NTP TECHNICAL REPORT

ON THE

# TOXICOLOGY AND CARCINOGENESIS

# STUDIES OF

# TRIETHANOLAMINE

(CAS NO. 102-71-6)

# IN F344/N RATS AND B6C3F$_1$ MICE

(DERMAL STUDIES)

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

November 1999

NTP TR 449

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

## FOREWORD

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

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

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

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

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

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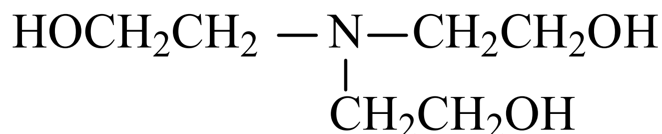
# ABSTRACT



**TRIETHANOLAMINE**

CAS No. 102-71-6

Chemical Formula: $C_6H_{15}NO_3$ Molecular Weight: 149.19

**Synonyms:** Nitrilo-2,2′,2′′-triethanol; 2,2′,2′′-nitrilotriethanol; 2,2′,2′′-nitrilotrisethanol; TEA; triaethanolamin-NG; triethanolamin; triethylolamine; tri(hydroxyethyl)amine; 2,2′,2′′-trihydroxytriethylamine; trihydroxytriethylamine; tris(hydroxyethyl)amine; tris(2-hydroxyethyl)amine; triethylolamine; trolamine
**Trade Names:** Daltogen; Sterolamide; Thiofaco T-35

Triethanolamine is widely used as an ingredient in emulsifiers, thickeners, wetting agents, detergents, and alkalinizing agents in cosmetic products; as a chemical intermediate for anionic and nonionic surfactants and surface active agents in household cleaning agents, textiles, herbicides, pharmaceutical ointments, and other products; as a vulcanization accelerator in the manufacture of rubber; and in many other industrial applications. The National Cancer Institute nominated triethanolamine for study because of its widespread use in cosmetics and other consumer products, its high potential for worker exposure due to its many industrial uses, and its potential for conversion to the carcinogen *N*-nitrosodiethanolamine. Dermal application was chosen as the route of exposure to mimic the principal means of human exposure to triethanolamine and because considerable systemic exposure is achieved with this route. Male and female F344/N rats and B6C3F$_1$ mice received triethanolamine (purity 98% or greater) by dermal application for 13 weeks or 2 years. Genetic toxicology studies were conducted in *Salmonella typhimurium*, cultured Chinese hamster ovary cells, *Drosophila melanogaster*, and mouse peripheral blood erythrocytes.

## 13-Week Study in Rats

Groups of 10 male and 10 female rats were topically administered 0, 125, 250, 500, or 1,000 mg triethanolamine per kilogram body weight in acetone or 2,000 mg/kg neat triethanolamine, 5 days per week, for 13 weeks. All rats survived to the end of the study. Final mean body weights and weight gains of males and females administered 2,000 mg/kg and the mean body weight gain of females administered 1,000 mg/kg were significantly less than those of the vehicle controls. Clinical observations included irritation, scaliness, and crustiness of the skin at the site of application for males and females. Males also had discoloration, and two males administered 2,000 mg/kg had ulceration at the site of application. Changes in clinical pathology parameters were minor and consistent with inflammation at the site of application.

Kidney weights were generally greater in males and females administered 500, 1,000, or 2,000 mg/kg than in the vehicle controls. Microscopic lesions attributed to triethanolamine administration included acanthosis and inflammation at the site of application,

nephropathy in females, and hypertrophy of the pituitary gland pars intermedia in males and females. These lesions generally occurred with dose-related increases in incidence and severity in males and females.

## 13-Week Study in Mice

Groups of 10 male and 10 female mice were topically administered 0, 250, 500, 1,000, or 2,000 mg triethanolamine per kilogram body weight in acetone or 4,000 mg/kg neat triethanolamine, 5 days per week, for 13 weeks. All mice survived to the end of the study. The final mean body weight and weight gain of males in the 250 mg/kg group were less than those of the vehicle controls. Clinical findings were observed only in mice in the 4,000 mg/kg groups and included scaliness, irritation, and discoloration at the site of triethanolamine application for males and females and skin erosion at this site in one male.

The absolute kidney and liver weights of males and females administered 4,000 mg/kg were greater than those of the vehicle controls; relative kidney weights of males administered 1,000 mg/kg or greater and females in all dosed groups were also greater than those of the vehicle controls.

Microscopic examination of the skin of dosed mice indicated acanthosis and inflammation at the site of application. Acanthosis occurred in all dosed groups and in one vehicle control female; the severity increased with increasing dose in males and females. Inflammation was observed in males and females in the 4,000 mg/kg groups and in one female in the 2,000 mg/kg group.

## 2-Year Study in Rats

Based on the presence of acanthosis and inflammation at the site of application at the higher doses in the 13-week study, triethanolamine doses selected for the 2-year study in rats were 32, 63, and 125 mg/kg for males and 63, 125, and 250 mg/kg for females. Groups of 60 male and 60 female rats were topically administered triethanolamine in acetone 5 days per week for 103 weeks. Ten male and ten female rats from each group were evaluated at 15 months for organ weights and histopathology.

### *Survival, Body Weights, Clinical Findings, and Organ Weights*

The survival rate of females in the 250 mg/kg group was slightly less than that of the vehicle controls. The mean body weight of females administered 250 mg/kg ranged from 9% to 12% less than that of the vehicle controls between weeks 73 and 93. Male and female rats receiving triethanolamine had irritated skin at the site of application; in dosed females, the site of application also had a crusty appearance. The number of animals in which these findings were observed increased with increasing dose. At the 15-month interim evaluation, the absolute left and right kidney weights and relative right kidney weight of females administered 250 mg/kg were significantly greater than those of the vehicle controls.

### *Pathology Findings*

The incidence of acanthosis at the site of application in males administered 125 mg/kg and the incidences of acanthosis, inflammation, and ulceration in dosed females were greater than in the vehicle controls at the 15-month interim evaluation and at the end of the 2-year study. Males in the 125 mg/kg group also had greater incidences of inflammation and ulceration than the vehicle controls, and females receiving 125 or 250 mg/kg had greater incidences of epidermal erosion than the vehicle controls at 2 years. There were no skin neoplasms at or away from the site of application that were considered related to treatment with triethanolamine.

At the end of the study, renal tubule adenomas were observed in seven dosed males and in one vehicle control female and one female in the 63 mg/kg group. One male in the 125 mg/kg group and one female in the 250 mg/kg group had renal tubule hyperplasia. Extended (step-section) evaluation of the kidneys of all male rats revealed additional renal tubule adenomas in one vehicle control male, one male in the 32 mg/kg group, two males in the 63 mg/kg group, and three males in the 125 mg/kg group (including one male from the 15-month interim evaluation). An oncocytoma was also identified in one male in the 32 mg/kg group. Hyperplasia was identified in eight additional vehicle control males and in 19 additional dosed males. The total incidences (combined standard and extended evaluations) of renal tubule adenoma in dosed male rats were slightly greater than the vehicle

control incidence (vehicle control, 1/50; 32 mg/kg, 2/50; 63 mg/kg, 6/49; 125 mg/kg, 4/50). The total incidence of hyperplasia in dosed and vehicle control males was similar (9/50, 8/50, 7/49, 6/50). The severity of hyperplasia in males in the 32 and 125 mg/kg groups was greater than that in the vehicle controls.

## 2-Year Study in Mice

Based on dose-related inflammation at the site of application in the 13-week study, triethanolamine doses selected for the 2-year study in mice were 200, 630, and 2,000 mg/kg for males and 100, 300, and 1,000 mg/kg for females. Groups of 60 male and 60 female mice were topically administered triethanolamine in acetone 5 days per week for 103 weeks. Ten male and ten female mice from each group were evaluated at 15 months for organ weights and histopathology.

### *Survival, Body Weights, Clinical Findings, and Organ Weights*

Survival rates of all dosed groups of males and females were similar to those of the vehicle controls. The mean body weight of males administered 2,000 mg/kg ranged from 8% to 10% less than that of the vehicle controls from week 69 through the end of the study. Clinical findings included irritation and discoloration of the skin at the site of application for most males in the 2,000 mg/kg group and a few females in the 1,000 mg/kg group; males administered 200 or 630 mg/kg also had skin irritation. At the 15-month interim evaluation, the right kidney weights of male mice that received 630 or 2,000 mg/kg and the left kidney weights of males that received 2,000 mg/kg were significantly greater than those of the vehicle controls.

### *Pathology Findings*

Acanthosis and inflammation of the skin were observed at the site of application in male and female mice at the 15-month interim evaluation and at the end of the 2-year study. In males in the 2,000 mg/kg group, the incidences of both lesions were significantly greater than those in the vehicle controls at both time points; however, the severities of acanthosis and inflammation did not increase with dose. At the end of the study, the incidence of inflammation in females in the 1,000 mg/kg group was significantly greater than that in the vehicle controls. One vehicle control male and two males in each of the 630 and 2,000 mg/kg groups had ulcers at the site of application.

At the 15-month interim evaluation, hepatocellular carcinomas were observed in dosed and vehicle control males and hepatocellular adenomas in dosed and vehicle control males and females; however, the incidences were not dose related. Nonneoplastic lesions observed at 15 months included foci of cellular alteration in a few dosed males and females; eosinophilic foci were also observed in two vehicle control females.

At the end of the 2-year study, females in the 1,000 mg/kg group had significantly greater incidences of hepatocellular adenoma and multiple adenomas and a greater combined incidence of hepatocellular adenoma and carcinoma than the vehicle controls (adenoma: vehicle control, 22/50; 100 mg/kg, 22/50; 300 mg/kg, 24/50; 1,000 mg/kg, 40/50; multiple adenomas: 11/50, 9/50, 13/50, 29/50; combined adenoma and carcinoma: 23/50, 26/50, 28/50, 41/50). Females in the 300 mg/kg group had significantly greater incidences of hepatocellular carcinoma (1/50, 4/50, 7/50, 5/50) and eosinophilic foci (9/50, 10/50, 18/50, 16/50) than the vehicle controls.

Incidences of hepatocellular adenoma and multiple adenomas in males in the 2,000 mg/kg group were significantly greater than those in the vehicle controls (adenoma: vehicle control, 27/50; 200 mg/kg, 27/50; 630 mg/kg, 29/50; 2,000 mg/kg, 37/50; multiple adenomas: 17/50, 18/50, 17/50, 29/50). Three males in the 2,000 mg/kg group had hepatoblastomas, and males in this group also had significantly greater incidences of hepatocellular neoplasms (combined) (adenoma, carcinoma, and hepatoblastoma: 31/50, 34/50, 33/50, 42/50) and eosinophilic foci (10/50, 17/50, 11/50, 23/50) than the vehicle controls.

Male mice had a pattern of nonneoplastic liver lesions along with silver-staining helical organisms within the liver which suggested an infection with *Helicobacter hepaticus*. With polymerase chain reaction-based assays and culture, the presence of an organism compatible with *H. hepaticus* was confirmed. An increased incidence of hepatocellular neoplasms in male mice has been shown to be associated with

*H. hepaticus* infection when hepatitis is also present. Therefore, interpretation of the increased incidence of hepatocellular neoplasms in mice was confounded.

## Genetic Toxicology

Triethanolamine was not mutagenic in any of the *in vitro* or *in vivo* short-term tests performed by the NTP. It did not induce mutations in *Salmonella typhimurium*, and no induction of sister chromatid exchanges or chromosomal aberrations in cultured Chinese hamster ovary cells exposed to triethanolamine was noted. These *in vitro* tests were conducted with and without S9 metabolic activation.

Triethanolamine did not induce sex-linked recessive lethal mutations in germ cells of adult male *Drosophila melanogaster* exposed by feeding or injection. No increase in the frequency of micronucleated erythrocytes was observed in peripheral blood samples of male and female mice that received dermal applications of triethanolamine for 13 weeks.

## Conclusions

Under the conditions of these dermal studies, there was *equivocal evidence of carcinogenic activity** of triethanolamine in male F344/N rats based on a marginal increase in the incidence of renal tubule cell adenoma. There was *no evidence of carcinogenic activity* in female F344/N rats receiving 63, 125, or 250 mg triethanolamine per kilogram body weight. The study in male and female B6C3F$_1$ mice was considered *inadequate*, because the presence of a *Helicobacter hepaticus* infection complicated interpretation of the relationship between triethanolamine administration and liver neoplasms in these animals.

Dosed rats and mice had varying degrees of acanthosis and inflammation, dosed rats had ulceration, and dosed female rats had epidermal erosion at the site of skin application.

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* Explanation of Levels of Evidence of Carcinogenic Activity is on page 11. A summary of the Technical Reports Review Subcommittee comments and the public discussion on this Technical Report appears on page 14.

## Summary of the 2-Year Carcinogenesis and Genetic Toxicology Studies of Triethanolamine

| | Male F344/N Rats | Female F344/N Rats | Male $B6C3F_1$ Mice | Female $B6C3F_1$ Mice |
|---|---|---|---|---|
| **Doses in acetone by dermal application** | 0, 32, 63, or 125 mg/kg | 0, 63, 125, or 250 mg/kg | 0, 200, 630, or 2,000 mg/kg | 0, 100, 300, or 1,000 mg/kg |
| **Body weights** | Dosed groups similar to vehicle controls | 250 mg/kg group slightly less than vehicle controls | 2,000 mg/kg group slightly less than vehicle controls | Dosed groups similar to vehicle controls |
| **2-Year survival rates** | 21/50, 11/50, 18/49, 19/50 | 25/50, 29/50, 25/50, 18/50 | 46/50, 40/50, 39/50, 41/50 | 39/50, 40/50, 38/50, 37/50 |
| **Nonneoplastic effects** | Skin, site of application: acanthosis (1/50, 1/50, 1/49, 9/50); inflammation (0/50, 2/50, 0/49, 8/50); ulcer (0/50, 0/50, 0/49, 5/50)<br>Kidney: severity of hyperplasia (standard and extended evaluations - 1.7, 2.6, 1.5, 2.5) | Skin, site of application: acanthosis (2/50, 10/50, 30/50, 32/50); inflammation (2/50, 10/50, 30/50, 32/50); ulcer (2/50, 7/50, 22/50, 27/50); epidermal erosion (1/50, 6/50, 16/50, 14/50) | Skin, site of application: acanthosis (2/50, 1/50, 6/50, 11/50); inflammation (2/50, 0/50, 7/50, 11/50)<br>Liver: eosinophilic foci (10/50, 17/50, 11/50, 23/50) | Skin, site of application: acanthosis (0/50, 2/50, 1/50, 3/50); inflammation (0/50, 2/50, 2/50, 5/50)<br>Liver: eosinophilic foci (9/50, 10/50, 18/50, 16/50) |
| **Neoplastic effects** | None | None | None | None |
| **Uncertain findings** | Kidney: renal tubule adenoma (standard evaluation - 0/50, 1/50, 4/49, 2/50; standard and extended evaluations combined - 1/50, 2/50, 6/49, 4/50) | None | Liver: hepatocellular adenoma (27/50, 27/50, 29/50, 37/50); hepatoblastoma (0/50, 0/50, 0/50, 3/50); hepatocellular adenoma, hepatocellular carcinoma, or hepatoblastoma (31/50, 34/50, 33/50, 42/50)<br>Incidences of liver neoplasms in mice could not be interpreted due to the presence of *Helicobacter hepaticus* infection. | Liver: hepatocellular adenoma (22/50, 22/50, 24/50, 40/50); hepatocellular carcinoma (1/50, 4/50, 7/50, 5/50); hepatocellular adenoma or carcinoma (23/50, 26/50, 28/50, 41/50) |
| **Level of evidence of carcinogenic activity** | Equivocal evidence | No evidence | Inadequate study (*H. hepaticus* infection) | Inadequate study (*H. hepaticus* infection) |

**Summary of the 2-Year Carcinogenesis and Genetic Toxicology Studies of Triethanolamine** (continued)

| **Genetic toxicology** | |
|---|---|
| *Salmonella typhimurium* gene mutations: | Negative in strains TA98, TA100, TA1535, and TA1537 with and without S9 |
| Sister chromatid exchanges | |
| Cultured Chinese hamster ovary cells *in vitro*: | Negative with and without S9 |
| Chromosomal aberrations | |
| Cultured Chinese hamster ovary cells *in vitro*: | Negative with and without S9 |
| Sex-linked recessive lethal mutations | |
| *Drosophila melanogaster*: | Negative when administered in feed or by injection |
| Micronucleated erythrocytes | |
| Mouse peripheral blood *in vivo*: | Negative |

## EXPLANATION OF LEVELS OF EVIDENCE OF CARCINOGENIC ACTIVITY

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

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

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

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

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

## NATIONAL TOXICOLOGY PROGRAM BOARD OF SCIENTIFIC COUNSELORS TECHNICAL REPORTS REVIEW SUBCOMMITTEE

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.

## November 29, 1994

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## October 30, 1998

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## SUMMARY OF TECHNICAL REPORTS REVIEW SUBCOMMITTEE COMMENTS

*November 29, 1994:* The draft Technical Report on the toxicology and carcinogenesis studies of triethanolamine first received public review by the National Toxicology Program's Board of Scientific Counselors' Technical Reports Review Subcommittee on 29 November 1994. The review meeting was held at the National Institute of Environmental Health Sciences, Research Triangle Park, NC.

Dr. J.R. Bucher, NIEHS, introduced the toxicology and carcinogenesis studies of triethanolamine by discussing the uses of the chemical, describing the experimental design, reporting on survival and body weight effects, and commenting on possible chemical-related neoplasms and nonneoplastic lesions in rats and mice. The proposed conclusions were *equivocal evidence of carcinogenic activity* in male F344/N rats and male B6C3F$_1$ mice, *no evidence of carcinogenic activity* in female F344/N rats, and *some evidence of carcinogenic activity* in female B6C3F$_1$ mice.

