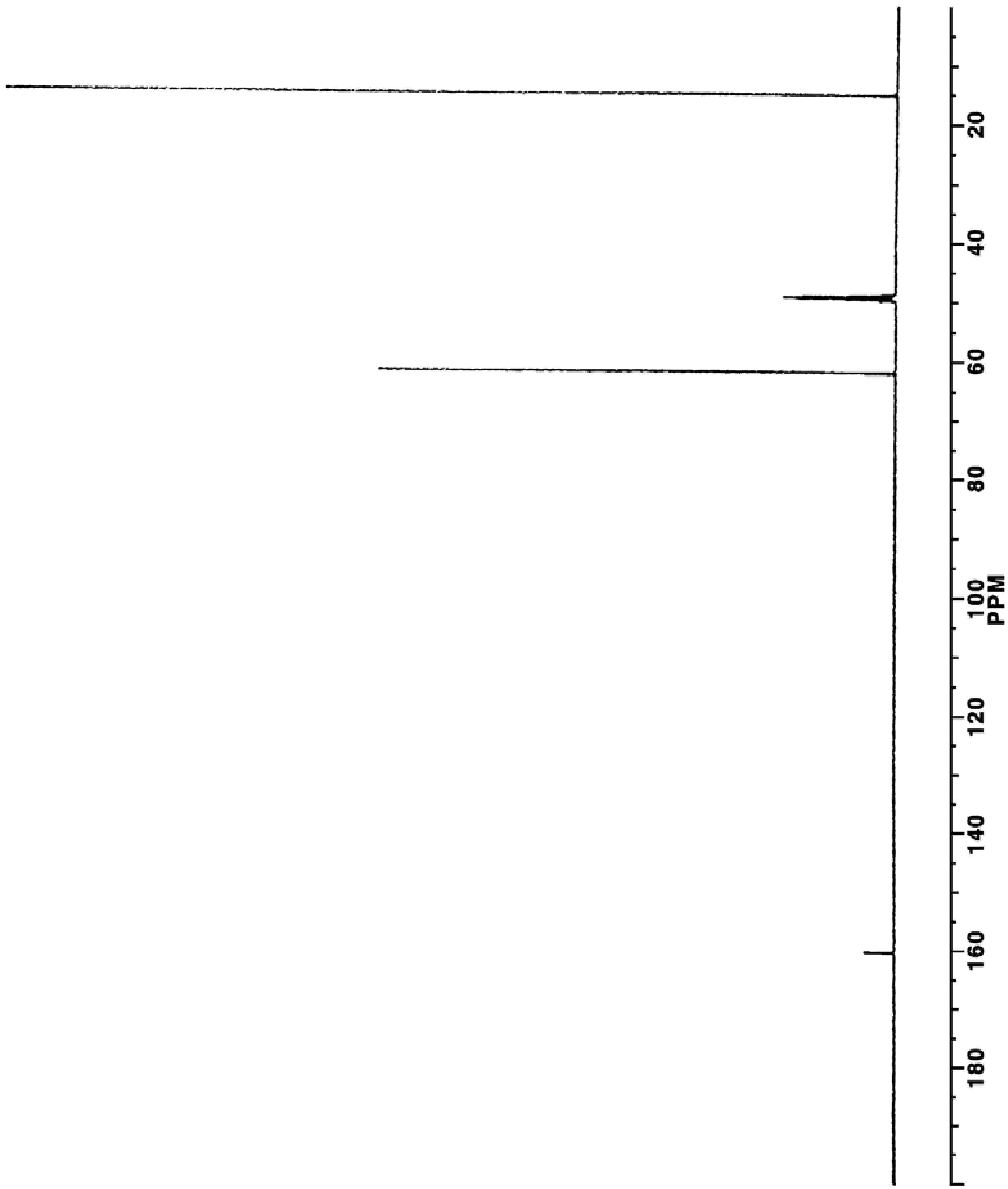

FIGURE I2
^{13}C-Nuclear Magnetic Resonance Spectrum of Urethane

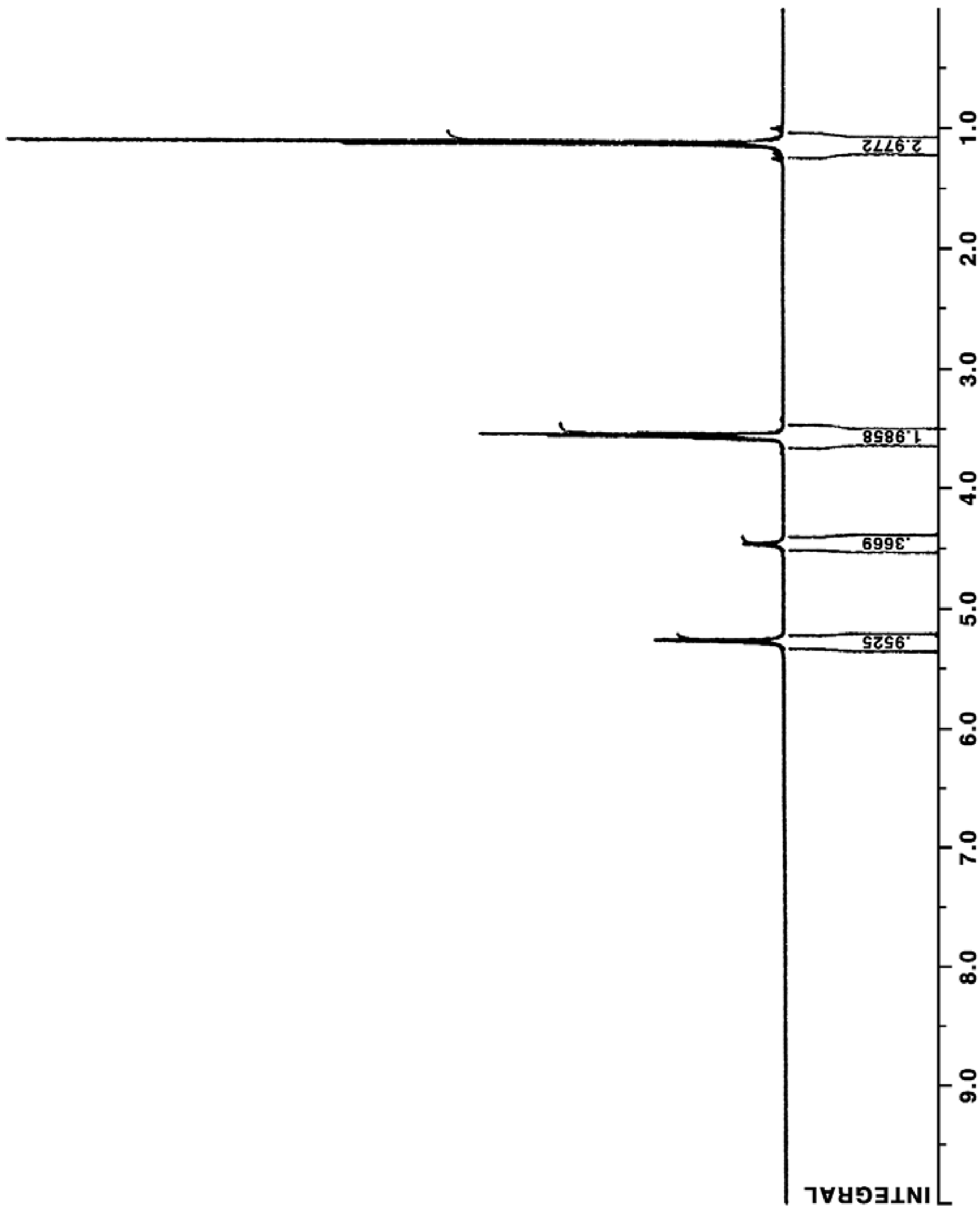

Figure I3
[1]H-Nuclear Magnetic Resonance Spectrum of Ethanol

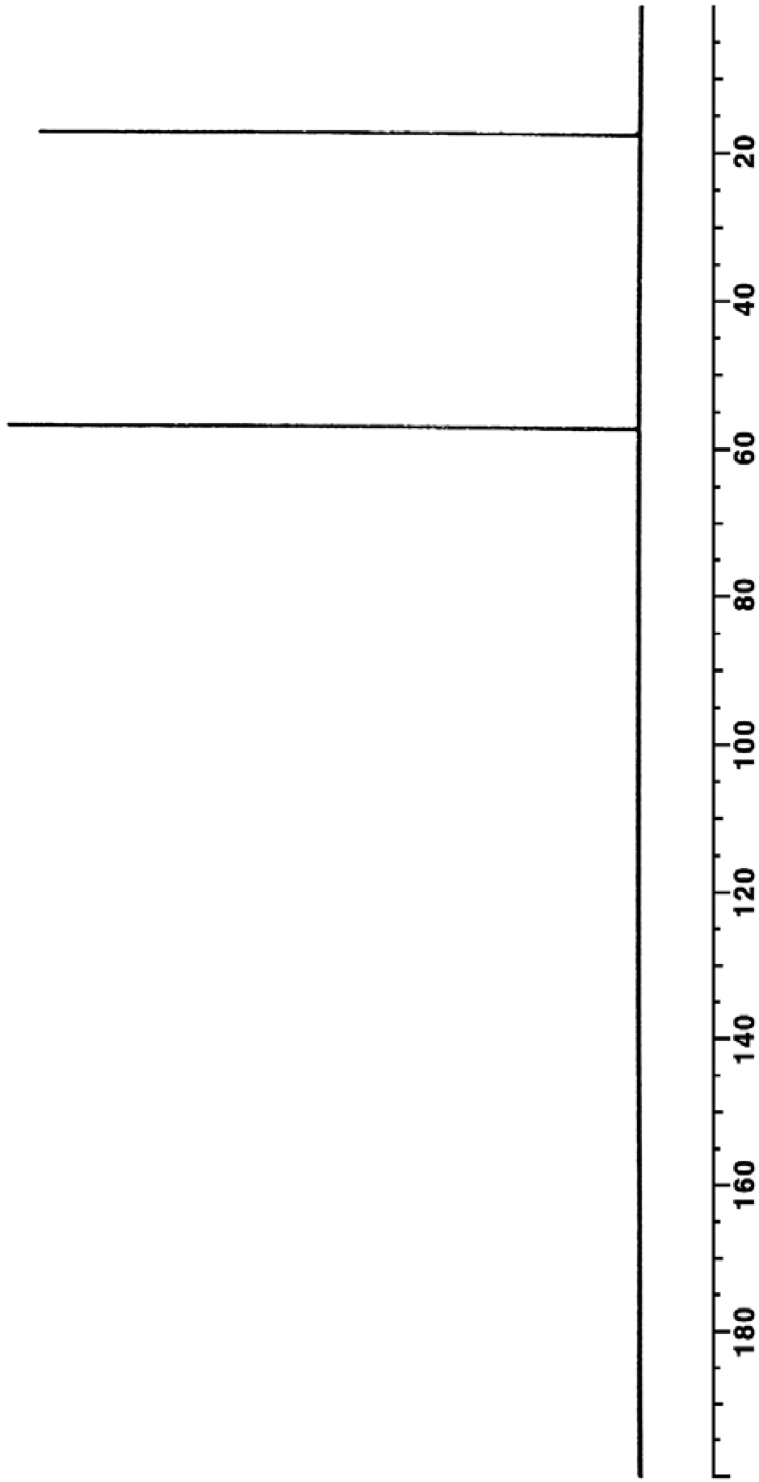

FIGURE I4
^{13}C-Nuclear Magnetic Resonance Spectrum of Ethanol

Table I1
Preparation and Storage of Dose Formulations in the 4-Week and 2-Year Drinking Water Studies of Urethane, Ethanol, and Urethane/Ethanol

Preparation

The urethane dose formulations were prepared by mixing urethane with distilled water and then filtering the solutions through sterile 0.45 µm nylon filters. The ethanol dose formulations were prepared by adding ethanol to Millipore-filtered tap water. The urethane solutions were added to Millipore-filtered tap water or to Millipore-filtered tap water containing ethanol. Dose formulations were prepared once weekly (4-week study) or approximately every 8 weeks (2-year study).