Dr. Bucher noted that *Helicobacter hepaticus* had first been described in the literature in 1994 by a member of the Subcommittee, Dr. Ward. He said the infection is associated with a chronic active hepatitis in many strains of mice and appears to affect males more than females. It causes a focal necrosis and inflammation progressing to hepatocytomegaly, oval cell hyperplasia, and cholangitis. In male mice this appears to lead to an increase in the incidence of liver neoplasms. Dr. J.R. Hailey, NIEHS, described the histopathologic appearance of livers from infected animals and the stain used to identify the bacteria. He reported that infection with *H. hepaticus* was suspected or confirmed in four other NTP studies in mice and that the impact on study interpretation was being assessed. Dr. G.N. Rao, NIEHS, said the presence of the bacteria has been reported in a number of laboratories and animal production facilities around the country. However, he stated that the NTP management procedure in production colonies of terminating and restarting colonies every 2 to 3 years made the problem self-limiting in NTP laboratories and believed that the colonies have been free of *H. hepaticus* since 1991 or before.

Dr. Ward, a principal reviewer, agreed with the proposed conclusions. He suggested that because of the infection, further information on sources of mice should be made clear in the Technical Report and would help to indicate that the infection is limited to certain suppliers of mice. Dr. Ward thought the rationale for using the dermal route was adequate but said the report should indicate that the skin application study was approximately equivalent to a low-dose oral study because of significant skin absorption. Dr. Bucher said there was not sufficient dose-response information to make quantitative comparison of oral versus skin absorption of the chemical.

Dr. Miller, the second principal reviewer, agreed with the proposed conclusions, although she said more clarification was needed on why the level of evidence for carcinogenicity in female mice was *some evidence* rather than *clear evidence*. Because triethanolamine is used extensively in more than 2,500 cosmetics, she said the chemical may also contact mucous membranes, especially around the eyes and mouth, and suggested consideration be given to oral/mucous membrane testing. Dr. Bucher said that Japanese studies using 1% and 2% drinking water solutions did not give any strong indication of carcinogenicity. Dr. Miller wondered how the doses used would compare with doses humans might encounter, e.g., in a 5% cream applied daily to the face. Dr. Bucher estimated from a personal communication that such a human dose would not differ greatly from the dose in rats.

Dr. Karol, the third principal reviewer, was unable to attend the meeting but had submitted her review, which Dr. L.G. Hart, NIEHS, read into the record. Dr. Karol agreed with the proposed conclusions. She said that justification was needed for selection of acetone as the solvent for the studies. Dr. Karol also said that in view of reports that the chemical has sensitization potential, the skin lesions and "active inflammation" should be discussed in connection with possible contact dermatitis. Dr. Bucher agreed that a case could be made for contact dermatitis being associated, but in looking at the lesions histologically, there was little evidence that the inflammatory process had an allergic component. There were no perivascular lymphoid infiltrates or edematous reactions with eosinophilic infiltrates which might be expected if contact dermatitis were present.

There was further discussion about the possible impact of *H. hepaticus* in female mice and whether or not infection could be a confounder in the etiology of the liver lesions as in male mice. Dr. Bucher said the diagnosis of oval cell hyperplasia or karyomegaly was observed in only one mid-dose female mouse, and although an exhaustive evaluation was not performed, the bacteria were not believed to be a factor in female mice.

Dr. Miller moved that the Technical Report on triethanolamine be accepted with the revisions discussed and with the conclusions as written: for male rats and mice, *equivocal evidence of carcinogenic activity*, for female rats, *no evidence of carcinogenic activity*, and for female mice, *some evidence of carcinogenic activity*. Dr. Russo seconded the motion, which was accepted unanimously with seven votes.

*Subsequent Investigations:* Subsequent to the 29 November 1994 public review, the NTP carried out an extensive investigation into the extent of evidence of *H. hepaticus* infection in NTP studies as well as the apparent influence of this infection on neoplasm rates in all organs in male and female mice (see Appendix L). B6C3$F_1$ mice from 12 NTP 2-year carcinogenesis studies were found to be infected with *H. hepaticus*. Many of the male mice from nine of these studies had an associated hepatitis, and these nine studies were considered "affected" studies. The incidences of neoplasms (both hepatocellular neoplasms and hemangiosarcoma) of the liver, but not of other organs, were found to be increased in control male mice in the affected studies compared to the incidences in control males from 26 unaffected contemporary studies. Other observations further differentiated control male mice from affected and unaffected studies. H-*ras* codon 61 CAA-to-AAA mutations were less common in liver neoplasms in males from affected studies compared to historical and unaffected study controls. In addition, increases in cell proliferation rates and apoptosis were observed in the livers of male mice with *H. hepaticus*-associated hepatitis. These data support the hypothesis that the increased incidence of liver neoplasms is associated with *H. hepaticus* and that hepatitis may be important in the pathogenesis. Therefore, it was concluded that the interpretation of carcinogenic effects in the liver of B6C3$F_1$ mice may be confounded if *H. hepaticus*-associated hepatitis is present, and that studies in which liver neoplasia was the only effect in male mice with evidence of *H. hepaticus*-associated hepatitis should be considered inadequate for evaluation of carcinogenesis.

This evaluation did not reveal a significant influence of *H. hepaticus* infection on the occurrence of any neoplasm type in female mice. Nonetheless, it was decided that to repeat the study with uninfected mice was the only way to rigorously rule out an effect of *H. hepaticus* on the triethanolamine-induced incidence of hepatocellular neoplasms in female mice. Therefore, in 1998 a second evaluation of triethanolamine was begun using the same study design and same chemical in the same laboratory as the study reported in this Technical Report. This study is being performed with male and female B6C3$F_1$ mice.

*October 30, 1998:* The proposal to change the level of evidence for the male mouse study from *equivocal evidence of carcinogenic activity* to *inadequate study* was brought before the NTP's Board of Scientific Counselors' Technical Reports Review Subcommittee on 30 October 1998. Dr. Bucher briefly reviewed the study findings and outlined the NTP's position concerning the interpretation of studies in which there was evidence of *H. hepaticus* infection. This position and the lines of evidence which led to its adoption were presented to the Subcommittee at their meeting on 11 and 12 December 1996 by Dr. Hailey.

Dr. Belinsky, a principal reviewer, began his comments with several suggestions concerning the discussion of the kidney neoplasm findings in male rats and then turned to concerns regarding the *H. hepaticus* issue. He said that while he understood the NTP's position, he was uncomfortable concluding that the evidence was sufficient to rule out a possible influence of *H. hepaticus* infection on the liver neoplasm response in female mice. He suggested that the study may not, in fact, have been totally adequate and that the conclusion of *some evidence of carcinogenic activity* in female mice be amended to indicate that these animals were infected with *H. hepaticus*.

Dr. Hecht, the second principal reviewer, also said that he had not fully understood that female mice also

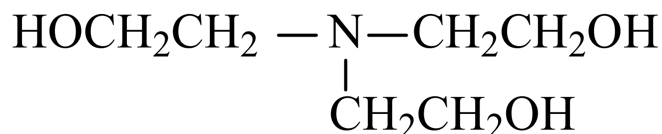
were infected with the organism in studies where male mice were infected and manifested microscopic changes in the liver from the infection. Dr. Hecht suggested that the conclusion for female mice should be reconsidered. Both he and Dr. Belinsky indicated that their proposal to reconsider the conclusion was influenced by the fact that the female mouse study was being repeated. Dr. Hecht also asked that additional information be added to the report concerning the possibility that *N*-nitrosodiethanolamine, a potential contaminant, might have influenced the results.

Dr. Bucher responded that the NTP had had technical difficulty with the assessment of possible *N*-nitrosodiethanolamine contamination in the triethanolamine and diethanolamine stocks used in the NTP studies. He pointed out that the potential carcinogenicity of *N*-nitrosodiethanolamine in mice has not been established, so it was difficult to predict the impact of this contaminant.

Dr. Fischer, the third principal reviewer, was unable to attend the meeting, but Dr. Hart read her written comments. She agreed with the proposal to designate the male mouse study as *inadequate* and questioned whether the doses administered to the female mice were high enough to adequately reveal possible neoplastic effects in the kidney.

The panel then returned to the discussion of the adequacy of the female mouse study. After listening to public comment on this issue, Dr. Carlson called for a motion. Dr. Belinsky moved that the conclusions of *equivocal evidence of carcinogenic activity* in male rats, *no evidence of carcinogenic activity* in female rats, and *inadequate study* in male mice, as proposed by the NTP, be accepted by the panel and that the study in female mice be judged *inadequate*. Dr. Hecht seconded the motion, which was accepted by three yes votes (Drs. Belinsky, Hecht, and Medinsky) to two no votes (Drs. Bailer and Cullen), with one abstention (Dr. Bus).

# INTRODUCTION



### TRIETHANOLAMINE

CAS No. 102-71-6

Chemical Formula: $C_6H_{15}NO_3$ Molecular Weight: 149.19

**Synonyms:** Nitrilo-2,2′,2′′-triethanol; 2,2′,2′′-nitrilotriethanol; 2,2′,2′′-nitrilotrisethanol; TEA; triaethanolamin-NG; triethanolamin; triethylolamine; tri(hydroxyethyl)amine; 2,2′,2′′-trihydroxytriethylamine; trihydroxytriethylamine; tris(hydroxyethyl)amine; tris(2-hydroxyethyl)amine; triethylolamine; trolamine
**Trade Names:** Daltogen; Sterolamide; Thiofaco T-35

## CHEMICAL AND PHYSICAL PROPERTIES

Triethanolamine, with a melting point of 21.6° C, is a colorless to pale yellow, viscous, hygroscopic liquid with a slight ammonia-like odor. It has a boiling point of 335.4° C at 760 mm, a specific gravity of 1.124 (20/4° C), and a vapor pressure less than 0.01 mm at 20° C. Triethanolamine is miscible with water, methanol, or acetone and is slightly soluble in ether or benzene; it readily forms salts with organic and inorganic acids and turns brown on exposure to air and light (*Remington's Pharmaceutical Sciences*, 1980; CIR, 1983; *Merck Index*, 1989). It is combustible when heated and may decompose to oxides of nitrogen (Lewis, 1990).

## PRODUCTION, USE, AND HUMAN EXPOSURE

Triethanolamine is commercially produced, together with mono- and diethanolamine, by aminating ethylene oxide with ammonia; triethanolamine is separated from the mixture by distillation (*Kirk-Othmer*, 1978). The reported annual production of triethanolamine in the United States during 1991 was 86 million kilograms (USITC, 1993).

Ethanolamines are chemically bifunctional and undergo reactions typical of both amines and alcohols (CIR, 1983). Industrially significant reactions of the ethanolamines include the reaction with long-chain fatty acids to form neutral ethanolamine soaps and "sweetening" of natural gas through reactions with sulfuric acid, carbon dioxide, or other acid constituents to form water-soluble salts (*Kirk-Othmer*, 1978; Melnick and Tomaszewski, 1990). Ethanolamines can also act as antioxidants in the autoxidation of animal and vegetable fats (CIR, 1983). Triethanolamine, in combination with fatty acids, is used extensively in cosmetic formulations including emulsifiers, thickeners, wetting agents, detergents, and alkalizing agents. In 1981, triethanolamine was reported to be present in 2,757 cosmetic products at concentrations of up to 5%; these products included creams, lotions, skin cleansers, shampoos, hair care and coloring agents, permanent wave lotions, deodorants, fragrances, makeup, nail polish and polish remover, and cuticle softeners and removers (CIR, 1983).

Triethanolamine is a chemical intermediate for both anionic and nonionic surfactants. It is widely used in the manufacture of emulsifiers and dispersing agents for household detergents and polishes; textiles (lubricants, dyes, and antistatic agents), agricultural chemicals (herbicides), mineral and vegetable oils, paraffin and waxes, pharmaceutical ointments, and petroleum demulsifiers. Triethanolamine is used in the rubber industry as a vulcanization accelerator, in the tanning of hides as a humectant and softening agent, and in the manufacture of synthetic resins, plasticizers, adhesives, and sealants. It is a solvent for casein, shellac, and dyes. It also increases the penetration of organic liquids into wood and paper. The metal-chelating properties of triethanolamine are used in many industrial applications such as corrosion inhibition, electroplating, metal cleaning and rust removal, and the preparation of photographic chemicals and soldering fluxes. The fatty acid salts of triethanolamine are used extensively in lubricating and metalworking fluids (cutting oils). Addition of small amounts of triethanolamine or its salts reduces particle agglomeration during the grinding of cement and reduces set time and increases the early strength of concrete (*Kirk-Othmer*, 1978; *Hawley's Condensed Chemical Dictionary*, 1987; *Merck Index*, 1989; Melnick and Tomaszewski, 1990). Articles intended for use in the production, processing, and packaging of food may contain triethanolamine (21 CFR, Parts 175, 176, 177, and 178).

The most widespread human exposure to ethanolamines occurs through the use of cosmetics (CIR, 1983). Dermal exposure also results from contact with household detergents, other surfactants containing this compound, pharmaceutical ointments, cutting fluids, adhesives, and sealants. Although the Pollutant Strategies Branch of the United States Environmental Protection Agency (USEPA) identified triethanolamine as an air pollutant (Melnick and Tomaszewski, 1990), significant industrial exposure to triethanolamine by inhalation of adhesives, sealants, or cutting fluids appears unlikely due to its low vapor pressure; the chief risk would be from direct local contact of the skin or eyes with the undiluted, unneutralized liquid (*Patty's*, 1981). The National Occupational Exposure Survey for 1981 to 1983 has estimated that more than 1.7 million workers were potentially exposed to triethanolamine in the United States (NIOSH, 1990). The threshold limit value for triethanolamine, adopted in 1993, was based primarily on skin and eye irritation and is 5 mg/m$^3$ (ACGIH, 1994).

The Cosmetic Ingredient Review (CIR) Expert Panel (1983) concluded that the use of mono-, di-, and triethanolamine is safe in cosmetic formulations designed for brief, discontinuous use followed by thorough rinsing of the skin. They further concluded that the concentration of ethanolamine should not exceed 5% in cosmetic products intended for prolonged contact with the skin. In the presence of nitrite, oxides of nitrogen, or 2-bromo-2-nitropropane-1,3-diol, an antimicrobial agent used in cosmetics, di- and triethanolamine may be readily nitrosated to *N*-nitrosodiethanolamine (CIR, 1983), which is a known liver, kidney, and nasal carcinogen in laboratory animals (Hoffmann *et al.*, 1982; Preussmann *et al.*, 1982; Lijinsky and Kovatch, 1985). *N*-Nitrosodiethanolamine has been identified in a variety of cosmetic products at concentrations up to 48,000 ppb (Fan *et al.*, 1977a); the CIR panel concluded, therefore, that di- and triethanolamines should not be used in cosmetic products that contain *N*-nitrosating agents as intentional ingredients or potential contaminants (CIR, 1983).

Fan *et al.* (1977b) reported that before 1977, the majority of synthetic cutting (metalworking) fluids used in the United States contained up to 45% triethanolamine and 18% sodium nitrite, with *N*-nitrosodiethanolamine present as an impurity at concentrations of up to 3%. Concern about potential human health risks posed by exposure to nitrosamines in metalworking fluids led the USEPA to issue a regulation prohibiting the use of nitrosating agents in any metalworking fluid containing a triethanolamine salt of a tricarboxylic acid complex (40 CFR, § 747.200). Furthermore, questions about the safety of hair color products containing di- and triethanolamine have been raised as a result of studies showing mutagenic activity in 89% (150/169) of oxidative-type hair dye formulations tested in *Salmonella typhimurium* (Ames *et al.*, 1975).

## Environmental Impact

Triethanolamine may be released into the environment in emissions or effluents from manufacturing or industrial sites, from the disposal of consumer products containing triethanolamine, from the application of agricultural chemicals in which triethanolamine is

used as a dispersing agent, or during use of an aquatic herbicide containing a copper-triethanolamine complex (*Hawley's Condensed Chemical Dictionary*, 1987). Residual triethanolamine in soil may also leach into the groundwater. The half-life of triethanolamine in soil and water ranges from days to weeks; it biodegrades fairly rapidly following acclimation (HSDB, 1994). Ethanolamines have been shown to be selectively toxic to green algae (*Scenedesmus quadricauda*) (Bringmann and Kühn, 1980). In the atmosphere, triethanolamine primarily exists in the vapor phase; the vapor, which has a half-life of 4 hours, is expected to react with photochemically generated hydroxyl radicals in the atmosphere. The complete solubility of triethanolamine in water suggests that this compound may also be removed from the atmosphere by precipitation. Volatilization of triethanolamine from water and moist soil surfaces has been estimated to be negligible (Eisenreich *et al.*, 1981; Atkinson, 1987; HSDB, 1994).

## ABSORPTION, DISTRIBUTION, METABOLISM, AND EXCRETION

### *Experimental Animals*

Triethanolamine may be absorbed through the skin and in the gastrointestinal tract. In a comparative pharmacokinetics and metabolism study, dermal absorption of [$^{14}$C]-triethanolamine was slower and less extensive in F344 rats than in C3H/HeJ mice, although the tissue distribution of radioactivity was similar (cited by Melnick and Tomaszewski, 1990; no further details were given). In mice that received a single 1,000 mg/kg dermal application, approximately 60% of the radioactivity was recovered from the urine and 20% was recovered from the feces 48 hours after dosing; less than 10% was detected in the skin at the site of application. More than 95% of the radioactivity recovered in the urine was identified as the parent compound, indicating that triethanolamine does not undergo extensive biotransformation in mice. The serum half-life of [$^{14}$C]-triethanolamine in mice was approximately 9.5 hours after either a 1 mg/kg intravenous injection or a 1,000 mg/kg dermal application (cited by Melnick and Tomaszewski, 1990). In rats, a single oral dose (2 to 3 mg/kg) of [$^{14}$C]-triethanolamine was rapidly absorbed and excreted mainly in the urine as unchanged parent compound (Kohri *et al.*, 1982). Twenty-four hours after dosing, 53% of the radioactivity was recovered in the urine and 20% was recovered in the feces. A small amount of a metabolite, triethanolamine glucuronide, was also detected.

### *Humans*

No information on the pharmacokinetics and metabolism of triethanolamine in humans was found in the literature.

## TOXICITY

### *Experimental Animals*

The toxicity of triethanolamine was the subject of a review by Knaak *et al.* (1997). The acute and chronic toxicity of triethanolamine is generally considered to be low (Kindsvatter, 1940; Melnick and Tomaszewski, 1990). Triethanolamine toxicity has been demonstrated in animals following administration by inhalation, injection, oral routes (gavage, feed, and drinking water), and dermal application. In a study comparing the relative toxicities of the ethanolamines (*Patty's*, 1981), symptoms in dogs following intravenous injection included increased blood pressure, diuresis, salivation, and pupillary dilation; larger doses caused sedation, coma, and death following a decrease in blood pressure and cardiac collapse. Symptoms were most severe with monoethanolamine and least severe with triethanolamine.

The acute oral $LD_{50}$ of triethanolamine was reported to be 8 to 9 g/kg in albino rats and 8 g/kg in guinea pigs (Kindsvatter, 1940; Smyth *et al.*, 1951). Gross lesions in the animals that died were confined to the gastrointestinal tract and included gastric dilatation, congestion, and focal hemorrhage in the stomach and dilatation of intestinal blood vessels. Kindsvatter (1940) suggested that the acute toxicity of triethanolamine was related to its alkalinity, based on the survival of one guinea pig fed 10 g/kg neutralized with hydrochloric acid; this dose exceeds the oral $LD_{50}$ (8 g/kg) of triethanolamine when administered as the free base. The acute oral $LD_{50}$ values for triethanolamine ranged from 4.2 to 11.3 g/kg in rats and 5.4 to 7.8 g/kg in mice (BIBRA, 1990).

In a 90-day study in Carworth-Wistar rats administered triethanolamine in feed at daily doses of 5 to 2,610 mg/kg, the no-observed-effect level (NOEL) was 80 mg/kg. Decreased body weight gains were observed in rats administered 1,270 mg/kg or above. Microscopic lesions of the kidney, liver, lung, or small intestine and a low incidence of mortality occurred at a concentration of 730 mg/kg or above. Liver and kidney weight effects occurred at concentrations as low as 170 mg/kg (Smyth *et al.*, 1951). In other studies (Kindsvatter, 1940), doses ranging from 200 to 1,600 mg/kg were administered to albino rats daily in feed for up to 17 weeks or to guinea pigs 5 days per week by gavage for up to 120 doses. Slight, reversible changes were present in the kidney (cloudy swelling of the convoluted tubules and Henle's loop) at all doses and in the liver (hepatocellular cloudy swelling and fatty change) at doses of 400 mg/kg and higher. Although liver toxicity was not apparent in a more recent 2-year study with Fischer 344/DuCrj rats administered 1% or 2% triethanolamine in drinking water *ad libitum*, the occurrence of dose-related kidney toxicity (acceleration of chronic nephropathy, mineralization of the renal papilla, nodular hyperplasia of the pelvic mucosa, and pyelonephritis with or without papillary necrosis) indicated that even the 1% dose level was not well tolerated by rats (Maekawa *et al.*, 1986); effects were more severe in females than in males. Due to increased mortality and decreased body weight gains in females that received 2% triethanolamine, doses administered to females were halved from week 69 to the end of the study. In contrast, $B6C3F_1$ mice tolerated the same concentrations of triethanolamine in drinking water for 82 weeks without adverse effects on survival or organ weights and with no increased incidences of histopathologic lesions (Konishi *et al.*, 1992); body weights of mice receiving 2% were slightly less than those of the controls, however.

The dermal toxicity of triethanolamine has been evaluated in mice, rats, rabbits, and guinea pigs under various experimental conditions. Guinea pigs dosed with 8 g/kg of undiluted triethanolamine daily by dermal application, 5 days per week, died after 2 to 17 applications (Kindsvatter, 1940). Histopathologic changes included generalized congestion of the lungs, kidneys, liver, adrenal glands, and peritoneum; extravasation of fibrin into the alveoli of the lungs; cloudy swelling of the kidneys and liver; fatty change in the liver; and cellular infiltration and inflammation at the site of application, indicating that dermal absorption of triethanolamine is capable of producing systemic toxicity (Kindsvatter, 1940; Melnick and Tomaszewski, 1990).

The acute dermal toxicity of a single 2 g/kg application of undiluted triethanolamine was evaluated over a 24-hour period with a closed-patch test in rabbits (CIR, 1983). Triethanolamine was applied to six rabbits with intact skin and six with abraded skin. Mild to moderate erythema without edema occurred on both intact and abraded skin and resolved within 10 days. In another dermal study, a single application of 560 mg/kg to rabbits resulted in erythema and slight edema at the application site. Dermal applications of 2 mL/kg per day of a 2.5% aqueous solution of triethanolamine for 28 days produced only mild dermatitis in New Zealand rabbits (CIR, 1983). Triethanolamine (1% to 100%), applied dermally to male C3H mice 5 days per week for 2 weeks in 50 $\mu$L acetone, caused mild epidermal hyperplasia at the site of application with dosage solutions as low as 25% (cited by Melnick and Tomaszewski, 1990). In a follow-up study in which male and female C3H mice received dermal applications of 0%, 10%, 33%, or 100% triethanolamine in 50 $\mu$L acetone three times per week for 13 weeks, mild hyperplasia at the application site was observed in all dosed groups (Melnick and Tomaszewski, 1990; DePass *et al.*, 1995).

In a combined dermal and drinking water study, CBA $\times$ $C_{57}Bl_6$ mice received dermal applications of a 6.5% or 13% aqueous solution of triethanolamine, 1 hour per day, 5 days per week for 6 months, with or without additional oral administration of 1.4 mg/L in the drinking water (Kostrodymova *et al.*, 1976; CIR, 1983). No toxic effects were present in mice receiving the 6.5% solution. However, functional changes in the liver and central nervous system occurred 1 month after treatment began with the 13% solution, with or without additional triethanolamine in the drinking water, indicating that systemic toxicity had resulted from percutaneous absorption. Clinical pathology changes at 3 months included elevated lymphocyte and segmented neutrophil counts.

The eye irritation potential of triethanolamine or cosmetics containing the chemical has been evaluated in rabbits and rhesus monkeys; these studies have been reviewed by the CIR Expert Panel (1983). In a study with albino rabbits, moderate irritation occurred when 0.1 mL triethanolamine was instilled (Griffith *et al.*, 1980); application of 0.01 mL caused only negligible damage. Application of 0.02 mL undiluted triethanolamine to the cornea of the rabbit eye with the lids retracted caused necrosis of 63% to 87% of the cornea; this reaction was graded as 5 on a scale of 1 to 10 (Carpenter and Smyth, 1946). Application of a 0.023 M aqueous solution of triethanolamine to rabbit eyes, following removal of the corneal epithelium to facilitate penetration, caused essentially no injuries when the solution was adjusted to pH 10; application of the same solution adjusted to pH 11 caused moderate corneal swelling and hyperemia of the iris and conjunctiva that reversed within 1 week (Grant, 1974).

Skin and eye irritation in rabbits were evaluated in a study comparing the effects of ethanolamines (mono-, di-, and triethanolamine) and three mixtures containing 69%, 74%, or 87% triethanolamine plus varying proportions of other ethanolamines (Dutertre-Catella *et al.*, 1982). Eye irritation was rated maximum for monoethanolamine, severe for diethanolamine, mild for the 69% and 74% mixtures, and minimum for triethanolamine and the 87% mixture. Skin irritation was rated severe for monoethanolamine, moderate for diethanolamine and the 69% mixture, and slight for triethanolamine and the 74% and 87% mixtures. Although skin sensitization occurs in humans, no skin sensitizing responses or delayed hypersensitivity reactions occurred in studies of guinea pigs treated dermally with 5% to 100% triethanolamine (one application per week for 3 weeks; up to 6 hours per application) and subsequently challenged with 25% to 100% triethanolamine after 1 to 3 weeks (CIR, 1983).

No clinical evidence of systemic toxicity or histopathology was observed when hair dye preparations containing 0.1% to 1.5% triethanolamine were applied to the clipped backs and sides of New Zealand white rabbits at doses of 1 mg/kg twice weekly for 13 weeks, with or without prior abrasion of the skin (Burnett *et al.*, 1976). However, in a similar 13-week rabbit study in which cosmetic formulations containing 14% triethanolamine stearate were applied to the clipped back five times per week in doses of 1 or 3 mg/kg, mild to moderate skin irritation occurred; the irritation, which cleared within 72 hours, was followed by moderate to heavy scaling (CIR, 1983). Signs of systemic toxicity included lower body weight and significantly greater kidney weights at the 3 mg/kg dose.

### *Humans*

There is no appreciable hazard to workers from normal industrial use of ethanolamines (*Kirk-Othmer*, 1978). However, these compounds may cause serious toxic effects when ingested, as well as causing local injury to the mouth, throat, and digestive tract. At ordinary temperatures, triethanolamine presents no hazard from vapor inhalation, but excessive vapor concentrations may occur when triethanolamine is heated. These vapors are irritating to the eyes and nose. Triethanolamine is a skin and eye irritant; however, it is less irritating to the skin and mucous membranes than most amines.

In a series of patch tests on healthy volunteers, the highest nonirritant concentration of triethanolamine, applied in petrolatum for 48 hours, was determined to be 50% (Meneghini *et al.*, 1971). In a different test, the irritancy potential of triethanolamine was designated as slight (5% concentration) or marked (10% concentration) when applied topically in ethanol within a chamber to the scarified forearm skin of volunteers once daily for 3 days; the threshold concentration for skin irritation was 100% on intact skin and 5% (in ethanol) on scarified skin (Frosch and Kligman, 1976).

There have been no reports of industrial injuries from triethanolamine (*Patty's*, 1981). However, Shrank (1985) reported that a lathe operator became sensitized to triethanolamine, which was an ingredient in a cutting oil, and 47 positive reactions to triethanolamine (10% in an aqueous solution) occurred in patch tests of 230 metal workers with occupational dermatitis (Alomar *et al.*, 1985). In this study, 43% of all positive responses were to triethanolamine. Triethanolamine was also found to be the most frequent sensitizer in a study in which patients with suspected cosmetic- or medicine-related contact dermatoses were patch tested with common emulsifying agents (Tosti *et al.*, 1990). It has been identified as a causative agent in patients with eczema or allergic contact dermatitis (Venediktova and Gudina, 1976; Angelini

*et al.*, 1985; Jones and Kennedy, 1988) and in a curious case of intractable sneezing caused by exposure to a laundry detergent (Herman, 1983).

In a study designed to evaluate allergic contact dermatitis to substances commonly found in pharmaceutical ointments, a 24-hour patch test with a 1% aqueous solution of triethanolamine in 773 patients gave positive reactions in four (0.5%) of these patients (Iden and Schroeter, 1977). Positive reactions also occurred in 2% of 100 subjects in another study with a 48-hour patch test using 5% triethanolamine in petrolatum (Fisher *et al.*, 1971; Iden and Schroeter, 1977). In clinical tests with triethanolamine and cosmetic products containing triethanolamine, mild skin irritation occurred at concentrations above 5%, but there was little skin sensitization. In addition, there was no evidence of phototoxicity or photosensitization reactions with products containing up to 20% triethanolamine (CIR, 1983). However, based on positive skin sensitivity reactions (patch-test results) in 1.6% of a patient population with eczematous dermatitis who were tested with 5% triethanolamine in petrolatum, Meneghini *et al.* (1971) recommended restricting the use of triethanolamine in cosmetics and pharmaceutical preparations.

Triethanolamine has been given a toxic hazard rating of slightly toxic, with a probable oral lethal dose in humans of 5 to 15 g/kg, which corresponds to between 1 pint and 1 quart for a 70 kg (150 lb) person (Gosselin *et al.*, 1984). Dreisbach (1980) estimated the lethal dose in humans to be 50 g. Assuming complete dermal absorption, a human weighing 50 kg would receive an approximate dose of 10 mg/kg through the use of 10 g of cosmetics containing 5% triethanolamine.

## Reproductive and Developmental Toxicity

### *Experimental Animals*

Triethanolamine has been shown to stimulate neuritogenesis in cultured chick embryo ganglia (Sisken *et al.*, 1985). However, it was embryotoxic when injected into 3-day chick embryos; the $LD_{50}$ value (the dose causing early death in 50% of the embryos) was 3 $\mu$mole (447 $\mu$g) per egg. Eleven days after the triethanolamine injection, there was no significant increase in the incidence of chick embryo malformations (Korhonen *et al.*, 1983; cited by Melnick and Tomaszewski, 1990).

In an *in vivo* assay for potential adverse reproductive effects in mice, di- and triethanolamine, administered daily by gavage on gestation days 6 through 15 in doses of 1,125 mg/kg per day, had no effect on maternal mortality, the number of viable litters, litter size, or survival and body weight of the pups. However, similar administration of 850 mg/kg per day of monoethanolamine resulted in 16% mortality in dams and fewer viable litters (NIOSH, 1987). A preliminary developmental toxicity test in mice, used in conjunction with a scoring system of indices of developmental toxicity, resulted in a classification of low priority for further study of monoethanolamine, intermediate priority or "no decision" for triethanolamine, and high priority for diethanolamine (York *et al.*, 1988).

In mating trial studies in male and female Fisher 344 rats, 0.5 g/kg of triethanolamine in acetone, applied dermally to the interscapular area of the clipped back in an approximate volume of 1.8 mL/kg daily for 10 weeks prior to mating, during breeding, and through gestation and lactation for females, had no effect on mating, fertility, or offspring growth and survival. In similar studies with Swiss (CD-1®) mice administered daily applications of 2 g/kg in an approximate volume of 3.6 mL/kg, no chemical-related effects occurred other than ruffled fur in females and irritation at the application site of males and females (Battelle, 1988a,b).

No embryotoxic or teratogenic effects were produced by topical administration of semipermanent hair dye preparations (2 mL/kg) containing 0.1% to 1.5% triethanolamine to the shaved backs of pregnant Charles River CD rats on gestation days 1, 4, 7, 10, 13, 16, and 19 (Burnett *et al.*, 1976).

### *Humans*

No information related to the reproductive or developmental toxicity of triethanolamine in humans was found in the literature.

## CARCINOGENICITY

### Experimental Animals

Triethanolamine was not carcinogenic in Fischer F344/DuCrj rats when administered *ad libitum* in drinking water at dose levels of 1% or 2%, but was nephrotoxic, especially in females (Maekawa *et al.*, 1986). Due to increased mortality associated with nephrotoxicity in females and decreased body weight gain in females in the 2% group, the doses of triethanolamine administered to the female groups were reduced by half after week 68 of the study. There were no statistically significant increased incidences of primary neoplasms in exposed groups compared to the controls when analyzed by the chi-square test. Because of nephrotoxicity, which appeared to have an adverse effect on the life expectancy of exposed animals, an age-adjusted statistical analysis was performed. The results showed a positive trend ($P<0.05$) in the incidence of hepatic neoplasms in males and uterine endometrial sarcomas and renal tubule adenomas in females. However, the incidence of these neoplasms in the control groups were lower than those in historical controls. In a similar study, triethanolamine had no carcinogenic activity in $B6C3F_1$ mice when administered in drinking water at a concentration of 1% or 2% for 82 weeks (Konishi *et al.*, 1992). Triethanolamine was not carcinogenic in male CBA $\times$ $C_{57}Bl_6$ mice when applied dermally for 14 to 18 months (Kostrodymova *et al.*, 1976; CIR, 1983).

Incidences of malignant lymphoma, particularly thymic lymphoma, were increased in female, but not in male, ICR-JCL mice fed diets containing 0.03% or 0.3% triethanolamine throughout their life span (Hoshino and Tanooka, 1978). The total incidences of malignant neoplasms in treated female mice were significantly greater than the control incidence ($P<0.01$); the incidences were 1/36 in controls, 10/37 in the 0.03% group, and 13/36 in the 0.3% group. In another long-term study with ICR mice (Inai *et al.*, 1979), the incidence of thymic lymphoma and nonthymic leukemia in control females at 109 weeks was 5/15. This rate is 10 times greater than the rate observed in the female control group of the Hoshino and Tanooka study, and is similar to that reported for triethanolamine-treated females.

Rust-proofing cutting fluid (containing low levels of triethanolamine, sodium nitrite, and polyethylene glycol) was carcinogenic in male Wistar rats (Wang *et al.*, 1988). Groups of 40 rats were administered either undiluted cutting fluid or a threefold dilution of the fluid in water *ad libitum* for 2 years. Treated rats had increased incidences of neoplasms, particularly pancreatic carcinoma. The total incidences of malignant neoplasms were 0% in the control group, 10% in the group given diluted cutting fluid, and 27.5% in the group that received the undiluted fluid. In another group of rats exposed to undiluted cutting fluid supplemented with ascorbic acid, the total incidence of malignant neoplasms was 1/40 (2.5%). Based on the protective action of ascorbic acid in this study, Wang *et al.* (1988) concluded that the carcinogenic agent was a nitrosamine formed *in vivo*; the inhibitory action of ascorbic acid on the *in vivo* formation of nitroso compounds has been documented (Mirvish *et al.*, 1975). Because the cutting fluid contained triethanolamine and sodium nitrite, the most probable nitrosamine formed during this study was *N*-nitrosodiethanolamine. However, the neoplasms induced in rats in previous experiments with *N*-nitrosodiethanolamine were primarily hepatocellular carcinomas, not pancreatic carcinomas (Lijinsky and Kovatch, 1985).