Chemical Lot Numbers

Urethane: 09101PN
Ethanol: 961730BB

Maximum Storage Time

56 (urethane) or 35 (ethanol) days

Study Laboratory

National Center for Toxicological Research (Jefferson, AR)

Table I2
Results of Analyses of Dose Formulations Administered to Mice in the 4-Week Drinking Water Study of Urethane, Ethanol, and Urethane/Ethanol

Date Prepared	Date Analyzed	Urethane Target Concentration (ppm)	Urethane Determined Concentration[a] (ppm)	Urethane Difference from Target (%)	Ethanol Target Concentration (%)	Ethanol Determined Concentration[a] (%)	Ethanol Difference from Target (%)
October 9, 1996	October 28, 1996	0	0.00	0	2.5	2.36	–6
		0	0.00	0	5	4.75	–5
		10	9.47	–5	0	0.01	0
		10	9.47	–5	2.5	2.37	–5
		10	9.45	–5	5	4.84	–3
		30	29.24	–3	0	0.02	0
		30	29.30	–2	2.5	2.35	–6
		30	29.03	–3	5	4.71	–6
		90	94.32	+5	0	0.01	0
		90	93.13	+3	2.5	2.40	–4
		90	92.82	+3	5	4.82	–4
October 16, 1996	October 28, 1996	0	0.00	0	2.5	2.34	–6
		0	0.00	0	5	4.80	–4
		10	9.87	–1	0	0.01	0
		10	9.32	–7	2.5	2.38	–5
		10	9.51	–5	5	4.89	–2
		30	30.89	+3	0	0.00	0
		30	28.90	–4	2.5	2.39	–4
		30	29.66	–1	5	4.94	–1
		90	93.72	+4	0	0.00	0
		90	93.64	+4	2.5	2.37	–5
		90	97.00	+8	5	4.94	–1
October 23, 1996	October 28, 1996	0	0.00	0	2.5	2.42	–3
		0	0.00	0	5	4.69	–6
		10	9.14	–9	0	0.00	0
		10	9.28	–7	2.5	2.40	–4
		10	9.53	–5	5	4.73	–5
		30	28.04	–7	0	0.00	0
		30	28.63	–5	2.5	2.41	–4
		30	28.29	–6	5	4.83	–3
		90	93.90	+4	0	0.00	0
		90	94.52	+5	2.5	2.42	–3
		90	91.67	+2	5	4.85	–3
October 30, 1996	October 31, 1996	0	0.00	0	2.5	2.39	–4
		0	0.00	0	5	4.69	–6
		10	9.11	–9	0	0.00	0
		10	9.06	–9	2.5	2.41	–4
		10	9.15	–8	5	4.79	–4
		30	28.56	–5	0	0.01	0
		30	28.26	–6	2.5	2.45	–2
		30	28.30	–6	5	4.84	–3
		90	93.09	+3	0	0.01	0
		90	92.95	+3	2.5	2.43	–3
		90	93.11	+3	5	4.88	–2

Table I2
Results of Analyses of Dose Formulations Administered to Mice in the 4-Week Drinking Water Study of Urethane, Ethanol, and Urethane/Ethanol

Date Prepared	Date Analyzed	Urethane Target Concentration (ppm)	Urethane Determined Concentration (ppm)	Urethane Difference from Target (%)	Ethanol Target Concentration (%)	Ethanol Determined Concentration (%)	Ethanol Difference from Target (%)
November 2, 1996	November 4, 1996	0	0.00	0	2.5	2.49	0
		0	0.00	0	5	5.23	+5
		10	10.58	+6	0	0.01	0
		10	9.92	–1	2.5	2.55	+2
		10	9.61	–4	5	4.62	–8
		30	32.49	+8	0	0.01	0
		30	31.24	+4	2.5	2.50	0
		30	29.96	0	5	4.78	–4
		90	91.51	+2	0	0.00	0
		90	92.61	+3	2.5	2.50	0
		90	91.64	+2	5	4.65	–7
November 6, 1996	November 8, 1996	0	0.00	0	2.5	2.38	–5
		0	0.00	0	5	4.75	–5
		10	9.11	–9	0	0.00	0
		10	9.17	–8	2.5	2.44	–2
		10	9.17	–8	5	4.79	–4
		30	29.60	–1	0	0.00	0
		30	29.40	–2	2.5	2.41	–4
		30	29.52	–2	5	4.88	–2
		90	92.76	+3	0	0.00	0
		90	94.11	+5	2.5	2.42	–3
		90	84.74	–6	5	4.89	–2
November 13, 1996	November 15, 1996	0	0.00	0	2.5	2.39	–4
		0	0.00	0	5	4.89	–2
		10	9.67	–3	0	0.00	0
		10	9.52	–5	2.5	2.37	–5
		10	9.34	–7	5	4.81	–4
		30	28.93	–4	0	0.00	0
		30	28.33	–6	2.5	2.31	–8
		30	29.98	0	5	4.76	–5
		90	93.60	+4	0	0.00	0
		90	92.35	+3	2.5	2.41	–4
		90	92.69	+3	5	4.84	–3
November 20, 1996	November 21, 1996	0	0.00	0	2.5	2.28	–9
		0	0.00	0	5	4.90	–2
		10	9.57	–4	0	0.00	0
		10	9.71	–3	2.5	2.25	–10
		10	9.75	–2	5	5.14	+3
		30	28.99	–3	0	0.00	0
		30	29.04	–3	2.5	2.35	–6
		30	28.78	–4	5	4.98	0
		90	94.30	+5	0	0.00	0
		90	91.77	+2	2.5	2.32	–7
		90	94.56	+5	5	5.00	0

Table I2
Results of Analyses of Dose Formulations Administered to Mice in the 4-Week Drinking Water Study of Urethane, Ethanol, and Urethane/Ethanol

		Urethane			Ethanol		
Date Prepared	Date Analyzed	Target Concentration (ppm)	Determined Concentration (ppm)	Difference from Target (%)	Target Concentration (%)	Determined Concentration (%)	Difference from Target (%)
November 25, 1996	November 26, 1996	0	0.00	0	2.5	2.40	–4
		0	0.00	0	5	4.93	–1
		10	9.52	–5	0	0.00	0
		10	9.59	–4	2.5	2.42	–3
		10	9.58	–4	5	4.88	–2
		30	29.32	–2	0	0.00	0
		30	29.51	–2	2.5	2.43	–3
		30	29.58	–1	5	4.89	–2
		90	94.58	+5	0	0.00	0
		90	94.51	+5	2.5	2.41	–4
		90	93.07	+3	5	4.98	0
December 4, 1996	December 5, 1996	0	0.00	0	2.5	2.38	–5
		0	0.00	0	5	4.94	–1
		10	9.80	–2	0	0.00	0
		10	9.94	–1	2.5	2.47	–1
		10	9.90	–1	5	4.99	0
		30	29.70	–1	0	0.00	0
		30	29.87	0	2.5	2.43	–3
		30	29.77	–1	5	4.90	–2
		90	95.98	+7	0	0.00	0
		90	95.16	+6	2.5	2.44	–2
		90	95.63	+6	5	4.91	–2

[a] Results of duplicate analyses

Table I3
Results of Analyses of Dose Formulations Administered to Mice in the 2-Year Drinking Water Study of Urethane, Ethanol, and Urethane/Ethanol

		Urethane			Ethanol		
Date Prepared	Date Analyzed	Target Concentration (ppm)	Determined Concentration[a] (ppm)	Difference from Target (%)	Target Concentration (%)	Determined Concentration[a] (%)	Difference from Target (%)
March 10, 1997	March 10, 1997	0	0.00	0	2.5	2.39	–4
		0	0.00	0	5	4.84	–3
		10	9.18	–8	0	0.00	0
		10	9.46	–5	2.5	2.39	–4
		10	9.34	–7	5	4.80	–4
		30	30.37	+1	0	0.00	0
		30	30.57	+2	2.5	2.42	–3
		30	30.16	+1	5	4.72	–6
		90	90.96	+1	0	0.00	0
		90	93.94	+4	2.5	2.37	–5
		90	91.56	+2	5	4.76	–5
March 13, 1997	March 17, 1997	0	0.00	0	2.5	2.47	–1
		0	0.00	0	5	4.95	–1
		10	9.57	–4	0	0.00	0
		10	9.79	–2	2.5	2.47	–1
		10	10.11	+1	5	4.82	–4
		30	31.29	+4	0	0.00	0
		30	31.05	+4	2.5	2.47	–1
		30	30.70	+2	5	4.81	–4
		90	85.80	–5	0	0.00	0
		90	90.02	0	2.5	2.46	–2
		90	87.87	–2	5	4.76	–5
March 19, 1997	March 21, 1997	0	0.00	0	2.5	2.47	–1
		0	0.00	0	5	5.03	+1
		10	9.03	–10	0	0.00	0
		10	9.33	–7	2.5	2.52	+1
		10	9.16	–8	5	5.07	+1
		30	28.48	–5	0	0.00	0
		30	28.22	–6	2.5	2.44	–2
		30	28.58	–5	5	5.03	+1
		90	88.36	–2	0	0.00	0
		90	87.85	–2	2.5	2.46	–2
		90	88.24	–2	5	5.14	+3
March 27, 1997	April 1, 1997	0	0.00	0	2.5	2.42	–3
		0	0.00	0	5	4.86	–3
		10	9.53	–5	0	0.00	0
		10	9.29	–7	2.5	2.41	–4
		10	8.80	–12	5	5.01	0
		30	28.16	–6	0	0.00	0
		30	28.48	–5	2.5	2.40	–4
		30	28.29	–6	5	4.97	–1
		90	86.78	–4	0	0.00	0
		90	87.39	–3	2.5	2.41	–4
		90	85.53	–5	5	5.01	0

Table I3
Results of Analyses of Dose Formulations Administered to Mice in the 2-Year Drinking Water Study of Urethane, Ethanol, and Urethane/Ethanol

		Urethane			Ethanol		
Date Prepared	Date Analyzed	Target Concentration (ppm)	Determined Concentration (ppm)	Difference from Target (%)	Target Concentration (%)	Determined Concentration (%)	Difference from Target (%)
May 30, 1997	June 3, 1997	0	0.00	0	2.5	2.42	–3
		0	0.00	0	5	4.96	–1
		10	9.15	–9	0	0.00	0
		10	9.50	–5	2.5	2.48	–1
		10	9.52	–5	5	5.03	+1
		30	29.07	–3	0	0.00	0
		30	29.08	–3	2.5	2.50	0
		30	29.67	–1	5	5.03	+1
		90	87.90	–2	0	0.00	0
		90	86.58	–4	2.5	2.42	–3
		90	88.01	–2	5	5.08	+2
July 23, 1997	July 28, 1997	0	0.00	0	2.5	2.55	+2
		0	0.00	0	5	4.96	–1
		10	8.81	–12	0	0.00	0
		10	9.16	–8	2.5	2.48	–1
		10	8.60	–14	5	4.79	–4
		30	27.07	–10	0	0.00	0
		30	27.70	–8	2.5	2.47	–1
		30	28.46	–5	5	5.10	+2
		90	89.04	–1	0	0.00	0
		90	85.27	–5	2.5	2.42	–3
		90	88.65	–2	5	5.01	0
September 17, 1997	September 23, 1997	0	0.00	0	2.5	2.47	–1
		0	0.00	0	5	5.00	0
		10	9.41	–6	0	0.00	0
		10	9.57	–4	2.5	2.41	–4
		10	9.71	–3	5	5.10	+2
		30	28.7	–4	0	0.00	0
		30	28.7	–4	2.5	2.49	0
		30	28.5	–5	5	5.04	+1
		90	87.5	–3	0	0.00	0
		90	86.8	–4	2.5	2.45	–2
		90	88.4	–2	5	5.10	+2
	September 17-23, 1997[b]	0	0.00	0	2.5	2.50	0
		0	0.00	0	5	5.00	0
		10	9.21	–8	0	0.00	0
		10	9.33	–7	2.5	2.46	–2
		10	9.45	–6	5	5.00	0
		30	27.8	–7	0	0.00	0
		30	28.0	–7	2.5	2.48	–1
		30	27.9	–7	5	4.98	0
		90	87.5	–3	0	0.00	0
		90	87.3	–3	2.5	2.46	–2
		90	87.5	–3	5	5.00	0

Table I3
Results of Analyses of Dose Formulations Administered to Mice in the 2-Year Drinking Water Study of Urethane, Ethanol, and Urethane/Ethanol

		Urethane			Ethanol		
Date Prepared	Date Analyzed	Target Concentration (ppm)	Determined Concentration (ppm)	Difference from Target (%)	Target Concentration (%)	Determined Concentration (%)	Difference from Target (%)
November 13, 1997	November 18, 1997	0	0.00	0	2.5	2.48	–1
		0	0.00	0	5	5.03	+1
		10	9.54	–5	0	0.00	0
		10	9.66	–3	2.5	2.45	–2
		10	9.58	–4	5	5.00	0
		30	29.7	–1	0	0.00	0
		30	34.8	+16	2.5	2.50	0
		30	31.9	+6	5	5.04	+1
		90	84.1	–7	0	0.00	0
		90	87.0	–3	2.5	2.49	0
		90	86.1	–4	5	5.07	+1
January 8, 1998	January 14, 1998	0	0.0	0	2.5	2.50	0
		0	0.0	0	5	5.10	+2
		10	9.5	–5	0	0.00	0
		10	9.5	–5	2.5	2.50	0
		10	9.6	–4	5	5.00	0
		30	19.0	–37[c]	0	0.00	0
		30	49.5	+65[c]	2.5	2.30[c]	–8
		30	18.8	–37[c]	5	5.20[c]	+4
		90	86.6	–4	0	0.00	0
		90	85.3	–5	2.5	2.50	0
		90	85.9	–5	5	5.10	+2
January 15, 1998	January 16, 1998	30	28.2[d]	–6	0	0.0	0
		30	28.3[d]	–6	2.5	2.5	0
		30	27.5[d]	–8	5	4.9	–2
January 26, 1998	February 3, 1998	0	0.0	0	2.5	2.5	0
		0	0.0	0	5	5.0	0
		10	9.8	–2	0	0.0	0
		10	10.4	+4	2.5	2.4	–4
		10	9.8	–2	5	4.9	–2
		30	29.8	–1	0	0.0	0
		30	28.6	–5	2.5	2.4	–4
		30	29.6	–1	5	5.1	+2
		90	92.5	+3	0	0.0	0
		90	94.1	+5	2.5	2.4	–4
		90	89.3	–1	5	5.0	0
January 27, 1998	February 3, 1998	0	0.0	0	2.5	2.4	–4
		0	0.0	0	5	4.8	–4
		10	10.3	+3	0	0.0	0
		10	10.1	+1	2.5	2.4	–4
		10	10.0	0	5	5.0	0
		30	29.3	–2	0	0.0	0
		30	29.2	–3	2.5	2.4	–4
		30	28.8	–4	5	5.0	0
		90	90.7	+1	0	0.0	0
		90	87.6	–3	2.5	2.3	–8
		90	89.6	0	5	5.1	+2

TABLE I3
Results of Analyses of Dose Formulations Administered to Mice in the 2-Year Drinking Water Study of Urethane, Ethanol, and Urethane/Ethanol

		Urethane			Ethanol		
Date Prepared	Date Analyzed	Target Concentration (ppm)	Determined Concentration (ppm)	Difference from Target (%)	Target Concentration (%)	Determined Concentration (%)	Difference from Target (%)
February 3, 1998	February 8, 1998	0	0.0	0	2.5	2.4	–4
		0	0.0	0	5	4.9	–2
		10	9.4	–6	0	0.0	0
		10	9.3	–7	2.5	2.4	–4
		10	9.3	–7	5	4.9	–2
		30	27.0	–10	0	0.0	0
		30	27.0	–10	2.5	2.4	–4
		30	27.0	–10	5	4.9	–2
		90	83.0	–8			
		90	84.0	–7	2.5	2.4	–4
		90	84.0	–7	5	5.0	0
February 10, 1998	February 12, 1998	0	0.0	0	2.5	2.5	0
		0	0.0	0	5	5.0	0
		10	9.3	–7	0	0.0	0
		10	9.3	–7	2.5	2.4	–4
		10	9.2	–8	5	4.9	–2
		30	27.4	–9	0	0.0	0
		30	27.3	–9	2.5	2.5	0
		30	27.4	–9	5	5.1	+2
		90	85.4	–5	0	0.0	0
		90	85.2	–5	2.5	2.4	–4
		90	84.6	–6	5	5.1	+2
February 17, 1998	February 18, 1998	0	0.0	0	2.5	2.4	–4
		0	0.0	0	5	5.0	0
		10	9.4	–6	0	0.0	0
		10	9.6	–4	2.5	2.5	0
		10	9.6	–4	5	5.1	+2
		30	28.8	–4	0	0.0	0
		30	28.7	–4	2.5	2.5	0
		30	28.9	–4	5	5.0	0
		90	85.5	–5	0	0.0	0
		90	85.7	–5	2.5	2.5	0
		90	85.6	–5	5	5.1	+2
February 24, 1998	February 25, 1998	0	0.0	0	2.5	2.4	–4
		0	0.0	0	5	5.0	0
		10	9.2	–8	0	0.0	0
		10	9.2	–8	2.5	2.4	–4
		10	9.3	–7	5	4.9	–2
		30	27.6	–8	0	0.0	0
		30	27.8	–7	2.5	2.4	–4
		30	28.3	–6	5	5.1	+2
		90	83.6	–7	0	0.0	0
		90	83.6	–7	2.5	2.4	–4
		90	83.4	–7	5	5.0	0

Table I3
Results of Analyses of Dose Formulations Administered to Mice in the 2-Year Drinking Water Study of Urethane, Ethanol, and Urethane/Ethanol

		Urethane			Ethanol		
Date Prepared	Date Analyzed	Target Concentration (ppm)	Determined Concentration (ppm)	Difference from Target (%)	Target Concentration (%)	Determined Concentration (%)	Difference from Target (%)
March 3, 1998	March 4, 1998	0	0.0	0	2.5	2.4	–4
		0	0.0	0	5	5.0	0
		10	9.2	–8	0	0.0	0
		10	9.3	–7	2.5	2.5	0
		10	9.4	–6	5	5.2	+4
		30	27.8	–7	0	0.0	0
		30	27.8	–7	2.5	2.5	0
		30	28.4	–5	5	5.1	+2
		90	86.7	–4	0	0.0	0
		90	86.7	–4	2.5	2.5	0
		90	87.3	–3	5	5.0	0
	March 4-5, 1998[b]	0	0.0	0	2.5	2.5	0
		0	0.0	0	5	5.0	0
		10	9.2	–8	0	0.0	0
		10	9.5	–5	2.5	2.5	0
		10	9.4	–6	5	4.9	–2
		30	27.6	–8	0	0.0	0
		30	28.5	–5	2.5	2.5	0
		30	28.3	–6	5	4.9	–2
		90	83.9	–7	0	0.0	0
		90	84.7	–6	2.5	2.5	0
		90	84.6	–6	5	5.0	0
March 10, 1998	March 12, 1998	0	0.0	0	2.5	2.5	0
		0	0.0	0	5	5.2	+4
		10	10.0	0	0	0.0	0
		10	10.1	+1	2.5	2.5	0
		10	10.0	0	5	5.2	+4
		30	30.7	+2	0	0.0	0
		30	30.7	+2	2.5	2.5	0
		30	30.6	+2	5	5.2	+4
		90	87.8	–2	0	0.0	0
		90	87.3	–3	2.5	2.4	–4
		90	87.8	–2	5	5.0	0
April 29, 1998	April 30, 1998	0	0.0	0	2.5	2.5	0
		0	0.0	0	5	5.2	+4
		10	10.0	0	0	0.0	0
		10	10.3	+3	2.5	2.5	0
		10	10.5	+5	5	5.2	+4
		30	31.9	+6	0	0.0	0
		30	31.7	+6	2.5	2.4	–4
		30	32.1	+7	5	5.5	+10
		90	89.2	–1	0	0.0	0
		90	90.6	+1	2.5	2.4	–4
		90	90.8	+1	5	5.4	+8

TABLE I3
Results of Analyses of Dose Formulations Administered to Mice in the 2-Year Drinking Water Study of Urethane, Ethanol, and Urethane/Ethanol

		Urethane			Ethanol		
Date Prepared	Date Analyzed	Target Concentration (ppm)	Determined Concentration (ppm)	Difference from Target (%)	Target Concentration (%)	Determined Concentration (%)	Difference from Target (%)
June 24, 1998	June 26, 1998	0	0.0	0	2.5	2.4	–4
		0	0.0	0	5	5.1	+2
		10	9.2	–8	0	0.0	0
		10	9.3	–7	2.5	2.4	–4
		10	9.5	–5	5	4.9	–2
		30	31.8	+6	0	0.0	0
		30	31.4	+5	2.5	2.4	–4
		30	31.9	+6	5	5.0	0
		90	88.3	–2	0	0.0	0
		90	89.7	0	2.5	2.5	0
		90	90.2	0	5	5.1	+2
August 19, 1998	August 20, 1998	0	0.0	0	2.5	2.5	0
		0	0.0	0	5	5.1	+2
		10	10.3	+3	0	0.0	0
		10	9.6	–4	2.5	2.5	0
		10	9.9	–1	5	5.1	+2
		30	32.0	+7	0	0.0	0
		30	31.9	+6	2.5	2.5	0
		30	31.7	+6	5	5.0	0
		90	90.3	0	0	0.0	0
		90	91.1	+1	2.5	2.4	–4
		90	91.4	+2	5	5.0	0
	August 19-21, 1998[b]	0	0.0	0	2.5	2.3	–8
		0	0.0	0	5	4.9	–2
		10	10.4	+4	0	0.0	0
		10	10.3	+3	2.5	2.3	–8
		10	10.4	+4	5	5.0	0
		30	31.1	+4	0	0.0	0
		30	32.5	+8	2.5	2.4	–4
		30	32.2	+7	5	4.9	–2
		90	88.1	–2	0	0.0	0
		90	90.6	+1	2.5	2.3	–8
		90	90.6	+1	5	4.8	–4
October 14, 1998	October 19, 1998	0	0.0	0	2.5	2.5	0
		0	0.0	0	5	5.0	0
		10	9.2	–8	0	0.0	0
		10	9.3	–7	2.5	2.5	0
		10	9.6	–4	5	5.2	+4
		30	30.9	+3	0	0.0	0
		30	30.9	+3	2.5	2.5	0
		30	30.3	+1	5	5.1	+2
		90	88.6	–2	0	0.0	0
		90	87.7	–3	2.5	2.5	0
		90	87.2	–3	5	5.0	0