### Humans

In an epidemiology study conducted by Järvholm *et al.* (1986), the mortality and cancer morbidity in 219 men exposed to cutting fluids for at least 5 years, including at least 1 year of exposure to a cutting fluid containing both amines and nitrites (primarily ethanolamines and sodium nitrite), were not significantly different from those of the general population. The authors concluded that although the results indicate that the use of cutting fluids in this industry did not lead to an increased risk of cancer, they were unable to exclude the possibility of an increased risk for cancer of a specific site because of the small sample population.

## GENETIC TOXICITY

The limited information on the mutagenicity of triethanolamine indicates that the chemical is not genotoxic. Triethanolamine did not induce DNA damage in *Escherichia coli* (Inoue *et al.*, 1982), mutations in *Salmonella typhimurium* (Inoue *et al.*, 1982; Dean *et al.*, 1985; Mortelmans *et al.*, 1986), or gene conversion in *Saccharomyces cerevisiae* (Dean *et al.*, 1985). No induction of sister chromatid

exchanges occurred in cultured Chinese hamster ovary cells treated with triethanolamine (Galloway *et al.*, 1987), and results of tests for induction of chromosomal aberrations in cultured rat liver cells (Dean *et al.*, 1985) and cultured Chinese hamster cells (Inoue *et al.*, 1982; Galloway *et al.*, 1987) were also negative. The *S. typhimurium* tests and the rodent cell cytogenetic tests were conducted with and without S9 metabolic activation enzymes. No increase in the frequency of sex-linked recessive lethal mutations was observed in germ cells of male *Drosophila melanogaster* administered triethanolamine by feeding or injection (Yoon *et al.*, 1985).

## STUDY RATIONALE

The National Cancer Institute nominated triethanolamine for study because of its widespread use in cosmetics and other consumer products, its high potential for worker exposure due to its many industrial uses, and its potential for conversion to the carcinogen *N*-nitrosodiethanolamine. Concern was also prompted by the increased incidences of lymphoma and total malignant neoplasms in female ICR-JCL mice receiving 0.03% or 0.3% triethanolamine in the diet (Hoshino and Tanooka, 1978). Dermal application was chosen as the route of exposure to mimic the principal means of human exposure to triethanolamine and because considerable systemic exposure is achieved with this route.

# MATERIALS AND METHODS

## PROCUREMENT AND CHARACTERIZATION OF TRIETHANOLAMINE

Triethanolamine was obtained from Texaco Chemical Company (Division of Texaco, Inc., Bellaire, TX) in two lots (3B-1-84 and 7G-60). Lot 3B-1-84 was used during the 13-week studies and lot 7G-60 was used during the 2-year studies. Identity, purity, and stability analyses were conducted by the analytical chemistry laboratory, Midwest Research Institute (Kansas City, MO; Appendix I). Reports on analyses performed in support of the triethanolamine studies are on file at the National Institute of Environmental Health Sciences (NIEHS).

The chemical, a clear, colorless, viscous liquid, was identified as triethanolamine by infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopy. The purity of both lots was determined by elemental analysis, Karl Fischer water analysis, functional group titration, thin-layer chromatography, and gas chromatography. Elemental analyses for carbon, hydrogen, and nitrogen were in reasonable agreement with theoretical values for triethanolamine. Karl Fischer water analysis indicated less than 0.5% water in either lot. Functional group titrations were performed to identify the presence of primary and secondary amines, which were assumed to be monoethanolamine and diethanolamine. Functional group titration indicated less than 0.4% primary or secondary amines. Thin-layer chromatography indicated a major spot and only trace impurities. For lot 3B-1-84, gas chromatography by two systems indicated a major peak and one to three impurities with areas totaling no more than 1.4% of the major peak area. For lot 7G-60, gas chromatography by two systems indicated a major peak and no impurities or one impurity with an area of 0.16% relative to the major peak. The overall purities of lot 3B-1-84 and lot 7G-60 were determined to be approximately 98% and 99%, respectively.

Lot 3B-1-84 was further characterized by National Formulary methods (USP XX/NF XV) of testing for trolamine, a mixture of alkanolamines consisting largely of triethanolamine, along with diethanolamine, and monoethanolamine. All results were consistent with NF XV requirements for trolamine.

The concentrations of nonpolar nitrosamines (*N*-nitrosodimethylamine, *N*-nitrosomethylethylamine, *N*-nitrosodiethylamine, *N*-nitrosodi-n-propylamine, *N*-nitrosodi-n-butylamine, *N*-nitrosopiperidine, *N*-nitrosopyrrolidine, and *N*-nitrosomorpholine) and the polar nitrosamine *N*-nitrosodiethanolamine in lot 7G-60 were determined by Covance Laboratories, Inc. (Madison, WI). No nonpolar nitrosamines or *N*-nitrosodiethanolamine were present at concentrations greater than the limits of detection.

Stability studies of the bulk chemical were performed by the analytical chemistry laboratory with gas chromatography. These studies indicated that triethanolamine was stable as a bulk chemical for 2 weeks when stored under a nitrogen headspace, protected from light, at temperatures up to 60° C. To ensure stability, the bulk chemical was stored at room temperature in amber glass containers under a nitrogen headspace during the 2-year studies. Stability was monitored by the study laboratory during the 13-week studies with gas chromatography and nonaqueous amine titration and during the 2-year studies with gas chromatography. No degradation of the bulk chemical was detected.

## PREPARATION AND ANALYSIS OF DOSE FORMULATIONS

In the 13-week studies, the highest doses were applied neat. The lower concentrations in the 13-week studies and all dose formulations in the 2-year studies were prepared by mixing triethanolamine and acetone to give the required concentration (Table I1). Acetone was chosen as the vehicle for these studies because it is miscible with triethanolamine and because acetone rapidly evaporates. The dose formulations were prepared once every 2 weeks and were stored at 5° C in amber glass bottles under a nitrogen head space,

protected from light, for up to 3 weeks. Stability studies of the dermal dose formulations were performed by the analytical chemistry laboratory; stability was confirmed for at least 3 weeks at room temperature in sealed glass vials, under a nitrogen head space, in the dark and for at least 3 hours under animal room conditions (open to air and light).

Periodic analyses of dose formulations of triethanolamine were conducted by the study laboratory and the analytical chemistry laboratory with gas chromatography. For the 13-week studies, the dose formulations were analyzed at the beginning, midpoint, and end of the studies; animal-room samples of the same dose formulations were also analyzed (Table I2). All dose formulations and animal-room samples were within 10% of the target concentrations. For the 2-year studies, the dose formulations were analyzed at the beginning of the studies and every 6 to 10 weeks thereafter; animal-room samples were analyzed every 22 to 26 weeks (Table I3). Of the doses analyzed, 95% (59/62) of the formulations for rats and all of the formulations for mice were within 10% of the target concentrations. All animal-room samples for rats and 97% (29/30) of the animal-room samples for mice were within 10% of the target concentrations. Results of periodic referee analyses performed by the analytical chemistry laboratory agreed with the results obtained by the study laboratory (Table I4).

## 13-Week Studies

The 13-week studies were conducted to evaluate the cumulative toxic effects of repeated exposure to triethanolamine and to determine the appropriate doses to be used in the 2-year studies.

Male and female F344/N rats and $B6C3F_1$ mice were obtained from Simonsen Laboratories (Gilroy, CA). On receipt, the rats and mice were 4 weeks old. Animals were quarantined for 11 to 14 days and were 6 weeks old on the first day of the studies. Before the studies began, five male and six female rats and mice were randomly selected for parasite evaluation and gross observation for evidence of disease. At the beginning of quarantine and at the beginning and the end of the studies, serologic analyses were performed on five male and five female rats and mice using the protocols of the NTP Sentinel Animal Program (Appendix K).

Doses for the 13-week studies were based on the results of 14- and 16-day comparative studies in which F344/N rats and $B6C3F_1$ mice received triethanolamine by the dermal route in acetone, in drinking water, or by inhalation. The results of the dermal studies included skin irritation of a severity that limited the highest dose for the 13-week studies to 2,000 mg/kg for rats and 4,000 mg/kg for mice. The 14- and 16-day triethanolamine studies are unpublished but are available from the NTP.

Based on the results of the earlier NTP studies, groups of 10 male and 10 female rats were topically administered 0, 125, 250, 500, 1,000, or 2,000 mg triethanolamine per kilogram body weight. Groups of 10 male and 10 female mice were topically administered 0, 250, 500, 1,000, 2,000, or 4,000 mg triethanolamine per kilogram body weight. Except for the highest dose, which was applied neat, all doses were administered in acetone. Dose volumes were adjusted weekly, if necessary, according to the average body weights of the dosed groups. For rats, if the dose volume exceeded 320 $\mu$L, half the total volume was administered in the morning and the remainder was administered in the afternoon. Doses were applied 5 days per week for 13 weeks to an area extending from the animal's mid-back to the dorsal intrascapular region; the site of application was clipped weekly during the studies. Additional groups of 10 male and 10 female rats and mice designated for clinical pathology evaluations received the same dermal exposures as the core study rats and mice. Feed and water were available *ad libitum*. Rats and mice were housed individually. Clinical findings were recorded weekly for core study rats and mice. All animals were weighed initially, weekly, and at the end of the studies. Details of the study design and animal maintenance are summarized in Table 1.

Clinical pathology studies were performed on rats and mice designated for clinical pathology testing. Hematology and clinical chemistry analyses were conducted during week 12 for rats and week 13 for mice. Blood for hematology and clinical chemistry analyses was drawn from the retroorbital sinus of rats and mice anesthetized with a mixture of 70%:30% carbon dioxide:air. Blood for hematology determinations was placed in tubes containing potassium EDTA as an anticoagulant. Blood for serum analyses was collected in tubes without anticoagulant, allowed to clot at room temperature, and centrifuged, and the serum

was separated. Hematology parameters were measured on an Ortho ELT-8/ds hematology analyzer (Ortho Instruments, Westwood, MA). Differential leukocyte counts and morphologic evaluation of blood cells were determined by light microscopic examination of blood films stained with a modified Romanowsky stain. Reticulocyte counts were determined by light microscopy from smears of whole blood stained with new methylene blue. Clinical chemistry parameters were measured on a Hitachi 704 chemistry analyzer (Boehringer Mannheim, Indianapolis, IN). Table 1 lists the hematology and clinical chemistry parameters measured.

Urinalysis studies were performed during weeks 1, 3, 7, and 13 for rats and weeks 7 and 12 for mice. For all urine studies, rats and mice were housed individually in polycarbonate metabolism cages (Maryland Plastics, New York) for a 16-hour collection period. The urine collection containers were immersed in an ice water bath during the sampling period to minimize evaporation and to suppress bacterial growth. Food was withheld, but water was available *ad libitum* during the collection period. Urine volume was measured and specific gravity was determined with a refractometer (American Optical, Buffalo, NY). Urine chemistry variables were measured on a Hitachi 704 chemistry analyzer; parameters measured are listed in Table 1.

At the end of the 13-week studies, samples were collected for sperm morphology and vaginal cytology evaluations from all rats in the 0, 500, 1,000, and 2,000 mg/kg groups and all mice in the 0, 1,000, 2,000, and 4,000 mg/kg groups. The parameters evaluated are listed in Table 1. Methods used were those described in the NTP's sperm morphology and vaginal cytology evaluations protocol (NTP, 1983). For 7 consecutive days before the scheduled terminal sacrifice, the vaginal vaults of the females were moistened with saline, if necessary, and samples of vaginal fluid and cells were stained. Relative numbers of leukocytes, nucleated epithelial cells, and large squamous epithelial cells were determined and used to ascertain estrous cycle stage (i.e., diestrus, proestrus, estrus, and metestrus). Male animals were evaluated for sperm morphology, count, and motility. The right epididymis and right testis were isolated and weighed. The tail of the epididymis (cauda epididymis) was then removed from the epididymal body (corpus epididymis) and weighed. Test yolk (rats) or modified Tyrode's buffer (mice) was applied to slides, and a small incision was made at the distal border of the cauda epididymis. The sperm effluxing from the incision were dispersed in the buffer on the slides, and the numbers of motile and nonmotile spermatozoa were counted for five fields per slide by two observers. Following completion of sperm motility estimates, each right cauda epididymis was placed in buffered saline solution. Caudae were finely minced, and the tissue was incubated in the saline solution and then heat fixed at 65° C. Sperm density was then determined microscopically with the aid of a hemacytometer. Four sperm morphology slides were prepared for each animal evaluated. An aliquot of killed sperm suspension was stained in a test tube, spread on a microscope slide under a coverslip, and examined.

A necropsy was performed on all core study animals. The brain, left epididymis, heart, right kidney, liver, lungs, spleen, left testis, and thymus were weighed. Tissues for microscopic examination were fixed and preserved in 10% neutral buffered formalin, processed and trimmed, embedded in paraffin, sectioned to a thickness of 5 to 6 μm, and stained with hematoxylin and eosin. A complete histopathologic examination was performed on core study rats in the vehicle control and 2,000 mg/kg groups and core study mice in the vehicle control and 4,000 mg/kg groups; the tissues and organs routinely examined are listed in Table 1. Additionally, the skin (site of application) of rats and mice and the kidney of female rats in the lower exposure groups were examined until a no-effect level was determined.

## 2-Year Studies

### Study Design

Groups of 60 male and 60 female rats and mice were topically administered triethanolamine in acetone. Male rats received 0, 32, 63, or 125 mg/kg. Female rats received 0, 63, 125, or 250 mg/kg. Male mice received 0, 200, 630, or 2,000 mg/kg. Female mice received 0, 100, 300, or 1,000 mg/kg. Dose volumes were adjusted weekly according to the average body weights of the dosed groups. Dose volumes ranged from 61 to 272 μL for male rats, 55 to 173 μL for female rats, 39 to 105 μL for male mice, and 33 to 102 μL for female mice. Doses were applied 5 days per week for 103 weeks to an area extending from the animal's mid-back to the intrascapular region; the site of application was clipped approximately once per

week during the studies. Ten male and ten female rats and mice from each group were evaluated at 15 months for histopathology and organ weights.

## Source and Specification of Animals

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Simonsen Laboratories, Inc. (Gilroy, CA), for use in the 2-year studies. Rats and mice were quarantined for 11 days before the studies began. Five male and five female rats and mice were selected for parasite evaluation and gross observation of disease. Serology samples were collected for viral screening. Rats and mice were approximately 6 weeks old at the beginning of the studies. The health of the animals was monitored during the studies according to the protocols of the NTP Sentinel Animal Program (Appendix K).

## Animal Maintenance

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

## Clinical Examinations and Pathology

All animals were observed twice daily. Clinical findings were recorded monthly; body weights were recorded at the beginning of the study, weekly for 13 weeks, monthly thereafter, and at the end of the studies.

A complete necropsy and microscopic examination were performed on all rats and mice. At the 15-month interim evaluation necropsy, the left kidney, right kidney, and liver of rats and mice were weighed. At necropsy, all organs and tissues were examined for grossly visible lesions, and all major tissues were fixed and preserved in 10% neutral buffered formalin, processed and trimmed, embedded in paraffin, sectioned to a thickness of 5 to 6 $\mu$m, and stained with hematoxylin and eosin for microscopic examination. For all paired organs (i.e., adrenal gland, kidney, ovary), samples from each organ were examined. Complete histopathologic examinations were performed on all animals. The tissues and organs routinely examined are listed in Table 1.

Microscopic evaluations were completed by the study laboratory pathologist, and the pathology data were entered into the Toxicology Data Management System. The slides, paraffin blocks, and residual wet tissues were sent to the NTP Archives for inventory, slide/block match, and wet tissue audit. The slides, individual animal data records, and pathology tables were evaluated by an independent quality assessment laboratory. The individual animal records and tables were compared for accuracy, the slide and tissue counts were verified, and the histotechnique was evaluated. For the 2-year studies, quality assessment pathologists evaluated slides from all tumors and all potential target organs, which included the skin and kidneys of male and female rats, the adrenal glands of male rats, and the skin, liver, lymph nodes, spleen, and thymus of male and female mice. Additionally, the livers of male and female rats were examined when the diagnosis of nodular hyperplasia had been made; the adrenal glands of male mice were examined when the diagnosis of adenomatous hyperplasia had been made. The standard evaluation of the kidneys in these studies included microscopic examination of a longitudinal section of the central portion of the left kidney and a cross section of the central portion of the right kidney. Step sections were made from the residual kidney wet tissue from all male rats because microscopic examination of the original kidney sections showed increased incidences of proliferative lesions. Kidneys were sectioned in increments of 0.5 mm to produce four additional sections per kidney, or eight sections per animal.

The quality assessment report and the reviewed slides were submitted to the NTP Pathology Working Group (PWG) chairperson, who reviewed the selected tissues and addressed any inconsistencies in the diagnoses made by the laboratory and quality assessment pathologists. Representative histopathology slides containing examples of lesions related to chemical administration, examples of disagreements in diagnoses between the laboratory and quality assessment pathologists, or lesions of general interest were presented by the chairperson to the PWG for review. The PWG consisted of the quality assessment pathologist and other pathologists experienced in rodent toxicologic pathology. This group examined the tissues without any knowledge of dose groups or

previously rendered diagnoses. When the PWG consensus differed from the opinion of the laboratory pathologist, the diagnosis was changed. Final diagnoses for reviewed lesions represent a consensus between the laboratory pathologist, reviewing pathologist(s), and the PWG. Details of these review procedures have been described, in part, by Maronpot and Boorman (1982) and Boorman *et al*. (1985). For subsequent analyses of the pathology data, the decision of whether to evaluate the diagnosed lesions for each tissue type separately or combined was generally based on the guidelines of McConnell *et al*. (1986).