TABLE I3
Results of Analyses of Dose Formulations Administered to Mice in the 2-Year Drinking Water Study of Urethane, Ethanol, and Urethane/Ethanol

		Urethane			Ethanol		
Date Prepared	Date Analyzed	Target Concentration (ppm)	Determined Concentration (ppm)	Difference from Target (%)	Target Concentration (%)	Determined Concentration (%)	Difference from Target (%)
December 9, 1998	December 14, 1998	0	0.0	0	2.5	2.5	0
		0	0.0	0	5	5.0	0
		10	8.9	–11	0	0.0	0
		10	9.4	–6	2.5	2.6	+4
		10	9.4	–6	5	5.1	+2
		30	28.2	–6	0	0.0	0
		30	32.8	+9	2.5	2.6	+4
		30	28.3	–6	5	4.5	–10
		90	97.8	+9	0	0.0	0
		90	90.2	0	2.5	2.6	+4
		90	89.0	–1	5	5.2	+4
February 3, 1999	February 5, 1999	0	0.0	0	2.5	2.5	0
		0	0.0	0	5	5.0	0
		10	9.3	–7	0	0.0	0
		10	9.3	–7	2.5	2.5	0
		10	9.6	–4	5	5.0	0
		30	29.1	–3	0	0.0	0
		30	30.8	+3	2.5	2.5	0
		30	30.4	+1	5	5.1	+2
		90	82.4	–8	0	0.0	0
		90	82.4	–8	2.5	2.4	–4
		90	82.8	–8	5	5.0	0
	February 3-8, 1999[b]	0	0.0	0	2.5	2.6	+4
		0	0.0	0	5	4.9	–2
		10	8.8	–12	0	0.0	0
		10	9.2	–8	2.5	2.6	+4
		10	9.5	–5	5	1.7	–66
		30	28.7	–4	0	0.0	0
		30	30.3	+1	2.5	2.5	0
		30	29.9	0	5	5.2	+4
		90	93.0	+3	0	0.0	0
		90	78.7	–13	2.5	2.6	+4
		90	81.8	–9	5	5.1	+2
February 11, 1999	February 16, 1999	90	91.5	+2	5	5.2	+4

TABLE I3
Results of Analyses of Dose Formulations Administered to Mice in the 2-Year Drinking Water Study of Urethane, Ethanol, and Urethane/Ethanol

Date Prepared	Date Analyzed	Urethane Target Concentration (ppm)	Urethane Determined Concentration (ppm)	Urethane Difference from Target (%)	Ethanol Target Concentration (%)	Ethanol Determined Concentration (%)	Ethanol Difference from Target (%)
March 31, 1999	April 1, 1999	0	0.0	0	2.5	2.5	0
		0	0.0	0	5	5.0	0
		10	9.7	–3	0	0.0	0
		10	9.9	–1	2.5	2.5	0
		10	9.8[e]	–2	5	4.3[e]	–14
		30	32.3	+8	0	0.0	0
		30	32.8	+9	2.5	2.5	0
		30	33.7[e]	+12	5	2.8[e]	–44
		90	93.9	+4	0	0.0	0
		90	94.3	+5	2.5	2.5	0
		90	95.3[e]	+6	5	3.6[e]	–28
April 2, 1999	April 2, 1999	10	9.3[d]	–7	5	5.1[d]	+2
		30	29.8[d]	–1	5	5.0[d]	0
		90	85.3[d]	–5	5	4.9[d]	–2
May 25, 1999	May 27, 1999	0	0.0	0	2.5	2.5	0
		0	0.0	0	5	5.1	+2
		10	9.0	–10	0	0.0	0
		10	9.3	–7	2.5	2.3	–8
		10	9.4	–6	5	5.1	+2
		30	30.9	+3	0	0.0	0
		30	30.0	0	2.5	2.2	–12
		30	30.9	+3	5	4.2	–16
		90	84.2	–6	0	0.0	0
		90	83.8	–7	2.5	2.4	–4
		90	86.5	–4	5	4.2	–16
May 28, 1999	May 31, 1999	30	30.8	+3	5	5.1	+2
		90	88.4	–2	5	5.1	+2

[a] Results of duplicate analyses
[b] Animal room samples
[c] Remixed; mice received dose formulation for no more than 2 days
[d] Results of remix
[e] Remixed; not used in study

APPENDIX J
WATER AND URETHANE CONSUMPTION IN THE 2-YEAR DRINKING WATER STUDY OF URETHANE, ETHANOL, AND URETHANE/ETHANOL

Table J1
Water and Urethane Consumption by Male Mice in the 2-Year Drinking Water Study of Urethane and 0% Ethanol

Week	0 ppm Urethane		10 ppm Urethane			30 ppm Urethane			90 ppm Urethane		
	Water (g)[a]	Body Weight (g)	Water (g)	Body Weight (g)	Dose (mg/kg)[b]	Water (g)	Body Weight (g)	Dose (mg/kg)	Water (g)	Body Weight (g)	Dose (mg/kg)
2	3.97	23.56	3.92	24.05	1.63	3.47	22.90	4.55	3.58	24.02	13.40
3	3.97	25.35	3.95	26.25	1.50	3.64	26.27	4.15	3.79	26.12	13.06
4	4.27	27.30	3.97	27.52	1.44	3.87	26.25	4.43	4.19	27.52	13.71
5	4.42	28.51	4.34	28.81	1.51	4.25	27.64	4.61	4.11	28.89	12.82
6	4.45	29.25	4.59	29.93	1.53	4.60	28.70	4.80	4.22	30.06	12.63
7	4.71	30.60	4.57	30.83	1.48	4.80	30.12	4.78	4.33	31.08	12.54
8	4.63	31.19	4.67	31.87	1.46	4.73	31.10	4.57	4.67	32.05	13.12
9	4.65	31.65	4.67	32.90	1.42	4.77	31.84	4.50	4.73	33.12	12.85
10	4.86	33.04	4.82	33.65	1.43	4.91	32.85	4.49	4.72	33.99	12.51
11	4.56	33.80	4.81	34.47	1.39	4.95	33.36	4.45	4.85	34.61	12.61
12	4.85	35.02	4.75	35.58	1.34	5.33	34.08	4.69	4.68	35.49	11.86
16	4.45	37.82	4.56	38.00	1.20	4.98	36.66	4.08	4.53	37.60	10.85
20	4.74	39.55	4.80	39.42	1.22	5.21	38.02	4.11	5.05	39.06	11.63
24	5.03	40.73	5.02	40.66	1.24	5.05	39.18	3.87	5.05	40.22	11.30
28	4.65	41.87	5.08	41.46	1.23	4.95	40.31	3.68	4.79	41.55	10.38
32	4.89	43.16	5.29	42.52	1.24	5.06	42.09	3.61	4.78	42.80	10.05
36	4.64	44.73	4.90	43.90	1.12	4.43	43.79	3.04	4.59	43.71	9.45
40	4.62	45.14	4.80	44.70	1.07	4.43	44.93	2.96	4.46	44.60	8.99
44	4.67	45.59	4.79	44.83	1.07	4.25	45.00	2.83	4.21	45.28	8.37
48	4.77	45.77	4.97	44.80	1.11	4.59	44.85	3.07	4.21	45.58	8.31
52	4.52	46.56	4.80	45.58	1.05	4.53	44.99	3.02	4.50	45.46	8.91
56	4.53	46.82	5.15	45.67	1.13	4.42	45.93	2.88	4.52	45.86	8.87
60	4.48	47.37	5.18	45.44	1.14	4.17	46.07	2.72	4.68	46.09	9.15
64	4.43	47.04	5.01	46.08	1.09	4.22	45.92	2.76	4.25	46.22	8.29
68	4.65	48.06	4.51	46.17	0.98	4.07	46.30	2.64	4.21	46.43	8.16
72	4.47	47.84	4.77	46.38	1.03	4.20	46.64	2.70	4.12	46.57	7.96
76	4.43	47.97	4.74	46.54	1.02	4.23	46.60	2.73	4.33	45.96	8.48
80	4.64	47.79	5.03	46.22	1.09	4.19	46.38	2.71	4.04	45.44	8.00
84	4.80	47.19	4.87	45.82	1.06	4.07	46.38	2.64	4.56	45.32	9.06
88	4.89	46.84	4.46	45.33	0.98	4.37	45.22	2.90	5.16	43.90	10.58
92	5.31	46.42	4.87	44.87	1.09	4.37	44.64	2.94	5.20	41.98	11.15
96	5.95	44.39	5.09	44.90	1.13	4.34	42.81	3.04	5.60	39.47	12.77
100	5.50	43.07	4.88	44.28	1.10	4.95	42.80	3.47	5.07	37.73	12.10
104	5.61	42.19	5.20	43.25	1.20	4.92	41.27	3.57	5.39	38.36	12.64
Mean for weeks											
1-13	4.49	29.20	4.46	29.77	1.50	4.48	28.78	4.67	4.35	29.90	13.10
14-52	4.70	43.09	4.90	42.59	1.15	4.75	41.98	3.39	4.62	42.59	9.76
53-104	4.90	46.38	4.90	45.46	1.08	4.35	45.15	2.89	4.70	43.79	9.67

[a] Grams of water consumed per animal per day
[b] Milligrams of urethane consumed per kilogram body weight per day

TABLE J2
Water and Urethane Consumption by Male Mice in the 2-Year Drinking Water Study of Urethane and 2.5% Ethanol

	0 ppm Urethane		10 ppm Urethane			30 ppm Urethane			90 ppm Urethane		
Week	Water (g)[a]	Body Weight (g)	Water (g)	Body Weight (g)	Dose (mg/kg)[b]	Water (g)	Body Weight (g)	Dose (mg/kg)	Water (g)	Body Weight (g)	Dose (mg/kg)
2	3.83	24.03	3.63	23.30	1.56	3.54	23.10	4.60	3.36	23.46	12.88
3	3.97	25.71	3.66	25.24	1.45	3.61	25.07	4.33	3.43	25.13	12.28
4	4.12	27.51	3.99	26.76	1.49	3.88	27.02	4.31	3.93	26.77	13.22
5	4.28	28.89	3.97	27.99	1.42	4.04	28.08	4.31	4.01	28.51	12.65
6	4.47	29.95	4.27	29.08	1.47	4.26	29.48	4.34	4.20	29.87	12.65
7	4.71	30.91	4.16	30.23	1.38	4.19	30.32	4.14	4.33	30.93	12.59
8	4.74	32.10	4.30	31.22	1.38	4.22	31.48	4.02	4.30	31.92	12.13
9	4.79	33.37	4.35	32.06	1.36	4.28	32.11	4.00	4.36	32.96	11.91
10	4.56	34.01	4.37	32.89	1.33	4.21	33.06	3.82	4.17	33.62	11.17
11	4.43	34.79	4.34	33.68	1.29	4.29	33.59	3.83	4.42	34.52	11.54
12	4.57	35.48	4.31	35.09	1.23	4.45	34.21	3.90	4.31	35.30	10.98
16	4.58	37.76	4.31	37.13	1.16	4.39	36.44	3.62	4.15	37.75	9.90
20	4.88	39.75	4.21	39.55	1.06	4.46	38.40	3.48	4.18	39.67	9.49
24	4.59	41.01	4.39	40.87	1.07	4.35	39.87	3.28	4.30	41.04	9.43
28	4.96	42.33	4.37	41.50	1.05	4.59	40.98	3.36	4.33	41.34	9.42
32	4.78	43.12	4.20	43.33	0.97	4.50	41.88	3.22	4.43	42.57	9.37
36	4.78	43.44	3.91	44.50	0.88	4.49	43.07	3.13	4.00	43.92	8.20
40	4.49	44.38	3.82	45.02	0.85	4.21	43.92	2.87	3.79	45.34	7.52
44	4.35	44.63	3.66	45.74	0.80	4.19	44.48	2.82	4.01	45.54	7.93
48	4.47	44.80	3.67	45.59	0.80	4.00	44.97	2.67	4.00	45.78	7.86
52	4.35	45.24	3.82	45.58	0.84	4.08	45.55	2.69	3.82	46.20	7.44
56	4.11	45.26	3.74	46.33	0.81	4.12	45.66	2.71	3.85	46.39	7.46
60	3.97	45.55	3.64	46.57	0.78	4.09	46.02	2.67	3.68	46.62	7.11
64	3.92	45.23	3.72	46.32	0.80	4.00	46.42	2.58	3.63	47.34	6.89
68	4.03	45.48	3.43	46.12	0.74	4.30	46.63	2.77	3.74	46.80	7.20
72	3.65	45.63	3.46	45.84	0.75	3.77	46.67	2.42	3.49	47.12	6.66
76	3.86	45.26	3.42	45.62	0.75	3.89	46.66	2.50	3.74	46.41	7.25
80	3.60	45.53	3.86	45.29	0.85	3.81	46.27	2.47	3.52	44.61	7.10
84	3.85	44.41	3.87	44.60	0.87	4.33	45.67	2.85	3.46	43.73	7.12
88	4.01	44.18	4.08	44.05	0.93	3.58	45.66	2.35	3.87	42.47	8.20
92	4.05	44.16	4.06	43.07	0.94	3.73	45.05	2.49	4.22	41.52	9.15
96	4.04	43.31	4.12	42.95	0.96	4.07	43.70	2.79	4.24	40.24	9.48
100	4.44	42.80	4.19	41.68	1.00	4.08	42.60	2.87	4.52	37.65	10.81
104	4.42	41.71	4.35	40.46	1.07	4.73	41.98	3.38	4.99	37.31	12.03
Mean for weeks											
1-13	4.41	29.87	4.12	29.01	1.42	4.09	29.07	4.22	4.07	29.49	12.43
14-52	4.62	42.65	4.04	42.88	0.94	4.33	41.96	3.09	4.10	42.92	8.60
53-104	4.00	44.50	3.84	44.53	0.86	4.04	45.31	2.67	3.92	43.71	8.07

[a] Grams of water consumed per animal per day
[b] Milligrams of urethane consumed per kilogram body weight per day

Table J3
Water and Urethane Consumption by Male Mice in the 2-Year Drinking Water Study of Urethane and 5% Ethanol

	0 ppm Urethane		10 ppm Urethane			30 ppm Urethane			90 ppm Urethane		
Week	Water (g)[a]	Body Weight (g)	Water (g)	Body Weight (g)	Dose (mg/kg)[b]	Water (g)	Body Weight (g)	Dose (mg/kg)	Water (g)	Body Weight (g)	Dose (mg/kg)
2	2.99	23.40	3.23	23.15	1.40	3.21	23.53	4.09	3.60	23.79	13.62
3	3.46	25.32	3.34	25.04	1.33	3.30	25.33	3.90	3.46	25.87	12.04
4	3.69	26.93	3.51	26.51	1.32	3.67	26.69	4.13	3.69	27.01	12.28
5	3.61	28.22	3.63	28.04	1.29	3.82	28.15	4.07	3.79	28.56	11.94
6	3.89	29.24	3.78	29.30	1.29	3.75	29.33	3.84	3.73	29.90	11.23
7	4.07	30.44	3.84	30.20	1.27	4.10	30.52	4.03	4.09	31.14	11.83
8	4.15	31.42	4.00	31.33	1.28	4.20	31.61	3.99	3.98	31.93	11.21
9	4.24	32.35	4.01	32.03	1.25	3.92	32.49	3.62	3.99	33.11	10.83
10	4.25	33.34	4.22	33.34	1.26	4.20	33.37	3.78	3.86	34.09	10.18
11	4.17	34.10	4.11	33.86	1.21	3.86	34.40	3.37	3.87	35.16	9.90
12	4.24	34.81	4.01	35.05	1.14	4.04	35.25	3.44	4.07	35.72	10.26
16	4.33	37.26	3.86	36.96	1.04	4.03	37.17	3.25	3.86	38.53	9.01
20	4.08	39.70	3.88	39.13	0.99	4.05	39.13	3.10	4.23	40.81	9.32
24	3.94	41.35	3.87	40.58	0.95	3.98	40.61	2.94	4.12	41.68	8.90
28	4.01	42.32	3.73	41.66	0.89	3.75	42.03	2.68	3.97	42.83	8.35
32	3.93	43.23	3.68	43.13	0.85	4.19	42.54	2.95	3.91	43.77	8.05
36	3.76	44.43	3.59	44.06	0.82	3.87	43.78	2.65	3.85	44.42	7.79
40	3.52	44.88	3.83	44.27	0.87	3.58	44.71	2.40	3.73	45.12	7.44
44	3.43	45.54	3.50	44.71	0.78	3.60	44.21	2.44	3.79	45.45	7.51
48	3.21	45.58	3.42	44.69	0.76	3.62	44.73	2.42	3.55	46.22	6.92
52	3.22	45.92	3.36	45.64	0.74	3.82	45.20	2.54	3.80	46.07	7.43
56	3.14	46.28	3.20	45.44	0.71	3.45	45.64	2.27	3.73	46.40	7.24
60	3.17	46.73	3.16	45.50	0.70	3.52	45.14	2.34	3.54	46.26	6.88
64	3.31	46.07	3.35	45.67	0.73	3.59	45.40	2.37	3.51	46.26	6.84
68	3.18	46.41	3.26	45.76	0.71	3.31	45.22	2.19	3.37	46.16	6.58
72	3.15	46.66	3.15	45.19	0.70	3.44	45.74	2.25	3.30	46.22	6.43
76	3.09	46.30	3.17	45.40	0.70	3.39	45.26	2.24	3.39	45.93	6.65
80	3.10	46.19	3.37	45.15	0.75	3.42	45.21	2.27	3.38	44.74	6.79
84	3.12	45.85	3.31	45.08	0.73	3.52	44.81	2.35	3.34	43.78	6.87
88	3.10	45.16	3.57	44.92	0.79	3.60	44.76	2.41	3.96	42.25	8.43
92	3.25	44.73	3.77	43.99	0.86	3.51	44.63	2.36	4.35	41.28	9.48
96	3.54	43.60	3.47	42.82	0.81	3.22	43.39	2.22	4.26	38.15	10.05
100	3.63	43.27	4.15	42.50	0.98	3.50	43.41	2.42	5.41	37.72	12.90
104	3.52	42.97	3.84	42.08	0.91	3.84	42.30	2.72	5.39	37.05	13.09
Mean for weeks											
1-13	3.89	29.25	3.79	29.08	1.30	3.82	29.29	3.92	3.83	29.84	11.55
14-52	3.74	43.02	3.67	42.48	0.86	3.85	42.41	2.72	3.88	43.49	8.03
53-104	3.26	45.40	3.44	44.58	0.77	3.48	44.69	2.34	3.92	43.25	8.15

[a] Grams of water consumed per animal per day
[b] Milligrams of urethane consumed per kilogram body weight per day

Table J4
Water and Urethane Consumption by Female Mice in the 2-Year Drinking Water Study of Urethane and 0% Ethanol

	0 ppm Urethane		10 ppm Urethane			30 ppm Urethane			90 ppm Urethane		
Week	Water (g)[a]	Body Weight (g)	Water (g)	Body Weight (g)	Dose (mg/kg)[b]	Water (g)	Body Weight (g)	Dose (mg/kg)	Water (g)	Body Weight (g)	Dose (mg/kg)
2	2.72	18.51	2.73	18.88	1.45	2.75	18.52	4.45	2.72	18.73	13.09
3	2.96	19.30	2.91	19.56	1.49	2.76	18.79	4.41	2.86	19.02	13.53
4	3.12	20.18	2.91	20.34	1.43	3.05	19.66	4.65	2.93	20.14	13.11
5	3.12	20.85	3.09	20.92	1.47	2.98	20.31	4.40	3.08	20.55	13.49
6	3.23	21.31	3.01	21.72	1.39	2.98	21.39	4.17	3.14	21.23	13.31
7	3.05	21.66	3.20	22.20	1.44	3.07	21.85	4.21	3.08	22.02	12.58
8	3.32	22.32	3.21	22.81	1.41	3.17	22.49	4.22	3.22	22.85	12.68
9	3.30	22.85	3.16	23.07	1.37	3.16	22.75	4.17	3.06	22.99	11.97
10	3.26	23.43	3.22	23.53	1.37	3.24	23.18	4.19	3.19	23.49	12.21
11	3.31	23.72	3.18	23.84	1.34	3.14	23.37	4.03	3.24	23.80	12.26
12	3.17	24.02	3.12	24.67	1.27	3.29	24.02	4.11	3.20	24.29	11.85
16	3.17	25.61	3.15	26.32	1.20	3.20	25.82	3.72	3.16	25.90	10.98
20	3.28	26.99	3.29	27.39	1.20	3.22	26.65	3.63	3.15	26.93	10.54
24	3.29	27.76	3.19	28.09	1.13	3.11	27.63	3.37	3.10	28.27	9.87
28	3.22	29.12	3.31	29.42	1.12	3.31	28.91	3.43	3.23	29.64	9.81
32	3.38	30.87	3.24	31.48	1.03	3.34	30.64	3.27	3.26	31.93	9.20
36	3.21	32.72	3.33	33.24	1.00	3.31	32.61	3.05	3.18	33.24	8.60
40	3.27	34.37	3.42	34.45	0.99	3.14	34.35	2.74	3.15	35.44	8.00
44	3.48	35.44	3.27	35.99	0.91	3.38	36.27	2.79	3.33	37.30	8.03
48	3.33	36.85	3.24	37.51	0.87	3.28	37.18	2.65	3.22	40.11	7.22
52	3.33	38.73	3.16	39.22	0.81	3.37	38.23	2.65	3.11	42.83	6.54
56	3.22	40.64	3.12	41.03	0.76	3.43	41.22	2.50	3.23	44.54	6.52
60	3.22	42.34	3.17	41.88	0.76	3.12	42.92	2.18	3.07	46.52	5.94
64	3.31	44.15	3.03	43.60	0.70	3.39	44.73	2.27	3.31	48.40	6.16
68	3.02	44.97	3.08	45.19	0.68	3.38	47.11	2.15	3.14	49.12	5.76
72	3.06	46.26	3.07	47.06	0.65	3.39	48.88	2.08	3.28	49.04	6.01
76	3.11	47.73	3.23	48.43	0.67	3.71	50.24	2.22	3.64	48.21	6.79
80	3.13	48.51	3.17	49.52	0.64	3.72	50.72	2.20	3.57	48.77	6.59
84	3.10	49.93	3.44	49.45	0.70	3.59	51.69	2.08	3.62	49.40	6.60
88	3.24	50.90	3.62	51.00	0.71	3.49	52.01	2.01	3.83	47.09	7.33
92	3.44	52.12	3.61	52.36	0.69	3.62	51.80	2.09	3.89	43.38	8.08
96	3.48	51.90	3.55	52.63	0.67	3.75	51.08	2.21	3.59	40.52	7.97
100	3.53	52.30	3.47	51.86	0.67	3.79	49.61	2.29	3.04	38.15	7.18
104	3.62	50.74	3.60	50.34	0.72	3.97	47.55	2.50	3.29	39.40	7.52
Mean for weeks											
1-13	3.14	21.32	3.07	21.57	1.42	3.05	21.09	4.34	3.07	21.34	12.93
14-52	3.30	31.85	3.26	32.31	1.01	3.27	31.83	3.08	3.19	33.16	8.66
53-104	3.27	47.88	3.32	48.03	0.69	3.56	48.43	2.21	3.42	45.58	6.76