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

| 13-Week Studies | 2-Year Studies |
|---|---|
| **Study Laboratory** | |
| Battelle Columbus Laboratories (Columbus, OH) | Battelle Columbus Laboratories (Columbus, OH) |
| **Strain and Species** | |
| Rats: F344/N<br>Mice: $B6C3F_1$ | Rats: F344/N<br>Mice: $B6C3F_1$ |
| **Animal Source** | |
| Simonsen Laboratories, Inc. (Gilroy, CA) | Simonsen Laboratories, Inc. (Gilroy, CA) |
| **Time Held Before Studies** | |
| 11 to 14 days | 11 days |
| **Average Age When Studies Began** | |
| 6 weeks | 6 weeks |
| **Date of First Dose** | |
| Rats: 30 June - 1 July (clinical pathology) or 2-3 July 1986<br>Mice: 11-12 August (clinical pathology) or 13-14 August 1986 | Rats: 14 November 1988<br>Mice: 31 October 1988 |
| **Duration of Dosing** | |
| 13 weeks (5 days/week) | 103 weeks (5 days/week) |
| **Date of Last Dose** | |
| Rats: 1 October (clinical pathology) or 2 October 1986<br>Mice: 12-13 November 1986 | Rats: 2 November 1990<br>Mice: 19 October 1990 |
| **Necropsy Dates** | |
| Rats: 2-3 October 1986<br>Mice: 13-14 November 1986 | Rats: 15-Month interim evaluation – 12 February (males) or 13 February (females) 1990<br>Terminal - 12-14 November 1990<br>Mice: 15-Month interim evaluation – 29 January (males) or 30 January (females) 1990<br>Terminal - 29 October - 1 November and 5 November 1990 |

**TABLE 1**
**Experimental Design and Materials and Methods in the Dermal Studies of Triethanolamine** (continued)

| 13-Week Studies | 2-Year Studies |
|---|---|
| **Average Age at Necropsy** | |
| 19 weeks | 15-Month interim evaluation -<br>Rats and mice: 72 weeks<br>Terminal -<br>Rats: 111 weeks<br>Mice: 111 weeks (males)<br>110-111 weeks (females) |
| **Size of Study Groups** | |
| 10 males and 10 females | 15-Month interim evaluation - 10 males and 10 females<br>Terminal - 50 males and 50 females |
| **Method of Distribution** | |
| Animals were distributed randomly into groups of approximately initial mean body weights. | Same as 13-week studies |
| **Animals per Cage** | |
| 1 | 1 |
| **Method of Animal Identification** | |
| Toe mark | Tail tattoo |
| **Diet** | |
| NIH-07 open formula pelleted diet (Zeigler Brothers, Inc., Gardners, PA), available *ad libitum*, changed weekly | Same as 13-week studies |
| **Water Distribution** | |
| Tap water (City of Columbus municipal supply) via automatic watering system (Edstrom Industries, Waterford, WI), available *ad libitum* | Same as 13-week studies |
| **Cages** | |
| Polycarbonate (Lab Products, Inc., Garfield, NJ), changed weekly | Polycarbonate (Lab Products, Inc., Maywood, NJ), changed weekly |
| **Bedding** | |
| Beta-Chips® hardwood chips (Northeastern Products, Inc., Warrensburg, NY), changed weekly | Sani-Chips® hardwood chips (P.J. Murphy Forest Products, Montville, NJ), changed weekly |
| **Cage Filters** | |
| DuPont 2024 spun-bonded polyester filter (Snow Filtration Co., Cincinnati, OH), changed every 2 weeks | Same as 13-week studies |
| **Racks** | |
| Stainless steel (Lab Products, Inc., Garfield, NJ), changed every 2 weeks | Stainless steel (Lab Products, Inc., Maywood, NJ), changed every 2 weeks |
| **Animal Room Environment** | |
| Temperature: 19.4° to 23.9° C (rats), 20.0° to 23.9° C (mice)<br>Relative humidity: 35% to 65%<br>Fluorescent light: 12 hours/day<br>Room air: minimum of 15 changes/hour | Temperature: 20.0° to 23.9° C (rats), 20.0° to 24.4° C (mice)<br>Relative humidity: 35% to 76% (rats), 24% to 82% (mice)<br>Fluorescent light: 12 hours/day<br>Room air: minimum of 10 changes/hour |

**Table 1**
**Experimental Design and Materials and Methods in the Dermal Studies of Triethanolamine** (continued)

| 13-Week Studies | 2-Year Studies |
|---|---|
| **Doses** | |
| Rats: 0, 125, 250, 500, or 1,000 mg/kg in acetone; 2,000 mg/kg neat<br>Mice: 0, 250, 500, 1,000, or 2,000 mg/kg in acetone; 4,000 mg/kg neat | Rats: 0, 32, 63, or 125 mg/kg (males) and 0, 63, 125, or 250 mg/kg (females) in acetone<br>Mice: 0, 200, 630, or 2,000 mg/kg (males) and 0, 100, 300, or 1,000 mg/kg (females) in acetone |
| **Type and Frequency of Observation** | |
| Observed twice daily; animals were weighed initially, weekly, and at the end of the studies; clinical findings of core study animals were recorded weekly. Dorsal skin lesions were diagramed. | Observed twice daily; clinical findings were recorded monthly. Animals were weighed initially, weekly for 13 weeks, monthly thereafter, and at the end of the studies. |
| **Method of Sacrifice** | |
| $CO_2$ asphyxiation | $CO_2$ asphyxiation |
| **Necropsy** | |
| Necropsy performed on all core study animals. Organs weighed were brain, left epididymis, heart, right kidney, liver, lungs, spleen, left testis, and thymus. | Necropsy performed on all animals. Organs weighed were left and right kidneys and liver. |
| **Clinical Pathology** | |
| Blood was collected from all clinical pathology group animals from the retroorbital sinus for hematology and clinical chemistry. Urine was collected overnight (16 hours) from clinical pathology group rats during weeks 1, 3, 7, and 13 and from clinical pathology group mice during weeks 7 and 12.<br>***Hematology:*** hematocrit; hemoglobin concentration; erythrocyte, reticulocyte, and nucleated erythrocyte counts; mean cell volume; mean cell hemoglobin; mean cell hemoglobin concentration; platelet count; and total leukocyte count and differentials<br>***Clinical chemistry:*** urea nitrogen, creatinine, glucose, total protein, albumin, alanine aminotransferase, aspartate aminotransferase, and sorbitol dehydrogenase<br>***Urinalysis:*** glucose, protein, volume, and specific gravity | None |
| **Histopathology** | |
| Complete histopathology was performed on core study rats in the vehicle control and 2,000 mg/kg groups and mice in the vehicle control and 4,000 mg/kg groups. In addition to gross lesions and tissue masses, the tissues examined included: adrenal gland, bone and marrow, brain, clitoral gland, epididymis, esophagus, gallbladder (mice), heart, kidney, large intestine (cecum, colon, and rectum), liver, lung, lymph nodes (mandibular and mesenteric), mammary gland, nose, ovary, pancreas, parathyroid gland, pituitary gland, preputial gland, prostate gland, salivary gland, seminal vesicle, skin (lesions and unaffected skin from site of application; inguinal skin), small intestine (duodenum, jejunum, and ileum), spinal cord and sciatic nerve (if neurologic signs were present), spleen, stomach (forestomach and glandular stomach), testis, thymus, thyroid gland, trachea, urinary bladder, uterus, and vagina (females in vaginal cytology studies only). Additionally, the kidney of female rats, pituitary gland of male and female rats, and skin (site of application) of male and female rats and mice in the lower exposure groups were examined until a no-effect level was reached. | Complete histopathology was performed on all rats and mice. In addition to gross lesions and tissue masses, the tissues examined included: adrenal gland, bone and marrow, brain, clitoral gland, epididymis, esophagus, gallbladder (mice), heart, kidney, large intestine (cecum, colon, and rectum), liver, lung, lymph nodes (mandibular and mesenteric), mammary gland, nose, ovary, pancreas, parathyroid gland, pituitary gland, preputial gland, prostate gland, salivary gland, seminal vesicle, skin (lesions and unaffected skin from site of application; inguinal skin), small intestine (duodenum, jejunum, and ileum), spinal cord and sciatic nerve (if neurologic signs were present), spleen, stomach (forestomach and glandular stomach), testis, thymus, thyroid gland, trachea, urinary bladder, and uterus. |

**TABLE 1**
**Experimental Design and Materials and Methods in the Dermal Studies of Triethanolamine** (continued)

| 13-Week Studies | 2-Year Studies |
|---|---|
| **Sperm Morphology and Vaginal Cytology Evaluations**<br>Rats in the 0, 500, 1,000, and 2,000 mg/kg groups and mice in the 0, 1,000, 2,000, and 4,000 mg/kg groups were evaluated. Sperm samples were collected at the end of the studies and evaluated for sperm count, motility, and morphology. The right cauda, epididymis, and testis were weighed. Vaginal samples were collected for 7 consecutive days before the end of the studies and evaluated for the relative frequency of estrous stages and for estrous cycle length. | None |

## STATISTICAL METHODS

### Survival Analyses

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

### Calculation of Incidence

The incidences of neoplasms or nonneoplastic lesions as presented in Tables A1, A5, B1, B4, C1, C5, D1, and D5 are given as the number of animals bearing such lesions at a specific anatomic site and the number of animals with that site examined microscopically. For calculation of statistical significance, the incidences of most neoplasms (Tables A3, B3, C3, and D3) and all nonneoplastic lesions are given as the numbers of animals affected at each site examined microscopically. However, when macroscopic examination was required to detect neoplasms in certain tissues (e.g., skin, intestine, harderian gland, and mammary gland) before microscopic evaluation, or when neoplasms had multiple potential sites of occurrence (e.g., leukemia or lymphoma), the denominators consist of the number of animals on which a necropsy was performed. Tables A3, B3, C3, and D3 also give the survival-adjusted neoplasm rate for each group and each site-specific neoplasm, i.e., the Kaplan-Meier estimate of the neoplasm incidence that would have been observed at the end of the study in the absence of mortality from all other competing risks (Kaplan and Meier, 1958).

### Analysis of Neoplasm Incidences

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

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

1979), procedures based on the overall proportion of neoplasm-bearing animals.

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

### Analysis of Nonneoplastic Lesion Incidences

Because all nonneoplastic lesions in this study were considered to be incidental to the cause of death or not rapidly lethal, the primary statistical analysis used was a logistic regression analysis in which nonneoplastic lesion prevalence was modeled as a logistic function of chemical exposure and time. For lesions detected at the interim evaluation, the Fisher exact test, a procedure based on the overall proportion of affected animals, was used.

### Analysis of Continuous Variables

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

### Historical Control Data

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

## Quality Assurance Methods

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

## Genetic Toxicology

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

The genetic toxicity studies of triethanolamine are part of a larger effort by the NTP to develop a database that would permit the evaluation of carcinogenicity in experimental animals from the molecular structure and the effects of the chemical in short-term *in vitro* and

*in vivo* genetic toxicity tests. These genetic toxicity tests were originally developed to study mechanisms of chemical-induced DNA damage and to predict carcinogenicity in animals, based on the electrophilicity theory of chemical carcinogenesis and the somatic mutation theory of cancer (Miller and Miller, 1977; Straus, 1981; Crawford, 1985).

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

The predictivity for carcinogenicity of a positive response in bone marrow chromosome aberration or micronucleus tests appears to be less than the *Salmonella* test (Shelby *et al.*, 1993; Shelby and Witt, 1995). Positive responses in long-term peripheral blood micronucleus tests have not been formally evaluated for their predictivity for rodent carcinogenicity. But, because of the theoretical and observed associations between induced genetic damage and adverse effects in somatic and germ cells, the determination of *in vivo* genetic effects is important to the overall understanding of the risks associated with exposure to a particular chemical.

# RESULTS

## RATS

### 13-WEEK STUDY

All rats survived to the end of the study (Table 2). Final mean body weights and weight gains of males and females in the 2,000 mg/kg groups were significantly less than those of the vehicle controls; the mean body weight gain of females in the 1,000 mg/kg group was also significantly less than that of the vehicle controls. Clinical findings related to triethanolamine administration occurred only at the site of application and included irritation, scaliness, and crustiness for males and females. Males also had discoloration, and two males administered 2,000 mg/kg had ulceration at the site of application.

**TABLE 2**
**Survival and Body Weights of Rats in the 13-Week Dermal Study of Triethanolamine**

| Dose (mg/kg) | Survival[a] | Mean Body Weight[b] (g) Initial | Final | Change | Final Weight Relative to Controls (%) |
|---|---|---|---|---|---|
| **Male** | | | | | |
| 0 | 10/10 | 98 ± 2 | 296 ± 6 | 198 ± 6 | |
| 125 | 10/10 | 94 ± 2 | 279 ± 5 | 185 ± 5 | 94 |
| 250 | 10/10 | 95 ± 2 | 279 ± 6 | 184 ± 5 | 94 |
| 500 | 10/10 | 96 ± 2 | 288 ± 5 | 193 ± 5 | 97 |
| 1,000 | 10/10 | 98 ± 3 | 290 ± 10 | 192 ± 9 | 98 |
| 2,000 | 10/10 | 95 ± 3 | 252 ± 9** | 156 ± 8** | 85 |
| **Female** | | | | | |
| 0 | 10/10 | 84 ± 2 | 176 ± 3 | 92 ± 3 | |
| 125 | 10/10 | 84 ± 2 | 171 ± 3 | 87 ± 2 | 97 |
| 250 | 10/10 | 86 ± 2 | 175 ± 3 | 89 ± 2 | 100 |
| 500 | 10/10 | 85 ± 2 | 173 ± 3 | 88 ± 3 | 98 |
| 1,000 | 10/10 | 87 ± 2 | 170 ± 3 | 83 ± 3* | 97 |
| 2,000 | 10/10 | 82 ± 1 | 156 ± 2** | 74 ± 2** | 89 |

* Significantly different ($P \leq 0.05$) from the vehicle control group by Williams' or Dunnett's test
** $P \leq 0.01$
[a] Number of animals surviving at 13 weeks/number initially in group
[b] Weights and weight changes are given as mean ± standard error.

Clinical pathology results are listed in Table G1. In general, changes were minimal to mild, occurred only in the 2,000 mg/kg groups, and are consistent with the marked chronic active skin inflammation observed microscopically. Mild increases in segmented neutrophil counts occurred in male and female rats in the 2,000 mg/kg groups; in males, this change was accompanied by increased leukocyte and eosinophil counts. These findings are consistent with the presence of a mild inflammatory leukogram related to the skin inflammation. Minimal decreases occurred in mean red cell volume in male and female rats administered 2,000 mg/kg and in hematocrit in females administered 2,000 mg/kg. These changes are consistent with a minimal depression of hematopoiesis related to chronic inflammation.

Minimal increases in albumin and urea nitrogen concentrations, likely representing minimal dehydration, occurred in females that received 2,000 mg/kg. Additionally, increased urine specific gravity in females in the 1,000 and 2,000 mg/kg groups at weeks 7 (day 44) and 13 and in male rats in the 2,000 mg/kg group at week 13 would be consistent with dehydration. Dehydration can be a sequela of inflammation. Serum aspartate aminotransferase activities were mildly increased in male rats receiving 250 mg/kg or greater and in females receiving 2,000 mg/kg. Aspartate aminotransferase has a wide tissue distribution, and, in the rat, the greatest tissue concentrations are found in the heart, liver, skeletal muscle, brain, and kidney (Boyd, 1983). In this study, the cause of the increased aspartate aminotransferase activity is unknown, but this increase could indicate mild cardiac/skeletal muscle or hepatic injury. Serum alanine aminotransferase activity was minimally increased in males in the 1,000 and 2,000 mg/kg groups. This enzyme is liver specific in the rat, and increases in serum activity would be consistent with a hepatic effect. However, the activity of sorbitol dehydrogenase, which is also liver specific, decreased minimally in females administered 500 or 1,000 mg/kg. Additionally, there was no microscopic evidence of hepatic injury or change in absolute liver weight in dosed rats. Urine protein excretion was decreased in males in the 2,000 mg/kg group on day 16, in males administered 500 mg/kg or greater at week 7, and in males in the 1,000 and 2,000 mg/kg groups at week 13. The cause for the decreased protein excretion is unknown.

Kidney weights were generally greater in males and females administered 500, 1,000, or 2,000 mg/kg than in the vehicle controls (Table F4). Other differences in organ weights of males and females administered 2,000 mg/kg were considered secondary to the lower body weights of these groups. There were no biologically significant differences in sperm morphology or vaginal cytology parameters between dosed and vehicle control rats (Table H1).

Gross lesions attributed to triethanolamine application included crust at the site of application for males and females administered 1,000 or 2,000 mg/kg. Yellow skin coloration in the lumbar region of vehicle control and treated males was attributed to the application of acetone. Microscopic lesions at the site of application included acanthosis and inflammation, which varied from minimal or mild in the lower dose groups to marked in the 2,000 mg/kg groups (Table 3). In rats with minimal acanthosis, the epidermis was as much as twice the normal thickness. The more severe lesions were focal to multifocal and included a thickened epidermis (three to four times the normal thickness); chronic active inflammation; and erosion, ulceration, or both. The underlying dermis was often thickened by chronic active inflammation, including fibrosis.

Dosed females had greater incidences of nephropathy than did the vehicle controls (Table 3). Nephropathy consisted of minimal to mild, focal or multifocal cortical tubules lined by hyperchromatic, basophilic tubule epithelium (regeneration). Mineralization, which also occurred with greater incidences and severity in dosed females, consisted of tiny lamellated concretions within tubule lumina and/or epithelium. The incidences of nephropathy were not increased in dosed males. The incidences of hypertrophy of the pituitary gland pars intermedia were significantly greater in males and females in the 2,000 mg/kg group than in the vehicle controls (Table 3). The pars intermedia is a thin section of tissue composed of compact clusters of polygonal cells that lies between the pars distalis and the pars nervosa. Because of its small size and because of some variation in sectioning of the pituitary gland, the pars intermedia was not always present in the section examined. In the animals with hypertrophy, the pars intermedia was as much as twice the normal size, with a somewhat nodular appearance. Individual cells were moderately

enlarged, apparently due to an increase in the amount of cytoplasm.