[a] Grams of water consumed per animal per day
[b] Milligrams of urethane consumed per kilogram body weight per day

Table J5
Water and Urethane Consumption by Female Mice in the 2-Year Drinking Water Study of Urethane and 2.5% Ethanol

	0 ppm Urethane		10 ppm Urethane			30 ppm Urethane			90 ppm Urethane		
Week	Water (g)[a]	Body Weight (g)	Water (g)	Body Weight (g)	Dose (mg/kg)[b]	Water (g)	Body Weight (g)	Dose (mg/kg)	Water (g)	Body Weight (g)	Dose (mg/kg)
2	2.72	19.15	2.78	18.79	1.48	2.62	18.61	4.23	2.60	18.35	12.76
3	2.78	19.74	2.84	19.38	1.47	2.76	19.37	4.27	2.77	19.03	13.09
4	3.18	20.50	3.28	20.21	1.62	2.97	20.35	4.38	2.88	20.09	12.91
5	3.18	21.56	3.07	21.02	1.46	2.92	20.66	4.25	2.94	20.72	12.75
6	3.24	22.19	3.15	21.78	1.45	3.07	21.56	4.27	2.97	21.26	12.56
7	3.22	22.87	3.14	22.16	1.42	3.04	21.85	4.18	3.08	22.05	12.59
8	3.20	23.47	3.16	22.61	1.40	3.21	22.15	4.34	3.15	22.43	12.66
9	3.28	23.63	3.21	23.07	1.39	3.12	23.27	4.02	3.12	22.68	12.37
10	3.38	24.13	3.32	23.43	1.42	3.12	23.29	4.02	3.18	23.38	12.23
11	3.32	24.60	3.38	23.90	1.42	3.04	23.73	3.85	3.19	23.92	11.98
12	3.24	25.22	3.32	24.30	1.37	3.20	24.45	3.93	3.26	24.10	12.17
16	3.33	26.91	3.30	26.01	1.27	3.06	25.61	3.58	3.19	25.64	11.20
20	3.21	28.32	3.24	27.27	1.19	2.94	26.94	3.27	3.19	26.83	10.69
24	3.18	29.80	3.35	29.32	1.14	3.15	28.40	3.33	3.06	27.96	9.87
28	3.33	31.74	3.38	30.10	1.12	3.23	29.71	3.26	3.06	29.35	9.38
32	3.38	33.95	3.42	31.81	1.08	3.13	31.34	3.00	3.11	30.97	9.05
36	3.03	35.89	3.44	33.63	1.02	3.27	33.41	2.94	3.16	32.54	8.74
40	3.13	37.28	3.19	35.17	0.91	3.30	34.45	2.87	3.07	34.55	8.00
44	3.06	39.11	3.29	36.77	0.89	3.11	36.00	2.60	3.02	36.71	7.41
48	3.09	40.32	3.18	38.07	0.84	3.15	37.65	2.51	3.07	38.61	7.16
52	3.09	41.61	3.10	39.28	0.79	3.33	39.10	2.55	3.06	40.96	6.71
56	3.20	43.80	3.08	41.11	0.75	3.08	40.56	2.28	2.98	43.39	6.19
60	2.98	45.25	3.05	42.26	0.72	3.00	42.44	2.12	2.86	44.91	5.73
64	2.85	46.35	3.06	43.98	0.70	3.03	43.88	2.07	2.87	45.88	5.63
68	2.77	47.30	2.93	46.06	0.64	3.03	44.94	2.02	2.85	46.55	5.51
72	2.76	48.28	2.97	47.01	0.63	3.10	46.62	1.99	2.88	47.66	5.44
76	2.80	48.92	3.08	47.98	0.64	3.11	48.43	1.93	2.84	48.55	5.27
80	2.88	48.51	3.13	48.51	0.65	3.07	48.99	1.88	2.86	48.06	5.36
84	2.91	49.99	3.05	49.04	0.62	3.06	49.72	1.85	3.15	46.18	6.13
88	2.91	50.26	3.05	49.00	0.62	3.40	48.60	2.10	2.91	44.60	5.88
92	2.84	50.44	3.13	49.44	0.63	3.31	46.61	2.13	3.10	43.18	6.46
96	2.92	50.78	3.25	48.59	0.67	3.38	45.60	2.22	3.33	39.64	7.56
100	2.98	50.69	3.26	48.06	0.68	3.68	44.15	2.50	3.43	36.31	8.49
104	2.89	50.06	3.37	47.22	0.71	3.95	43.37	2.73	3.10	33.46	8.33
Mean for weeks											
1-13	3.16	22.07	3.15	21.51	1.46	3.01	21.36	4.22	3.01	21.24	12.76
14-52	3.18	34.49	3.29	32.74	1.00	3.17	32.26	2.95	3.10	32.41	8.61
53-104	2.90	48.51	3.11	46.79	0.66	3.25	45.68	2.13	3.01	43.72	6.20

[a] Grams of water consumed per animal per day
[b] Milligrams of urethane consumed per kilogram body weight per day

TABLE J6
Water and Urethane Consumption by Female Mice in the 2-Year Drinking Water Study of Urethane and 5% Ethanol

Week	0 ppm Urethane Water (g)[a]	0 ppm Urethane Body Weight (g)	10 ppm Urethane Water (g)	10 ppm Urethane Body Weight (g)	10 ppm Urethane Dose (mg/kg)[b]	30 ppm Urethane Water (g)	30 ppm Urethane Body Weight (g)	30 ppm Urethane Dose (mg/kg)	90 ppm Urethane Water (g)	90 ppm Urethane Body Weight (g)	90 ppm Urethane Dose (mg/kg)
2	2.49	18.48	2.59	18.57	1.40	2.55	18.54	4.13	2.60	18.75	12.46
3	2.75	19.10	2.90	19.05	1.52	2.73	19.44	4.21	2.86	19.08	13.48
4	2.87	19.84	2.97	20.03	1.48	2.99	20.30	4.41	2.81	20.10	12.58
5	2.89	20.43	3.09	21.10	1.47	3.06	21.02	4.37	3.04	20.84	13.15
6	2.95	21.25	3.05	21.44	1.42	3.10	21.70	4.28	2.99	21.49	12.54
7	3.02	22.14	3.27	21.76	1.50	3.05	22.04	4.16	3.22	22.00	13.18
8	3.21	22.35	3.34	22.66	1.48	3.32	22.61	4.40	3.18	22.64	12.63
9	3.10	22.80	3.31	23.10	1.43	3.32	22.99	4.33	3.37	23.32	13.01
10	3.23	23.36	3.30	23.52	1.40	3.24	23.74	4.09	3.17	23.65	12.05
11	3.16	23.83	3.27	23.71	1.38	3.36	24.29	4.15	3.21	24.35	11.86
12	3.33	24.37	3.51	24.23	1.45	3.17	24.46	3.88	3.33	24.77	12.12
16	3.29	25.93	3.34	25.53	1.31	3.28	26.07	3.77	3.27	26.18	11.24
20	3.34	26.80	3.35	26.92	1.24	3.28	27.17	3.62	3.26	27.65	10.62
24	3.19	27.95	3.35	28.22	1.19	3.30	28.25	3.50	3.15	28.50	9.94
28	3.31	29.41	3.50	29.37	1.19	3.24	29.68	3.28	3.29	29.93	9.88
32	3.19	31.00	3.52	31.29	1.12	3.43	30.94	3.33	3.31	31.52	9.45
36	3.23	32.38	3.31	33.36	0.99	3.22	32.31	2.99	3.31	32.98	9.03
40	3.13	33.58	3.31	34.85	0.95	3.28	34.18	2.88	3.14	35.16	8.04
44	3.24	35.28	3.32	35.34	0.94	3.05	35.15	2.60	3.26	37.57	7.82
48	3.15	37.54	3.51	36.80	0.95	3.04	36.53	2.50	3.11	39.59	7.07
52	3.03	38.44	3.24	38.32	0.85	3.17	38.79	2.45	3.08	41.85	6.63
56	3.08	39.32	3.22	39.42	0.82	3.15	40.98	2.30	3.04	43.77	6.24
60	3.16	40.56	3.17	40.81	0.78	3.15	43.02	2.20	3.02	45.42	5.98
64	2.86	41.81	3.19	42.29	0.75	2.96	44.75	1.98	3.02	46.68	5.83
68	2.88	43.64	3.05	43.98	0.69	2.83	46.84	1.81	2.85	48.34	5.31
72	2.80	44.84	3.11	45.88	0.68	3.12	48.41	1.93	2.89	48.93	5.32
76	2.85	45.52	3.03	47.47	0.64	2.90	48.60	1.79	2.91	48.97	5.34
80	2.88	46.47	3.07	48.35	0.64	2.98	49.00	1.82	3.06	48.38	5.69
84	2.82	46.32	3.16	49.45	0.64	3.10	48.94	1.90	2.99	47.68	5.65
88	2.86	47.33	3.15	50.07	0.63	3.39	49.02	2.08	3.23	47.03	6.19
92	2.90	48.20	2.96	49.24	0.60	3.38	48.10	2.11	3.68	43.99	7.53
96	2.97	48.21	2.97	49.16	0.60	3.60	48.15	2.25	3.84	41.30	8.38
100	3.02	47.13	3.15	47.31	0.67	3.42	46.69	2.20	3.62	38.20	8.53
104	3.18	47.33	2.95	45.88	0.64	3.60	44.97	2.40	3.81	42.52	8.07
Mean for weeks											
1-13	3.00	21.24	3.15	21.35	1.47	3.08	21.54	4.29	3.07	21.54	12.83
14-52	3.21	31.83	3.38	32.00	1.05	3.23	31.91	3.04	3.22	33.09	8.75
53-104	2.94	45.13	3.09	46.10	0.67	3.20	46.73	2.05	3.23	45.48	6.39