*Dose Selection Rationale:* Based on decreased body weight gain and progression in the severity of acanthosis and inflammation at the site of application at higher doses in the 13-week studies, triethanolamine doses selected for use in the 2-year dermal study in rats were 32, 63, and 125 mg/kg for males and 63, 125, and 250 mg/kg for females.

**TABLE 3**
**Incidences of Selected Nonneoplastic Lesions in Rats in the 13-Week Dermal Study of Triethanolamine**

| | 0 mg/kg | 125 mg/kg | 250 mg/kg | 500 mg/kg | 1,000 mg/kg | 2,000 mg/kg |
|---|---|---|---|---|---|---|
| **Male** | | | | | | |
| Skin, Site of Application[a] | 10 | 10 | 10 | 10 | 10 | 10 |
| Acanthosis[b] | 0 | 0 | 6** (1.2)[c] | 9** (1.2) | 10** (2.0) | 10** (3.5) |
| Inflammation, Chronic Active | 0 | 0 | 2 (1.5) | 2 (2.0) | 10** (2.7) | 10** (4.0) |
| Pituitary Gland, Pars Intermedia | 9 | 6 | 7 | 8 | 9 | 8 |
| Hypertrophy | 0 | 0 | 0 | 0 | 0 | 5** (1.0) |
| **Female** | | | | | | |
| Skin, Site of Application | 10 | 10 | 10 | 10 | 10 | 10 |
| Acanthosis | 0 | 0 | 0 | 4* (1.3) | 8** (1.6) | 10** (2.8) |
| Inflammation, Chronic Active | 0 | 0 | 0 | 1 (2.0) | 5* (2.6) | 10** (3.9) |
| Kidney, Renal Tubule | 10 | 10 | 10 | 10 | 10 | 10 |
| Regeneration (Nephropathy) | 2 (1.0) | 3 (1.0) | 5 (1.0) | 7* (1.0) | 10** (1.4) | 8* (1.4) |
| Mineralization | 3 (1.0) | 9** (1.1) | 6 (1.0) | 7 (1.6) | 9** (1.9) | 9** (1.4) |
| Pituitary Gland, Pars Intermedia | 6 | 8 | 8 | 8 | 6 | 9 |
| Hypertrophy | 0 | 0 | 0 | 0 | 1 (1.0) | 9** (1.7) |

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

## 2-Year Study

### *Survival*

Estimates of 2-year survival probabilities for male and female rats are shown in Table 4 and in the Kaplan-Meier survival curves (Figure 1). The survival rates of males receiving 32 mg/kg and females receiving 250 mg/kg were slightly less than those of the vehicle controls.

### *Body Weights and Clinical Findings*

Mean body weights are given in Figure 2 and Tables 5 and 6. The mean body weight of females administered 250 mg/kg ranged from 9% to 12% less than that of the vehicle controls between weeks 73 and 93; however, at the end of the study, the mean body weight of this group was only 7% less than that of the vehicle controls. Mean body weights of dosed males were similar to those of the vehicle controls throughout the study. Male and female rats receiving triethanolamine had irritated skin at the site of application; in dosed females, the site of application also had a crusty appearance. The number of animals in which these findings were observed increased with increasing dose.

### *Organ Weights*

At the 15-month interim evaluation, the absolute left and right kidney weights and relative right kidney weight of females administered 250 mg/kg were slightly greater than those of the vehicle controls (Table F2); the organ weights of dosed males were similar to those of the vehicle controls.

**TABLE 4**
**Survival of Rats in the 2-Year Dermal Study of Triethanolamine**

| | 0 mg/kg | 32 mg/kg | 63 mg/kg | 125 mg/kg |
|---|---|---|---|---|
| **Male** | | | | |
| Animals initially in study | 60 | 60 | 60 | 60 |
| 15-Month interim evaluation[a] | 10 | 10 | 10 | 10 |
| Accidental deaths[a] | 2 | 0 | 0 | 0 |
| Missexed[a] | 0 | 0 | 1 | 0 |
| Moribund | 18 | 27 | 25 | 23 |
| Natural deaths | 9 | 12 | 6 | 8 |
| Animals surviving to study termination | 21 | 11 | 18 | 19 |
| Percent probability of survival at the end of study[b] | 45 | 22 | 37 | 38 |
| Mean survival (days)[c] | 645 | 651 | 641 | 653 |
| Survival analysis[d] | P=0.861 | P=0.053 | P=0.645 | P=0.481 |

| | 0 mg/kg | 63 mg/kg | 125 mg/kg | 250 mg/kg |
|---|---|---|---|---|
| **Female** | | | | |
| Animals initially in study | 60 | 60 | 60 | 60 |
| 15-Month interim evaluation[a] | 10 | 10 | 10 | 10 |
| Moribund | 11 | 4 | 12 | 17 |
| Natural deaths | 14 | 17 | 13 | 15 |
| Animals surviving to study termination | 25 | 29 | 25 | 18[e] |
| Percent probability of survival at the end of study | 50 | 58 | 50 | 36 |
| Mean survival (days) | 678 | 676 | 672 | 605 |
| Survival analysis | P=0.017 | P=0.658N | P=1.000 | P=0.056 |

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

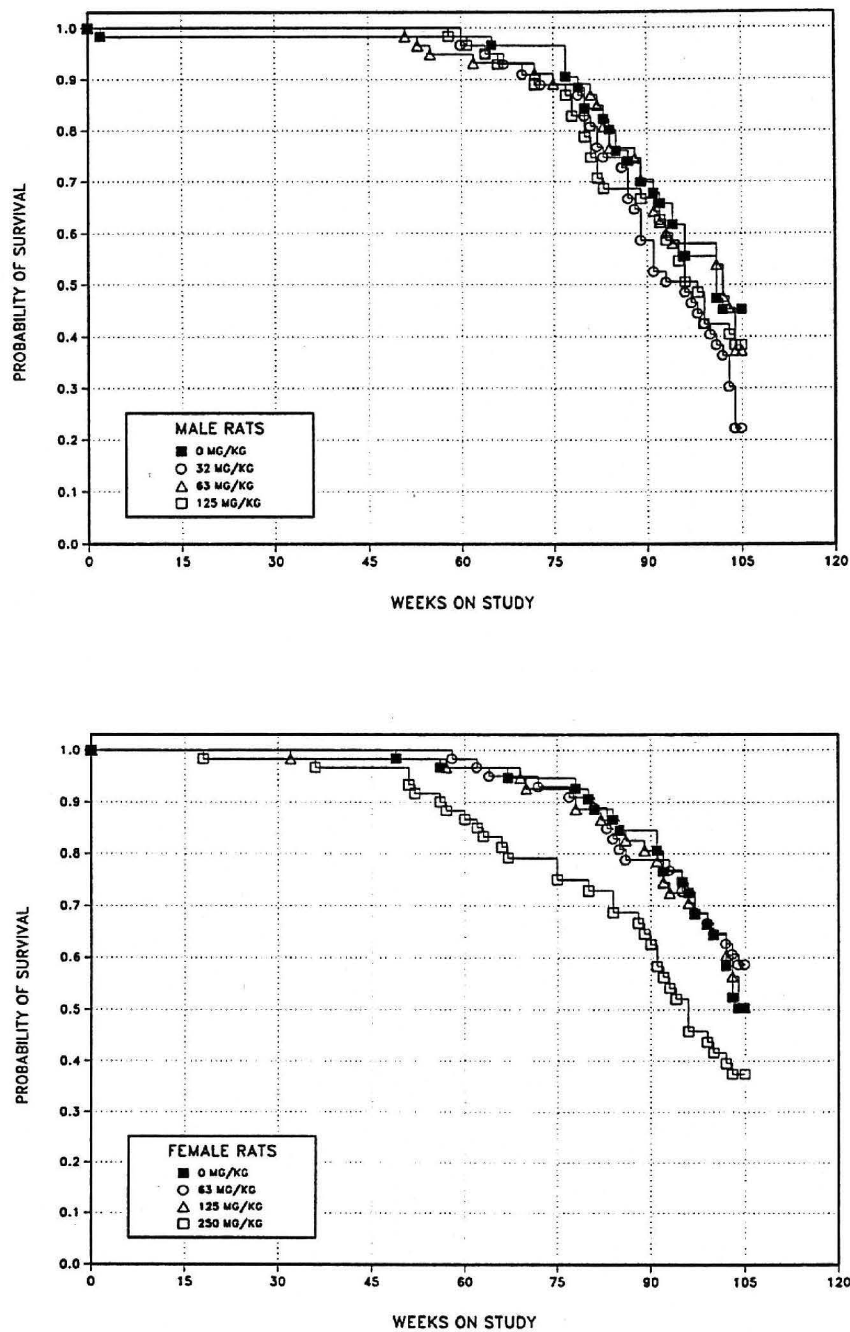
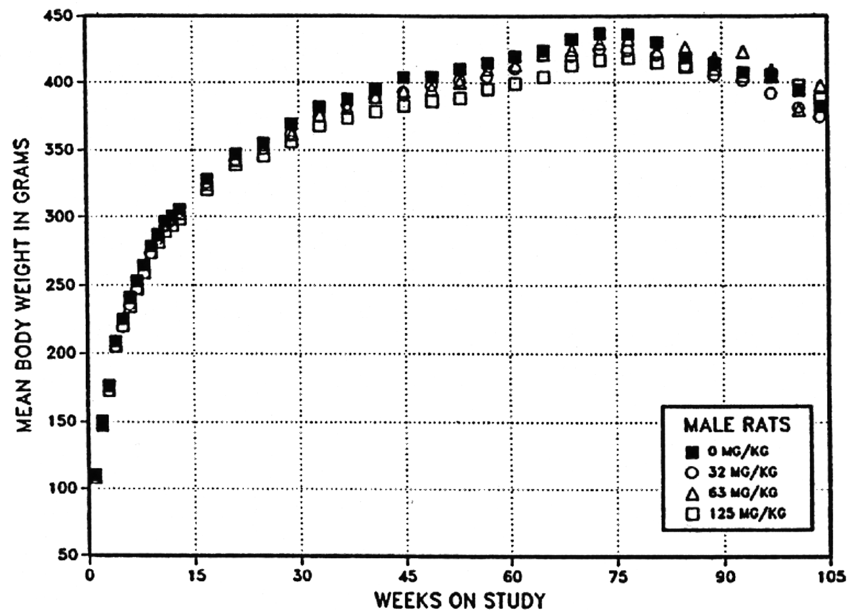



**FIGURE 1**
**Kaplan-Meier Survival Curves for Male and Female Rats Administered Triethanolamine in Acetone by Dermal Application for 2 Years**



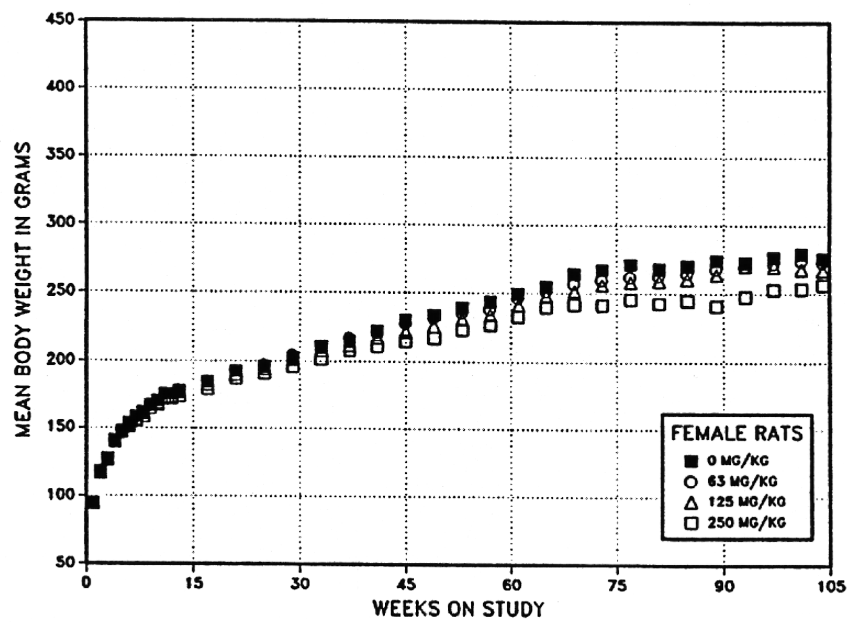




FIGURE 2
**Growth Curves for Male and Female Rats Administered Triethanolamine in Acetone by Dermal Application for 2 Years**

**Table 5**
**Mean Body Weights and Survival of Male Rats in the 2-Year Dermal Study of Triethanolamine**

| Weeks on Study | 0 mg/kg | | 32 mg/kg | | | 63 mg/kg | | | 125 mg/kg | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Av. Wt. (g) | No. of Survivors | Av. Wt. (g) | Wt. (% of controls) | No. of Survivors | Av. Wt. (g) | Wt. (% of controls) | No. of Survivors | Av. Wt. (g) | Wt. (% of controls) | No. of Survivors |
| 1 | 110 | 60 | 107 | 97 | 60 | 110 | 100 | 59 | 108 | 98 | 60 |
| 2 | 151 | 60 | 148 | 98 | 60 | 150 | 100 | 59 | 147 | 98 | 60 |
| 3 | 177 | 59 | 173 | 98 | 60 | 176 | 100 | 59 | 173 | 98 | 60 |
| 4 | 209 | 59 | 205 | 98 | 60 | 209 | 100 | 59 | 205 | 98 | 60 |
| 5 | 225 | 59 | 219 | 97 | 60 | 226 | 101 | 59 | 220 | 98 | 60 |
| 6 | 242 | 59 | 235 | 97 | 60 | 241 | 100 | 59 | 234 | 97 | 60 |
| 7 | 253 | 59 | 247 | 98 | 60 | 253 | 100 | 59 | 247 | 98 | 60 |
| 8 | 265 | 59 | 259 | 98 | 60 | 265 | 100 | 59 | 259 | 98 | 60 |
| 9 | 279 | 59 | 274 | 98 | 60 | 279 | 100 | 59 | 274 | 98 | 60 |
| 10 | 287 | 59 | 283 | 99 | 60 | 287 | 100 | 59 | 281 | 98 | 60 |
| 11 | 297 | 59 | 293 | 99 | 60 | 294 | 99 | 59 | 289 | 97 | 60 |
| 12 | 301 | 59 | 297 | 99 | 60 | 299 | 99 | 59 | 294 | 98 | 60 |
| 13 | 306 | 59 | 303 | 99 | 60 | 302 | 99 | 59 | 298 | 98 | 60 |
| 17 | 328 | 59 | 325 | 99 | 60 | 324 | 99 | 59 | 320 | 98 | 60 |
| 21 | 347 | 59 | 342 | 99 | 60 | 342 | 99 | 59 | 338 | 97 | 60 |
| 25 | 355 | 59 | 351 | 99 | 60 | 352 | 99 | 59 | 345 | 97 | 60 |
| 29 | 369 | 59 | 362 | 98 | 60 | 361 | 98 | 59 | 356 | 96 | 60 |
| 33 | 382 | 59 | 375 | 98 | 60 | 375 | 98 | 59 | 368 | 96 | 60 |
| 37 | 388 | 59 | 384 | 99 | 60 | 382 | 98 | 59 | 374 | 96 | 60 |
| 41 | 395 | 59 | 389 | 99 | 60 | 390 | 99 | 59 | 379 | 96 | 60 |
| 45 | 404 | 59 | 393 | 97 | 60 | 394 | 98 | 59 | 383 | 95 | 60 |
| 49 | 404 | 59 | 398 | 98 | 60 | 396 | 98 | 59 | 387 | 96 | 60 |
| 53 | 411 | 59 | 402 | 98 | 60 | 401 | 98 | 57 | 389 | 95 | 60 |
| 57 | 415 | 59 | 405 | 98 | 60 | 410 | 99 | 56 | 396 | 95 | 60 |
| 61 | 420 | 59 | 411 | 98 | 58 | 413 | 98 | 56 | 399 | 95 | 59 |
| 65 | 424 | 59 | 420 | 99 | 57 | 422 | 99 | 55 | 404 | 95 | 57 |
| 69[a] | 433 | 47 | 420 | 97 | 46 | 425 | 98 | 45 | 413 | 95 | 46 |
| 73 | 437 | 47 | 425 | 97 | 44 | 430 | 98 | 44 | 417 | 95 | 44 |
| 77 | 437 | 46 | 424 | 97 | 44 | 432 | 99 | 43 | 418 | 96 | 43 |
| 81 | 430 | 41 | 420 | 98 | 41 | 423 | 98 | 42 | 415 | 97 | 37 |
| 85 | 419 | 37 | 412 | 99 | 37 | 426 | 102 | 37 | 412 | 98 | 34 |
| 89 | 414 | 35 | 405 | 98 | 30 | 419 | 101 | 35 | 410 | 99 | 33 |
| 93 | 408 | 32 | 402 | 99 | 26 | 423 | 104 | 30 | 405 | 99 | 30 |
| 97 | 406 | 27 | 392 | 97 | 24 | 410 | 101 | 28 | 404 | 100 | 25 |
| 101 | 395 | 26 | 382 | 97 | 19 | 380 | 96 | 26 | 398 | 101 | 21 |
| 104 | 382 | 22 | 375 | 98 | 13 | 398 | 104 | 18 | 388 | 101 | 19 |
| **Mean for weeks** | | | | | | | | | | | |
| 1-13 | 239 | | 234 | 98 | | 238 | 100 | | 233 | 97 | |
| 14-52 | 375 | | 369 | 98 | | 368 | 98 | | 361 | 96 | |
| 53-104 | 417 | | 407 | 98 | | 415 | 100 | | 405 | 97 | |

[a] Interim evaluation occurred during week 66.

**TABLE 6**
**Mean Body Weights and Survival of Female Rats in the 2-Year Dermal Study of Triethanolamine**

| Weeks on Study | 0 mg/kg | | 63 mg/kg | | | 125 mg/kg | | | 250 mg/kg | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Av. Wt. (g) | No. of Survivors | Av. Wt. (g) | Wt. (% of controls) | No. of Survivors | Av. Wt. (g) | Wt. (% of controls) | No. of Survivors | Av. Wt. (g) | Wt. (% of controls) | No. of Survivors |
| 1 | 95 | 60 | 95 | 100 | 60 | 94 | 100 | 60 | 95 | 100 | 60 |
| 2 | 117 | 60 | 118 | 101 | 60 | 117 | 101 | 60 | 118 | 101 | 60 |
| 3 | 127 | 60 | 128 | 100 | 60 | 127 | 100 | 60 | 126 | 99 | 60 |
| 4 | 141 | 60 | 140 | 100 | 60 | 140 | 100 | 60 | 140 | 99 | 60 |
| 5 | 147 | 60 | 148 | 101 | 60 | 148 | 101 | 60 | 146 | 99 | 60 |
| 6 | 153 | 60 | 154 | 100 | 60 | 152 | 100 | 60 | 151 | 99 | 60 |
| 7 | 158 | 60 | 157 | 100 | 60 | 157 | 99 | 60 | 155 | 98 | 60 |
| 8 | 162 | 60 | 161 | 100 | 60 | 161 | 99 | 60 | 158 | 98 | 60 |
| 9 | 167 | 60 | 168 | 101 | 60 | 167 | 100 | 60 | 164 | 99 | 60 |
| 10 | 170 | 60 | 170 | 100 | 60 | 169 | 99 | 60 | 167 | 98 | 60 |
| 11 | 176 | 60 | 175 | 100 | 60 | 173 | 99 | 60 | 171 | 98 | 60 |
| 12 | 175 | 60 | 176 | 100 | 60 | 173 | 99 | 60 | 171 | 98 | 60 |
| 13 | 177 | 60 | 178 | 100 | 60 | 176 | 99 | 60 | 173 | 98 | 60 |
| 17 | 184 | 60 | 185 | 100 | 60 | 182 | 99 | 60 | 179 | 97 | 60 |
| 21 | 193 | 60 | 193 | 100 | 60 | 190 | 99 | 60 | 187 | 97 | 59 |
| 25 | 196 | 60 | 197 | 101 | 60 | 194 | 99 | 60 | 191 | 97 | 59 |
| 29 | 202 | 60 | 204 | 101 | 60 | 201 | 99 | 60 | 196 | 97 | 59 |
| 33 | 211 | 60 | 210 | 100 | 60 | 208 | 99 | 59 | 201 | 96 | 59 |
| 37 | 214 | 60 | 217 | 101 | 60 | 212 | 99 | 59 | 208 | 97 | 58 |
| 41 | 222 | 60 | 221 | 100 | 60 | 217 | 98 | 59 | 211 | 95 | 58 |
| 45 | 230 | 60 | 227 | 99 | 60 | 222 | 96 | 59 | 215 | 94 | 58 |
| 49 | 234 | 59 | 231 | 99 | 60 | 226 | 97 | 59 | 217 | 93 | 58 |
| 53 | 239 | 59 | 235 | 99 | 60 | 231 | 97 | 59 | 223 | 93 | 55 |
| 57 | 243 | 58 | 238 | 98 | 60 | 234 | 96 | 59 | 227 | 93 | 53 |
| 61 | 250 | 58 | 246 | 99 | 59 | 241 | 97 | 58 | 233 | 93 | 52 |
| 65 | 255 | 58 | 251 | 99 | 57 | 248 | 97 | 58 | 240 | 94 | 50 |
| 69[a] | 264 | 47 | 257 | 97 | 47 | 252 | 95 | 47 | 242 | 92 | 38 |
| 73 | 267 | 47 | 260 | 97 | 46 | 256 | 96 | 46 | 241 | 90 | 38 |
| 77 | 271 | 47 | 262 | 97 | 45 | 258 | 95 | 46 | 246 | 91 | 36 |
| 81 | 268 | 45 | 263 | 98 | 44 | 259 | 97 | 44 | 243 | 91 | 35 |
| 85 | 270 | 43 | 265 | 98 | 41 | 261 | 96 | 42 | 245 | 90 | 33 |
| 89 | 274 | 42 | 268 | 98 | 39 | 264 | 96 | 40 | 241 | 88 | 31 |
| 93 | 273 | 38 | 270 | 99 | 38 | 270 | 99 | 36 | 248 | 91 | 26 |
| 97 | 277 | 34 | 272 | 98 | 35 | 270 | 98 | 34 | 253 | 92 | 22 |
| 101 | 280 | 32 | 274 | 98 | 32 | 268 | 96 | 32 | 254 | 91 | 20 |
| 104 | 276 | 26 | 273 | 99 | 30 | 267 | 97 | 27 | 257 | 93 | 18 |
| **Mean for weeks** | | | | | | | | | | | |
| 1-13 | 151 | | 151 | 100 | | 150 | 99 | | 149 | 99 | |
| 14-52 | 210 | | 209 | 100 | | 206 | 98 | | 201 | 96 | |
| 53-104 | 265 | | 260 | 98 | | 256 | 97 | | 242 | 91 | |

[a] Interim evaluation occurred during week 66.

### *Pathology and Statistical Analyses*

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

*Skin:* Gross lesions attributed to triethanolamine administration consisted of multiple, small, randomly located, red or brown lesions or crusts at the site of application in females. Increased incidences of nonneoplastic lesions at the site of application in dosed rats were observed at the 15-month interim evaluation and at the end of the 2-year study (Table 7). Lesions occurred more frequently in females than in males receiving equivalent doses. Lesions consisted of thickened epidermis (acanthosis) and ulceration with associated chronic active inflammation in dosed males and females, as well as erosion in dosed females.

At the 15-month interim evaluation, two males in the 125 mg/kg group had minimal acanthosis at the site of application. Females receiving 125 or 250 mg/kg had acanthosis, inflammation, and ulceration. Acanthosis and inflammation were of mild average severity; the average severity of ulceration was mild in the 125 mg/kg group and moderate in the 250 mg/kg group. At 2 years, the incidence of acanthosis in males administered 125 mg/kg and the incidences of acanthosis, inflammation, and ulceration in dosed females were greater than in the vehicle controls; additionally, males in the 125 mg/kg group had greater incidences of inflammation and ulceration than the vehicle controls. The incidences of erosion, which was diagnosed only in areas distinctly removed from ulceration, were significantly greater in females receiving 125 or 250 mg/kg than in the vehicle controls at 2 years.

The epidermis covering the entire site of application was generally mildly thickened (two to four times) relative to that of the vehicle controls (Plates 1 and 2), with neutrophils occasionally observed within the epidermis. Ulcers were random and multifocal and were of mild to moderate severity. Ulcers were characterized by complete segmental necrosis of epidermis, with variable erosion of the dermis and associated chronic active inflammation (neutrophils, lymphocytes, and macrophages). Ulcerated areas were covered with cellular debris, keratin, fibrin, and inflammatory cells composing the "crusts" noted grossly. Erosion consisted of necrosis of the superficial layers of epidermis and did not extend into the dermis.

At 2 years, one male in the 125 mg/kg group had a keratoacanthoma at the site of application (Tables 7 and A1). However, the incidences of keratoacanthoma and squamous cell papilloma of the skin (all sites) were slightly less in dosed males than in the vehicle controls (Table A3). No keratoacanthomas or squamous cell papillomas occurred in vehicle control male rats in the only other dermal study with an acetone vehicle in the NTP database; however, the incidences of keratoacanthoma (10%) and squamous cell papilloma (6%) in the vehicle controls in the present study fall within the historical range for these neoplasms in male rats in NTP feed studies (keratoacanthoma, 0%-10%; squamous cell papilloma, 0%-8%). One vehicle control male had a basal cell adenoma at the site of application; this neoplasm did not occur in dosed males (Tables 7 and A1). Additionally, one vehicle control female had a squamous cell papilloma and one female in the 63 mg/kg group had a keratoacanthoma away from the site of application; no skin neoplasms occurred in females administered 125 or 250 mg/kg triethanolamine (Table B1). Squamous cell papillomas were observed in 6 of 1,202 females in NTP feed studies (range 0%-2%) but did not occur in the other dermal study.

**TABLE 7**
**Incidences of Neoplasms and Nonneoplastic Lesions of the Skin at the Site of Application in Rats in the 2-Year Dermal Study of Triethanolamine**

| | 0 mg/kg | 32 mg/kg | 63 mg/kg | 125 mg/kg |
|---|---|---|---|---|
| **Male** | | | | |
| **15-Month Interim Evaluation** | | | | |
| Number Examined Microscopically | 10 | 10 | 10 | 10 |
| Acanthosis[a] | 0 | 0 | 0 | 2 (1.0)[b] |
| **2-Year Study** | | | | |
| Number Examined Microscopically | 50 | 50 | 49 | 50 |
| Acanthosis | 1 (1.0) | 1 (1.0) | 1 (1.0) | 9** (1.7) |
| Inflammation, Chronic Active | 0 | 2 (1.0) | 0 | 8** (1.9) |
| Ulcer | 0 | 0 | 0 | 5* (3.2) |
| Erosion | 0 | 0 | 0 | 1 (3.0) |
| Basal Cell Adenoma | 1 | 0 | 0 | 0 |
| Keratoacanthoma | 0 | 0 | 0 | 1 |
| | **0 mg/kg** | **63 mg/kg** | **125 mg/kg** | **250 mg/kg** |
| **Female** | | | | |
| **15-Month Interim Evaluation** | | | | |
| Number Examined Microscopically | 10 | 10 | 10 | 10 |
| Acanthosis | 0 | 1 (2.0) | 7** (2.3) | 6** (2.0) |
| Inflammation, Chronic Active | 0 | 1 (2.0) | 7** (2.1) | 6** (2.0) |
| Ulcer | 0 | 1 (2.0) | 7** (2.1) | 6** (2.5) |
| **2-Year Study** | | | | |
| Number Examined Microscopically | 50 | 50 | 50 | 50 |
| Acanthosis | 2 (2.0) | 10* (2.1) | 30** (2.1) | 32** (2.0) |
| Inflammation, Chronic Active | 2 (2.5) | 10* (2.3) | 30** (2.1) | 32** (2.2) |
| Ulcer | 2 (3.5) | 7 (3.4) | 22** (3.2) | 27** (2.7) |
| Erosion | 1 (3.0) | 6 (3.0) | 16** (3.0) | 14** (2.7) |

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

*Kidney:* No kidney lesions were observed at the 15-month interim evaluation; however, the absolute kidney weights of females in the 250 mg/kg group were greater than those of the vehicle controls. At 2 years, the incidence of adenoma of the renal tubule epithelium in males in the 63 mg/kg group was marginally greater than that in the vehicle controls (Tables 8 and A3). No renal tubule adenomas occurred in vehicle control male F344/N rats in the other dermal study in the NTP database with an acetone vehicle; the incidence of this neoplasm in untreated control males ranged from 0% to 6% (Table A4). Although the neoplasm incidence observed in the 63 mg/kg group exceeds the incidence in untreated controls in the NTP database, an equal or greater incidence did not occur in males in the 125 mg/kg group, and the neoplasms in all groups were small and were detected only microscopically. Additionally, the incidences of hyperplasia were not increased in dosed males (Tables 8 and A5). Because of these uncertain findings, an extended evaluation of the kidneys of vehicle control and dosed males was conducted. In this extended evaluation, additional proliferative lesions (hyperplasia and adenoma) were identified, with similar incidences in all groups (Table 8); however, the incidence of adenoma was marginally, although not significantly, greater in the 125 mg/kg group than in the vehicle controls. Nephropathy was observed in nearly all male rats in all groups (Table 8); there was no apparent difference in the severity of this lesion between dosed and vehicle control groups.

The proliferative lesions were phenotypically similar to those spontaneously occurring in F344/N rats. Focal renal tubule hyperplasia consisted of single or multiple adjacent tubule profiles containing three or more layers of epithelial cells that partially or completely filled the tubule lumens and that usually caused slight dilatation of the tubule. The hyperplastic cells were generally slightly larger than normal epithelial cells and were polygonal, with abundant eosinophilic cytoplasm. All adenomas were small (less than 0.9 cm) and expansile and usually consisted of multiple, variably sized tubule profiles, some with necrotic centers. Cells of adenomas were generally larger than normal and polygonal, with abundant eosinophilic cytoplasm.

*Thyroid Gland:* The incidence of C-cell adenoma or carcinoma (combined) was marginally greater in female rats in the 250 mg/kg group than in the vehicle controls (0 mg/kg, 1/50; 63 mg/kg, 2/50; 125 mg/kg, 2/50; 250 mg/kg, 6/49; Tables B1 and B3). This greater incidence was not considered to be related to the administration of triethanolamine. Thyroid gland C-cell neoplasms are relatively common, spontaneously occurring neoplasms in male and female rats, occurring in 6 of 46 vehicle control females (13%) in the other NTP dermal study with an acetone vehicle and in 175 of 1,196 untreated control females (15%) in NTP feed studies. Further, of the 24 feed studies in the database, no control group had an incidence of less than 6% for C-cell neoplasms. Additionally, proliferative lesions of the thyroid gland C-cells generally represent a morphological and biological continuum, with progression from hyperplasia to adenoma to carcinoma. In this study, there was often difficulty in determining whether the proliferative lesions were adenomas or hyperplasia. The incidences of hyperplasia in dosed females (8/50, 4/50, 10/50, 2/49; Table B4) did not support a treatment effect, and when the incidences of hyperplasia and neoplasms were combined, the results indicated no increased incidences of proliferative thyroid gland C-cell lesions in dosed female rats.

**TABLE 8**
**Incidences of Neoplasms and Nonneoplastic Lesions of the Renal Tubule in Rats in the 2-Year Dermal Study of Triethanolamine**

| | 0 mg/kg | 32 mg/kg | 63 mg/kg | 125 mg/kg |
|---|---|---|---|---|
| **Male** | | | | |
| **15-Month Interim Evaluation** | | | | |
| **Single Sections (Standard Evaluation)** | | | | |
| Number Examined Microscopically | 10 | 10 | 10 | 10 |
| Nephropathy, Chronic[a] | 10 (2.0)[b] | 9 (2.0) | 10 (2.0) | 10 (1.6) |
| **Step Sections (Extended Evaluation)** | | | | |
| Number Examined Microscopically | 10 | 10 | 10 | 10 |
| Adenoma | 0 | 0 | 0 | 1 |
| **Single Sections and Step Sections (Combined)** | | | | |
| Number Examined Microscopically | 10 | 10 | 10 | 10 |
| Nephropathy, Chronic | 10 (2.0) | 9 (2.0) | 10 (2.0) | 10 (1.6) |
| Adenoma | 0 | 0 | 0 | 1 |
| **2-Year Study** | | | | |
| **Single Sections (Standard Evaluation)** | | | | |
| Number Examined Microscopically | 50 | 50 | 49 | 50 |
| Hyperplasia[c] | 1 (3.0) | 0 | 1 (1.0) | 1 (3.0) |
| Nephropathy, Chronic | 48 (2.6) | 49 (2.6) | 49 (2.6) | 50 (2.7) |
| Adenoma[d] | 0 | 1 | 4 | 2 |
| **Step Sections (Extended Evaluation)** | | | | |
| Number Examined Microscopically | 50 | 50 | 49 | 50 |
| Hyperplasia | 8 (1.5) | 8 (2.6)[e] | 6 (1.6) | 5 (2.4) |
| Adenoma | 1 | 1 | 2 | 2 |
| Oncocytoma | 0 | 1 | 0 | 0 |
| **Single Sections and Step Sections (Combined)** | | | | |
| Number Examined Microscopically | 50 | 50 | 49 | 50 |
| Hyperplasia[c] | 9 (1.7) | 8 (2.6) | 7 (1.5) | 6 (2.5) |
| Nephropathy, Chronic | 48 (2.6) | 49 (2.6) | 49 (2.6) | 50 (2.7) |
| Adenoma | 1 | 2 | 6 | 4 |
| Oncocytoma | 0 | 1 | 0 | 0 |

(continued)

**TABLE 8**
**Incidences of Neoplasms and Nonneoplastic Lesions of the Kidney in Rats in the 2-Year Dermal Study of Triethanolamine** (continued)

| | 0 mg/kg | 63 mg/kg | 125 mg/kg | 250 mg/kg |
|---|---|---|---|---|
| **Female** | | | | |
| **15-Month Interim Evaluation** | | | | |
| Number Examined Microscopically | 10 | 10 | 10 | 10 |
| Nephropathy, Chronic | 9 (1.0) | 8 (1.0) | 8 (1.0) | 4* (1.3) |
| **2-Year Study** | | | | |
| Number Examined Microscopically | 50 | 50 | 50 | 50 |
| Hyperplasia | 0 | 0 | 0 | 1 (1.0) |
| Nephropathy, Chronic | 45 (1.7) | 44 (1.5) | 41 (1.7) | 42 (1.5) |
| Adenoma | 1 | 1 | 0 | 0 |

* Significantly different (P≤0.05) from the vehicle control group by the Fisher exact test
[a] Number of animals with lesion
[b] Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked
[c] Includes hyperplasia and renal tubule hyperplasia
[d] Historical incidence for 2-year NTP dermal studies with acetone vehicle control groups (mean ± standard deviation): 0/100. Historical incidence for 2-year NTP feed studies with untreated control groups: 9/1,200 (0.8% ± 1.5%); range, 0%-6%.
[e] Severity grade was not given for one animal in this group.

*Uterus:* The incidence of stromal polyp of the uterus was marginally increased in females in the 125 mg/kg group, but not in the 250 mg/kg group (2/50, 1/50, 8/50, 5/50; Tables B1 and B3). Stromal polyps are relatively common, spontaneously occurring, benign neoplasms in female rats, occurring in 3 of 50 vehicle control females (6%) in the other dermal study with an acetone vehicle in the NTP database and in 178/1,202 untreated control females (16%) in NTP feed studies. Also, the vehicle control incidence of 4% is well below the historical incidence for untreated controls, and the incidence in the 125 mg/kg group is the same as the historical incidence for untreated controls. Therefore, the increased incidence of stromal polyp in females in the 125 mg/kg group was not considered to be related to triethanolamine administration.