[a] Grams of water consumed per animal per day
[b] Milligrams of urethane consumed per kilogram body weight per day

APPENDIX K
FEED CONSUMPTION
IN THE 2-YEAR DRINKING WATER STUDY
OF URETHANE, ETHANOL,
AND URETHANE/ETHANOL

TABLE K1
Feed Consumption by Male Mice in the 2-Year Drinking Water Study of Urethane and 0% Ethanol[a]

Week	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
2	4.18	4.15	3.91	4.06
3	4.25	4.35	4.07	4.18
4	4.58	4.67	4.35	4.41
5	4.73	5.20	4.64	4.90
6	4.94	5.11	5.05	5.08
7	5.17	5.59	5.06	4.96
8	5.30	5.49	5.33	5.31
9	5.44	5.78	5.14	5.37
10	5.58	5.92	5.62	5.45
11	5.71	6.03	5.59	5.47
12	5.84	5.50	6.00	5.53
16	5.81	5.89	5.79	5.59
20	5.91	5.67	5.80	5.80
24	5.93	5.75	5.81	5.66
28	5.71	5.98	5.82	5.80
32	5.73	5.61	5.54	5.63
36	5.82	5.81	5.56	5.52
40	5.82	5.63	5.53	5.48
44	5.92	5.75	5.66	5.91
48	5.88	5.89	5.71	5.78
52	6.14	5.93	5.62	5.64
56	5.92	5.86	5.60	5.76
60	5.66	6.07	5.65	5.76
64	5.63	5.96	5.52	5.53
68	5.94	5.87	5.79	5.39
72	6.38	6.12	6.00	5.55
76	5.84	6.64	5.97	5.58
80	6.71	6.43	5.49	5.78
84	6.59	6.14	5.67	5.61
88	6.51	6.16	5.83	5.88
92	6.30	6.01	5.37	6.11
96	6.61	5.97	5.40	6.23
100	6.51	5.75	5.77	6.57
104	5.67	6.10	5.44	7.06
Mean for weeks				
1-13	5.06	5.25	4.98	4.97
14-52	5.87	5.79	5.68	5.68
53-104	6.17	6.08	5.65	5.91

[a] Grams of feed consumed per animal per day

Table K2
Feed Consumption by Male Mice in the 2-Year Drinking Water Study of Urethane and 2.5% Ethanol[a]

Week	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
2	4.00	3.88	3.97	3.88
3	4.21	4.06	4.15	4.13
4	4.57	4.46	4.47	4.43
5	4.70	4.95	4.53	4.57
6	5.33	5.07	4.84	4.70
7	4.99	4.96	5.15	5.28
8	5.67	5.55	5.24	5.75
9	5.58	5.04	5.22	4.89
10	5.76	5.43	5.22	5.47
11	5.63	5.21	5.22	5.21
12	5.55	5.45	5.16	5.38
16	5.63	5.65	5.29	5.52
20	5.62	5.36	5.48	5.58
24	5.44	5.74	5.35	5.52
28	5.82	5.33	5.21	5.29
32	5.67	5.41	5.40	5.30
36	5.43	5.32	5.54	5.41
40	5.84	5.63	5.55	5.14
44	5.96	5.45	5.44	5.38
48	5.76	5.55	5.48	5.45
52	5.47	5.64	5.61	5.39
56	5.52	5.42	5.49	5.35
60	5.59	5.34	5.41	5.35
64	5.71	5.56	5.45	5.44
68	5.72	5.63	5.39	5.78
72	5.84	5.38	6.06	5.24
76	6.18	5.58	6.03	5.15
80	5.38	5.39	5.48	4.89
84	5.04	5.34	5.73	4.91
88	5.15	5.21	5.50	4.92
92	5.45	5.13	5.53	5.18
96	5.17	5.20	5.58	5.29
100	5.49	5.78	5.48	5.70
104	5.12	5.57	5.78	5.65
Mean for weeks				
1-13	5.09	4.91	4.83	4.88
14-52	5.66	5.51	5.43	5.40
53-104	5.49	5.43	5.61	5.30

[a] Grams of feed consumed per animal per day

Table K3
Feed Consumption by Male Mice in the 2-Year Drinking Water Study of Urethane and 5% Ethanol[a]

Week	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
2	3.53	3.65	3.76	3.78
3	3.85	3.80	4.01	4.21
4	4.09	4.05	4.16	4.04
5	4.43	4.68	4.61	4.42
6	4.87	5.03	4.60	4.71
7	5.14	4.96	4.84	4.89
8	5.11	4.81	5.25	4.78
9	5.12	4.79	4.82	4.99
10	5.50	4.95	4.92	5.03
11	5.54	5.08	5.16	5.24
12	5.36	5.28	5.01	4.94
16	5.44	5.14	5.04	5.53
20	5.31	5.08	5.67	5.30
24	5.64	5.10	5.27	5.51
28	5.33	5.12	5.19	5.38
32	5.09	5.16	5.16	5.33
36	5.06	4.95	5.24	5.12
40	5.16	5.13	5.24	5.43
44	5.31	5.27	5.16	5.39
48	5.27	5.18	5.15	5.61
52	5.12	5.18	5.28	5.48
56	5.18	5.07	5.58	5.45
60	5.25	5.25	5.61	5.61
64	5.29	4.85	5.22	5.58
68	5.26	5.06	5.12	5.73
72	5.71	5.25	5.47	5.73
76	5.31	5.32	5.23	5.30
80	5.67	5.29	5.66	5.64
84	5.34	5.28	5.04	5.43
88	5.32	4.77	4.96	5.67
92	5.71	5.47	4.86	4.77
96	5.33	5.18	4.93	5.10
100	5.37	5.48	5.29	5.64
104	5.38	5.40	5.33	5.67
Mean for weeks				
1-13	4.78	4.64	4.65	4.64
14-52	5.27	5.13	5.24	5.41
53-104	5.39	5.20	5.25	5.49

[a] Grams of feed consumed per animal per day

Table K4
Feed Consumption by Female Mice in the 2-Year Drinking Water Study of Urethane and 0% Ethanol[a]

Week	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
2	3.06	3.32	3.09	3.05
3	3.33	3.48	3.43	3.21
4	3.53	3.44	3.49	3.43
5	3.76	3.61	3.74	3.53
6	3.87	3.81	4.14	3.75
7	4.08	3.96	4.12	3.85
8	4.22	4.04	4.20	3.95
9	4.22	4.03	4.18	4.09
10	4.30	4.12	4.30	4.11
11	4.39	4.26	4.20	4.07
12	4.53	4.17	4.30	4.20
16	4.50	4.36	4.56	4.21
20	4.63	4.42	4.56	4.23
24	4.49	4.25	4.26	4.35
28	4.29	4.45	4.39	4.31
32	4.49	4.41	4.31	4.32
36	4.51	4.59	4.26	4.41
40	4.73	4.74	4.50	4.69
44	5.10	4.85	4.95	4.69
48	5.23	4.77	4.93	4.97
52	5.03	4.72	5.08	4.78
56	5.17	4.75	5.12	4.62
60	5.30	4.61	5.05	4.96
64	5.36	4.76	5.11	5.39
68	5.36	4.66	5.52	5.01
72	5.54	5.17	5.56	4.81
76	5.49	5.17	5.72	5.00
80	5.43	5.16	5.41	5.27
84	5.38	5.22	5.76	5.44
88	5.43	5.37	5.56	4.95
92	5.67	5.34	5.77	5.07
96	5.55	5.34	5.63	5.01
100	5.38	5.21	6.06	5.42
104	5.81	5.49	5.79	7.78
Mean for weeks				
1-13	3.93	3.84	3.93	3.75
14-52	4.70	4.55	4.58	4.50
53-104	5.45	5.10	5.54	5.29

[a] Grams of feed consumed per animal per day

Table K5
Feed Consumption by Female Mice in the 2-Year Drinking Water Study of Urethane and 2.5% Ethanol[a]

Week	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
2	3.03	2.95	2.94	3.09
3	3.10	3.19	3.03	3.11
4	3.49	3.39	3.30	3.42
5	3.54	3.52	3.42	3.60
6	3.73	3.68	3.59	3.77
7	3.86	3.77	3.66	3.82
8	4.07	4.02	3.74	3.88
9	4.07	3.91	3.96	4.16
10	4.00	3.94	3.92	4.07
11	4.04	4.02	4.07	4.18
12	4.28	3.98	4.17	4.09
16	4.27	4.26	4.08	4.18
20	4.47	4.32	4.15	4.00
24	4.31	4.28	4.31	4.37
28	4.37	4.30	4.26	4.27
32	4.49	4.16	4.35	4.28
36	4.46	4.28	4.32	4.23
40	4.51	4.27	4.40	4.52
44	4.65	4.53	4.40	4.53
48	4.84	4.52	4.62	4.62
52	4.78	4.56	4.57	4.74
56	4.88	4.60	4.54	4.87
60	4.79	4.61	4.69	4.77
64	4.98	4.90	4.94	4.74
68	5.03	5.09	4.92	5.49
72	5.39	4.93	5.20	4.88
76	5.16	4.81	5.51	5.08
80	5.14	4.99	5.09	5.10
84	5.00	5.04	5.21	4.80
88	5.22	4.64	5.07	5.20
92	5.31	5.32	5.32	5.17
96	5.28	4.85	5.19	4.82
100	5.38	5.34	5.38	5.34
104	5.18	5.22	5.85	4.53
Mean for weeks				
1-13	3.75	3.67	3.62	3.75
14-52	4.52	4.35	4.34	4.37
53-104	5.13	4.95	5.15	4.98

[a] Grams of feed consumed per animal per day

TABLE K6
Feed Consumption by Female Mice in the 2-Year Drinking Water Study of Urethane and 5% Ethanol[a]

Week	0 ppm Urethane	10 ppm Urethane	30 ppm Urethane	90 ppm Urethane
2	2.81	2.76	2.80	2.90
3	2.94	2.95	3.02	3.08
4	3.21	3.23	3.41	3.20
5	3.28	3.44	3.40	3.37
6	3.44	3.51	3.57	3.47
7	3.66	3.61	3.47	3.51
8	3.64	3.75	3.66	3.70
9	3.69	3.79	3.82	3.94
10	3.82	3.83	3.90	3.94
11	3.86	3.88	4.09	4.09
12	4.00	3.85	4.21	3.96
16	4.07	4.06	4.16	4.05
20	4.01	4.06	4.32	4.56
24	4.16	4.15	4.41	4.13
28	4.00	4.07	3.99	4.07
32	4.00	4.11	4.13	4.11
36	4.03	4.39	4.10	4.27
40	4.14	4.29	4.33	4.31
44	4.24	4.29	4.60	4.80
48	4.57	4.50	4.89	4.64
52	4.51	4.82	4.66	4.81
56	3.99	4.47	4.58	4.48
60	4.51	4.59	4.68	4.74
64	4.68	4.65	4.60	4.61
68	4.90	4.74	5.03	4.80
72	4.71	4.84	5.14	5.39
76	4.70	4.74	5.08	5.25
80	4.34	5.02	5.18	4.99
84	4.54	5.21	4.87	4.95
88	4.70	5.18	5.26	4.80
92	4.77	4.85	5.04	4.31
96	4.77	4.96	5.39	5.03
100	4.89	5.39	5.01	5.28
104	5.07	4.97	5.37	5.19
Mean for weeks				
1-13	3.49	3.51	3.58	3.56
14-52	4.17	4.27	4.36	4.38
53-104	4.66	4.89	5.02	4.91

[a] Grams of feed consumed per animal per day

APPENDIX L
INGREDIENTS, NUTRIENT COMPOSITION, AND CONTAMINANT LEVELS IN NIH-31 RAT AND MOUSE RATION

Table L1
Ingredients of NIH-31 Rat and Mouse Ration

Ingredients[a]	Percent by Weight
Ground #2 yellow shelled corn	21.0
Ground whole hard wheat	35.5
Ground whole oats	10.0
Soybean meal (49% protein)	5.0
Fish meal (60% protein)	9.0
Wheat middlings	10.0
Alfalfa meal (17% protein)	2.0
Corn gluten meal (60% protein)	2.0
Soy oil	1.5
Dried brewer's yeast	1.0
Dicalcium phosphate (food grade)	1.5
Ground limestone	0.5
Salt	0.5
Premixes (vitamin and mineral)	0.5

[a] Ingredients were ground to pass through a U.S. Standard Screen No. 16 before being mixed.

Table L2
Vitamins and Minerals in NIH-31 Rat and Mouse Ration[a]

	Amount	Source
Vitamins		
A	22,000,000 IU	Vitamin A palmitate or acetate
D_3	3,800,000 IU	D-activated animal sterol
K_3	20 g	Menadione activity
d-α-Tocopheryl acetate	15 g	
Choline	700 g	Choline chloride
Folic acid	1 g	
Niacin	20 g	
d-Pantothenic acid	25 g	*d*-Calcium pantothenate
Riboflavin	5 g	
Thiamine	65 g	Thiamine mononitrate
B_{12}	14 g	
Pyridoxine	2 g	Pyridoxine hydrochloride
Biotin	0.120 g	*d*-Biotin
Minerals		
Iron	60 g	Iron sulfate
Magnesium	400 g	Magnesium oxide
Manganese	100 g	Manganous oxide
Zinc	10 g	Zinc oxide
Copper	4 g	Copper sulfate
Iodine	1.5 g	Calcium iodate
Cobalt	0.4 g	Cobalt carbonate

[a] Per ton (2,000 lb) of finished product

TABLE L3
Nutrient Composition of NIH-31 Rat and Mouse Ration[a]

Nutrient	Mean ± Standard Deviation[b]
Crude protein (% by weight)	19.2 ± 1.0
Crude fat (% by weight)	5.55 ± 0.92
Vitamins	
Vitamin A (µg/g)	11.7 ± 1.2
Vitamin B_1 (mg/g)	0.094 ± 0.019
Vitamin E (ppm)	60.4 ± 5.6
Minerals	
Selenium (ppm)	0.36 ± 0.11

a Prior to autoclaving
b Average of 37 diet production lots

TABLE L4
Contaminant Levels in NIH-31 Rat and Mouse Ration[a]

	Mean ± Standard Deviation[b]
Contaminants	
Arsenic (ppb)	107 ± 48
Cadmium (ppb)	62 ± 37
Lead (ppm)	0.39 ± 0.15
Aflatoxin B_1 (ppb)	<0.25
Aflatoxin B_2 (ppb)	<0.25
Aflatoxin G_1 (ppb)	<0.25
Aflatoxin G_2 (ppb)	<0.12
Fumonisin B_1 (ppb)	31.6 ± 24.3
Total fumonisin (ppb)	50.4 ± 22.7
Volatiles (%)	6.68 ± 0.96
Pesticides (ppb)	
Heptachlor	<10
DDT, total[c]	<5
Dieldrin	<5
PCB	26 ± 34
Malathion	86 ± 53
Lindane	<1

a Prior to autoclaving
b Average of 8, 9, 10, 25, or 37 diet production lots; for values less than the limit of detection, the detection limit is given as the mean.
c DDE+DDT+DDD

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 mice during the 2-year study. Blood from each animal was collected and allowed to clot, and the serum was separated. The samples were processed appropriately and sent to the Surveillance/Diagnostic Program, Division of Microbiology, at the NCTR for determination of antibody titers. In addition to the serology testing, all sentinel animals were examined for ectoparasites, endoparasites, and bacterial pathogens. The laboratory serology methods and viral agents for which testing was performed are tabulated below; the times at which blood was collected during the study are also listed.

Method and Test	Time of Analysis
ELISA	
Ectromelia virus	6, 12, and 18 months, study termination
GDVII (mouse encephalomyelitis virus)	6, 12, and 18 months, study termination
LCM (lymphocytic choriomeningitis virus)	6, 12, and 18 months, study termination
MVM (minute virus of mice)	6, 12, and 18 months, study termination
MHV (mouse hepatitis virus)	6, 12, and 18 months, study termination
Mycoplasma arthritidis	6, 12, and 18 months, study termination
Mycoplasma pulmonis	6, 12, and 18 months, study termination
PVM (pneumonia virus of mice)	6, 12, and 18 months, study termination
Polyoma virus	6, 12, and 18 months, study termination
Reovirus 3	6, 12, and 18 months, study termination
Sendai	6, 12, and 18 months, study termination

Results

Six of eight mice at 6 months and three of eight mice at 18 months had positive titers for MHV. Mice used in this study were loaded from a breeding colony that had previously tested positive for MHV antibodies. Colon samples from the breeder colony were sent to Yale University School of Medicine, Section of Comparative Medicine, for molecular characterization of the virus. The conclusion was that the virus was likely a coronavirus intermediate to known MHV and rat coronavirus strains and was considered only mildly or nonpathogenic to the mice.

All other test results were negative.

National Toxicology Program Technical Reports

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Chemical	TR No.
Acetaminophen	394
Acetonitrile	447
Acrylonitrile	506
Agar	230
Allyl Glycidyl Ether	376
Allyl Isothiocyanate	234
Allyl Isovalerate	253
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2-Amino-5-Nitrophenol	334
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Ampicillin Trihydrate	318
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Asbestos, Chrysotile (Rats)	295
Asbestos, Crocidolite	280
Asbestos, Tremolite	277
L-Ascorbic Acid	247
AZT and AZT/α-Interferon A/D	469
Barium Chloride Dihydrate	432
Benzaldehyde	378
Benzene	289
Benzethonium Chloride	438
Benzofuran	370
Benzyl Acetate (Gavage)	250
Benzyl Acetate (Feed)	431
Benzyl Alcohol	343
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o-Benzyl-*p*-Chlorophenol (Mouse Skin)	444
2-Biphenylamine Hydrochloride	233
2,2-Bis(Bromomethyl)-1,3-Propanediol	452
Bis(2-Chloro-1-Methylethyl) Ether	239
Bisphenol A	215
Boric Acid	324
Bromodichloromethane	321
Bromoethane	363
1,3-Butadiene	288
1,3-Butadiene	434
t-Butyl Alcohol	436
Butyl Benzyl Phthalate	213
Butyl Benzyl Phthalate	458
n-Butyl Chloride	312
t-Butylhydroquinone	459
γ-Butyrolactone	406
Caprolactam	214
d-Carvone	381
Chloral Hydrate	502
Chloral Hydrate	503
Chlorinated and Chloraminated Water	392
Chlorendic Acid	304
Chlorinated Paraffins: C_{23}, 43% Chlorine	305
Chlorinated Paraffins: C_{12}, 60% Chlorine	308
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2-Chloroacetophenone	379
p-Chloroaniline Hydrochloride	351
Chlorobenzene	261
Chlorodibromomethane	282
Chloroethane	346
2-Chloroethanol	275
3-Chloro-2-Methylpropene	300
Chloroprene	467
1-Chloro-2-Propanol	477
Chlorpheniramine Maleate	317
C.I. Acid Orange 3	335
C.I. Acid Orange 10	211
C.I. Acid Red 14	220
C.I. Acid Red 114	405
C.I. Basic Red 9 Monohydrochloride	285
C.I. Direct Blue 15	397
C.I. Direct Blue 218	430
C.I. Disperse Blue 1	299
C.I. Disperse Yellow 3	222
C.I. Pigment Red 3	407
C.I. Pigment Red 23	411
C.I. Solvent Yellow 14	226
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Citral	505
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Coconut Oil Acid Diethanolamine Condensate	479
Codeine	455
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D&C Yellow No. 11	463
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Diallyl Phthalate (Mice)	242
Diallyl Phthalate (Rats)	284
4,4′-Diamino-2,2′-Stilbenedisulfonic Acid, Disodium Salt	412
2,4-Diaminophenol Dihydrochloride	401
1,2-Dibromo-3-Chloropropane	206
1,2-Dibromoethane	210
2,3-Dibromo-1-Propanol	400
1,2-Dichlorobenzene (*o*-Dichlorobenzene)	255
1,4-Dichlorobenzene (*p*-Dichlorobenzene)	319
p,p′-Dichlorodiphenyl sulfone	501
2,4-Dichlorophenol	353
2,6-Dichloro-*p*-Phenylenediamine	219
1,2-Dichloropropane	263
1,3-Dichloropropene (Telone II)	269
Dichlorvos	342
Dietary Restriction	460
Diethanolamine	478
Di(2-Ethylhexyl) Adipate	212
Di(2-Ethylhexyl) Phthalate	217
Diethyl Phthalate	429
Diglycidyl Resorcinol Ether	257
3,4-Dihydrocoumarin	423
1,2-Dihydro-2,2,4-Trimethylquinoline (Monomer)	456
Dimethoxane	354
3,3′-Dimethoxybenzidine Dihydrochloride	372
N,N-Dimethylaniline	360
3,3′-Dimethylbenzidine Dihydrochloride	390
Dimethyl Hydrogen Phosphite	287
Dimethyl Methylphosphonate	323
Dimethyl Morpholinophosphoramidate	298
Dimethylvinyl Chloride	316
Diphenhydramine Hydrochloride	355
5,5-Diphenylhydantoin	404
Dipropylene Glycol	511
Elmiron®	512
Emodin	493
Ephedrine Sulfate	307
Epinephrine Hydrochloride	380

Chemical	TR No.
1,2-Epoxybutane	329
Erythromycin Stearate	338
Ethyl Acrylate	259
Ethylbenzene	466
Ethylene Glycol	413
Ethylene Glycol Monobutyl Ether	484
Ethylene Oxide	326
Ethylene Thiourea	388
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FD&C Yellow No. 6	208
Fumonisin B_1	496
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Furfural	382
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4-Hexylresorcinol	330
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Methylene Chloride	306
4,4´-Methylenedianiline Dihydrochloride	248
Methyleugenol	491
Methyl Methacrylate	314
N-Methylolacrylamide	352
Methylphenidate Hydrochloride	439
Mirex	313
Molybdenum Trioxide	462
Monochloroacetic Acid	396
Monuron	266
Nalidixic Acid	368
Naphthalene (Mice)	410
Naphthalene (Rats)	500
Nickel (II) Oxide	451

Chemical	TR No.
Nickel Sulfate Hexahydrate	454
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p-Nitrobenzoic Acid	442
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