*Pituitary Gland:* The incidences of hemosiderin pigment in the pituitary gland pars distalis increased with increasing dose in male rats (0 mg/kg, 23/50; 32 mg/kg, 24/50; 63 mg/kg, 32/48; 125 mg/kg, 35/50), and the incidence of angiectasis was also marginally greater in males administered 125 mg/kg than in the vehicle controls (30/50, 36/50, 29/48, 39/50) (Table A5). These are minimal changes in the incidence of common incidental lesions of uncertain biological significance. Conversely, the incidences of these lesions were lower in females administered 250 mg/kg than in the vehicle controls (hemosiderin pigmentation: 33/50, 29/50, 27/50, 22/50; angiectasis: 37/50, 35/50, 36/50, 29/50) (Table B4).

# MICE

## 13-WEEK STUDY

All mice survived to the end of the study (Table 9). The final mean body weight and weight gain of males in the 250 mg/kg group were less than those of the vehicle controls; the final mean body weights and weight gains of dosed females were similar to those of the vehicle controls. Clinical findings were observed only in mice in the 4,000 mg/kg groups and included scaliness, irritation, and discoloration at the site of triethanolamine application for males and females and skin erosion at this site in one male.

Clinical pathology results are listed in Table G2. The most prominent difference from vehicle control values involved serum sorbitol dehydrogenase activity; treatment-related decreases in sorbitol dehydrogenase activities occurred in all dosed groups of males and females. Typically, an increase in serum sorbitol dehydrogenase activity indicates an increase in hepatocellular leakage or permeability; decreases in enzyme activity are often seen but can be explained only infrequently. Decreases in enzyme activity could reflect altered enzyme synthesis, release from hepatocytes, catabolism, inactivation, inhibition, or excretion (Schmidt and Schmidt, 1987, 1989; Pappas, 1989).

**TABLE 9**
**Survival and Body Weights of Mice in the 13-Week Dermal Study of Triethanolamine**

| Dose (mg/kg) | Survival[a] | Mean Body Weight[b] (g) Initial | Final | Change | Final Weight Relative to Controls (%) |
|---|---|---|---|---|---|
| **Male** | | | | | |
| 0 | 10/10 | 23.3 ± 0.6 | 33.8 ± 0.5 | 10.5 ± 0.3 | |
| 250 | 10/10 | 22.5 ± 0.5 | 30.7 ± 0.7** | 8.2 ± 0.7* | 91 |
| 500 | 10/10 | 22.6 ± 0.5 | 31.8 ± 0.6 | 9.2 ± 0.8 | 94 |
| 1,000 | 10/10 | 22.7 ± 0.5 | 32.7 ± 0.7 | 9.9 ± 0.4 | 97 |
| 2,000 | 10/10 | 22.9 ± 0.3 | 32.2 ± 0.8 | 9.3 ± 0.5 | 95 |
| 4,000 | 10/10 | 22.4 ± 0.4 | 31.9 ± 0.6 | 9.4 ± 0.5 | 94 |
| **Female** | | | | | |
| 0 | 10/10 | 18.7 ± 0.4 | 28.3 ± 0.7 | 9.6 ± 0.5 | |
| 250 | 10/10 | 19.0 ± 0.3 | 28.2 ± 0.5 | 9.2 ± 0.4 | 100 |
| 500 | 10/10 | 18.5 ± 0.2 | 28.8 ± 0.6 | 10.2 ± 0.6 | 102 |
| 1,000 | 10/10 | 18.9 ± 0.3 | 28.8 ± 0.7 | 9.9 ± 0.5 | 102 |
| 2,000 | 10/10 | 19.0 ± 0.4 | 28.4 ± 0.5 | 9.4 ± 0.4 | 100 |
| 4,000 | 10/10 | 18.7 ± 0.3 | 27.5 ± 0.7 | 8.7 ± 0.6 | 97 |

* Significantly different ($P \leq 0.05$) from the vehicle control group by Williams' or Dunnett's test
** $P \leq 0.01$
[a] Number of animals surviving at 13 weeks/number initially in group
[b] Weights and weight changes are given as mean ± standard error.

Differences in other hematology and clinical chemistry parameters were minimal or transient and were not considered to be biologically relevant.

The absolute kidney and liver weights of males and females in the 4,000 mg/kg groups were significantly greater than those of the vehicle controls; relative kidney weights of males administered 1,000 mg/kg or greater and of all dosed groups of females were also greater than those of the vehicle controls (Table F9). The absolute and relative spleen weights of females in the 4,000 mg/kg group were significantly greater than those of the vehicle controls. Males administered 4,000 mg/kg had a greater relative heart weight than the vehicle controls.

No statistically significant differences in sperm morphology or vaginal cytology parameters occurred between dosed and vehicle control mice (Table H2).

At necropsy, the skin of males and females administered 4,000 mg/kg was crusted (7/10 males, 4/10 females) and white (1/10 males, 8/10 females), scaly (1/10 males), or both (5/10 males, 2/10 females) at the site of application. One female in the 2,000 mg/kg group also had crusted skin. Minimal epidermal thickening (acanthosis), up to twice the normal thickness, occurred in nearly all dosed animals and in one vehicle control female (Table 10); the severity of acanthosis was greater in the 4,000 mg/kg groups than in the lower dose groups. Chronic active inflammation occurred in the 4,000 mg/kg groups and in one female in the 2,000 mg/kg group, with some animals having erosion, inflammation, or both. In these animals, the underlying dermis was often thickened by chronic active inflammation, including fibrosis.

*Dose Selection Rationale:* Based on the presence of chronic inflammation at the site of application in the higher dose groups in the 13-week study, triethanolamine doses selected for use in the 2-year dermal study in mice were 200, 630, and 2,000 mg/kg for males and 100, 300, and 1,000 mg/kg for females.

**TABLE 10**
**Incidences of Selected Nonneoplastic Lesions of the Skin at the Site of Application in Mice in the 13-Week Dermal Study of Triethanolamine**

| | 0 mg/kg | 250 mg/kg | 500 mg/kg | 1,000 mg/kg | 2,000 mg/kg | 4,000 mg/kg |
|---|---|---|---|---|---|---|
| **Male** | | | | | | |
| Number Examined Microscopically | 10 | 10 | 10 | 10 | 10 | 10 |
| Acanthosis[a] | 0 | 8** (1.0)[b] | 9** (1.0) | 10** (1.0) | 10** (1.0) | 10** (2.0) |
| Inflammation, Chronic Active | 0 | 0 | 0 | 0 | 0 | 7** (2.9) |
| **Female** | | | | | | |
| Number Examined Microscopically | 10 | 10 | 10 | 10 | 10 | 10 |
| Acanthosis | 1 (1.0) | 10** (1.0) | 9** (1.0) | 10** (1.1) | 9** (1.1) | 10** (2.4) |
| Inflammation, Chronic Active | 0 | 0 | 0 | 0 | 1 (4.0) | 4* (3.0) |

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

## 2-YEAR STUDY

### *Survival*

Estimates of 2-year survival probabilities for male and female mice are shown in Table 11 and in the Kaplan-Meier survival curves (Figure 3). Survival rates of all dosed groups of males and females were similar to those of the vehicle controls.

### *Body Weights and Clinical Findings*

The mean body weight of males administered 2,000 mg/kg ranged from 8% to 10% less than that of the vehicle controls from week 69 through the end of the study; mean body weights of dosed and vehicle control females were similar throughout the study (Tables 12 and 13 and Figure 4).

Clinical findings included irritation and discoloration of the skin at the site of application for most males in the 2,000 mg/kg group and a few females in the 1,000 mg/kg group; males administered 200 or 630 mg/kg also had skin irritation. In the 2,000 mg/kg group, one male had thin skin and one male had crusty skin at the site of application. Clinical findings at sites other than the site of application included hair discoloration for males in the 2,000 mg/kg group and females in the 1,000 mg/kg group.

### *Organ Weights*

At the 15-month interim evaluation, the right kidney weights of male mice in the 630 and 2,000 mg/kg groups and the left kidney weights of males in the 2,000 mg/kg group were significantly greater than those of the vehicle controls (Table F4).

**TABLE 11**
**Survival of Mice in the 2-Year Dermal Study of Triethanolamine**

| | 0 mg/kg | 200 mg/kg | 630 mg/kg | 2,000 mg/kg |
|---|---|---|---|---|
| **Male** | | | | |
| Animals initially in study | 60 | 60 | 60 | 60 |
| 15-Month interim evaluation[a] | 10 | 10 | 10 | 10 |
| Moribund | 2 | 5 | 3 | 6 |
| Natural deaths | 2 | 5 | 8 | 3 |
| Animals surviving to study termination | 46 | 40[e] | 39 | 41 |
| Percent probability of survival at the end of study[b] | 92 | 80 | 78 | 82 |
| Mean survival (days)[c] | 718 | 712 | 700 | 715 |
| Survival analysis[d] | P=0.623 | P=0.151 | P=0.087 | P=0.231 |
| | **0 mg/kg** | **100 mg/kg** | **300 mg/kg** | **1,000 mg/kg** |
| **Female** | | | | |
| Animals initially in study | 60 | 60 | 60 | 60 |
| 15-Month interim evaluation[a] | 10 | 10 | 10 | 10 |
| Moribund | 7 | 4 | 5 | 11 |
| Natural deaths | 4 | 6 | 7 | 2 |
| Animals surviving to study termination | 39[e] | 40 | 38 | 37 |
| Percent probability of survival at the end of study | 78 | 80 | 76 | 74 |
| Mean survival (days) | 669 | 695 | 697 | 694 |
| Survival analysis | P=0.661 | P=0.915N | P=1.000 | P=0.895 |

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

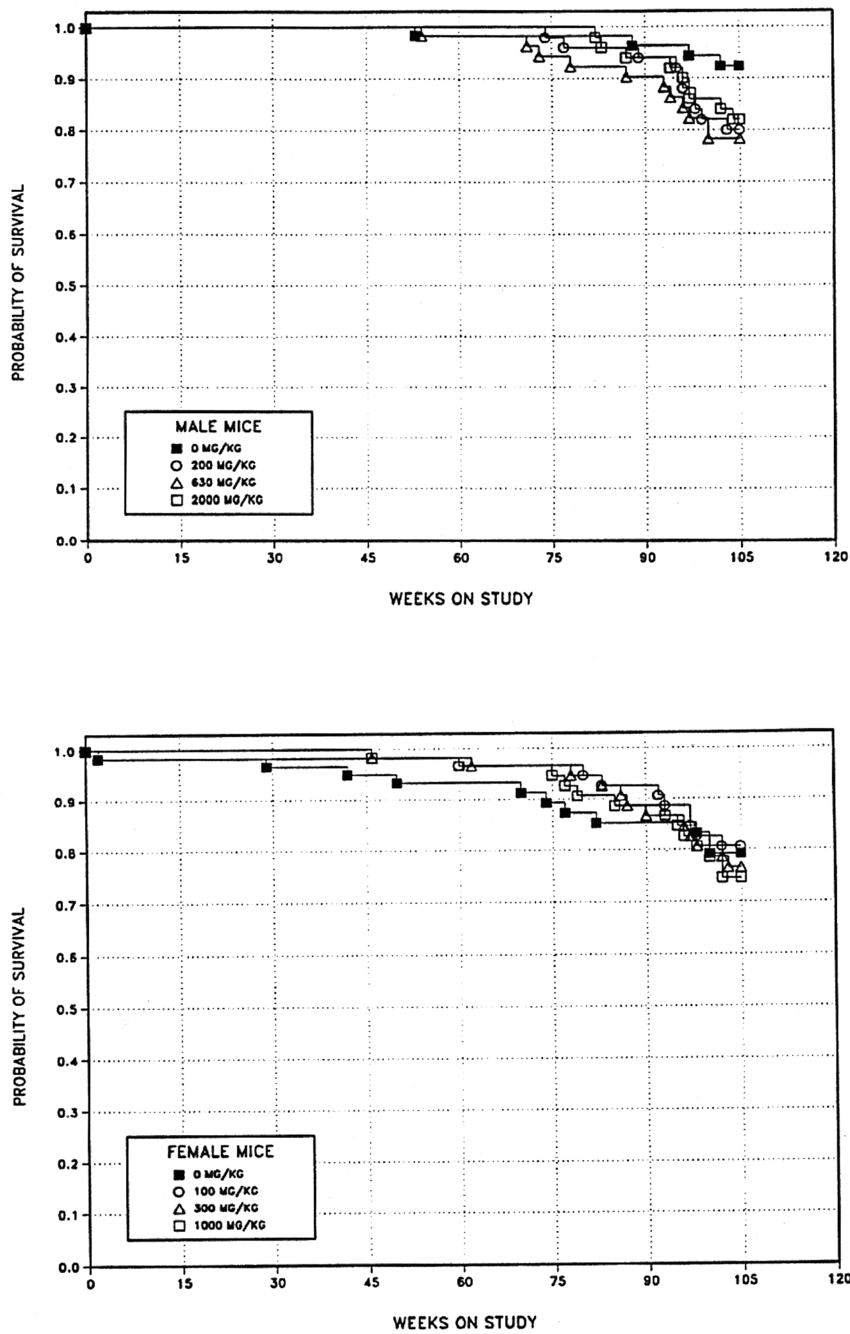



FIGURE 3
**Kaplan-Meier Survival Curves for Male and Female Mice Administered Triethanolamine in Acetone by Dermal Application for 2 Years**

**TABLE 12**
**Mean Body Weights and Survival of Male Mice in the 2-Year Dermal Study of Triethanolamine**

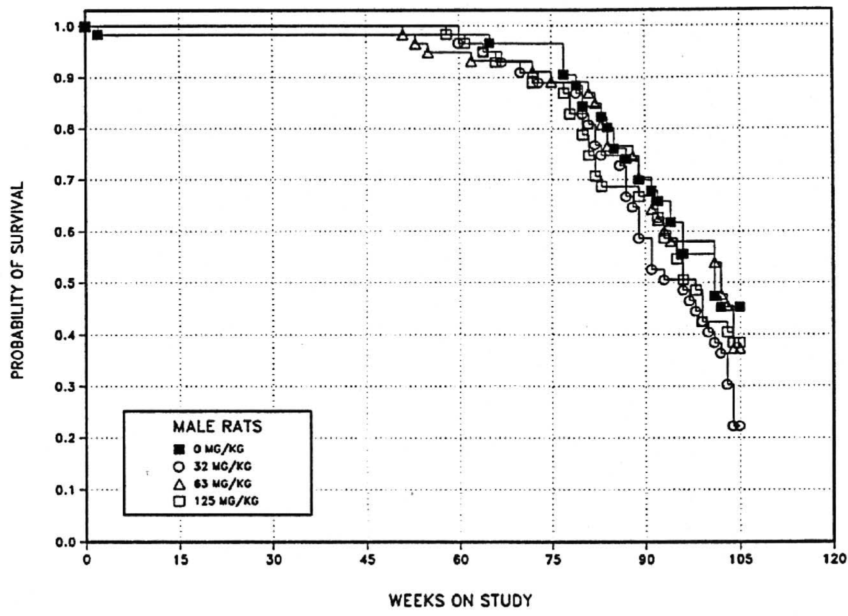
| Weeks on Study | 0 mg/kg | | 200 mg/kg | | | 630 mg/kg | | | 2,000 mg/kg | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Av. Wt. (g) | No. of Survivors | Av. Wt. (g) | Wt. (% of controls) | No. of Survivors | Av. Wt. (g) | Wt. (% of controls) | No. of Survivors | Av. Wt. (g) | Wt. (% of controls) | No. of Survivors |
| 1 | 21.3 | 60 | 21.2 | 100 | 60 | 20.6 | 97 | 60 | 20.7 | 97 | 60 |
| 2 | 23.3 | 60 | 23.6 | 101 | 60 | 23.3 | 100 | 60 | 23.6 | 101 | 60 |
| 3 | 25.5 | 60 | 25.2 | 99 | 60 | 25.1 | 98 | 60 | 25.6 | 100 | 60 |
| 4 | 26.1 | 60 | 25.9 | 99 | 60 | 26.0 | 100 | 60 | 26.6 | 102 | 60 |
| 5 | 26.4 | 60 | 26.4 | 100 | 60 | 26.7 | 101 | 60 | 26.8 | 102 | 60 |
| 6 | 27.0 | 60 | 27.0 | 100 | 60 | 27.0 | 100 | 60 | 27.3 | 101 | 60 |
| 7 | 27.7 | 60 | 27.5 | 99 | 60 | 27.7 | 100 | 60 | 28.1 | 101 | 60 |
| 8 | 28.5 | 60 | 28.6 | 100 | 60 | 28.8 | 101 | 60 | 29.1 | 102 | 60 |
| 9 | 29.7 | 60 | 29.7 | 100 | 60 | 29.7 | 100 | 60 | 30.1 | 101 | 60 |
| 10 | 30.2 | 60 | 30.2 | 100 | 60 | 30.4 | 101 | 60 | 30.9 | 102 | 60 |
| 11 | 30.2 | 60 | 30.4 | 101 | 60 | 30.5 | 101 | 60 | 31.0 | 103 | 60 |
| 12 | 31.1 | 60 | 31.3 | 101 | 60 | 31.3 | 101 | 60 | 31.6 | 102 | 60 |
| 13 | 31.8 | 60 | 32.0 | 101 | 60 | 31.9 | 100 | 60 | 32.0 | 101 | 60 |
| 17 | 34.1 | 60 | 34.5 | 101 | 60 | 34.6 | 102 | 60 | 34.5 | 101 | 60 |
| 21 | 36.3 | 60 | 36.2 | 100 | 60 | 36.4 | 100 | 60 | 36.6 | 101 | 60 |
| 25 | 38.1 | 60 | 38.2 | 100 | 60 | 38.3 | 101 | 60 | 38.5 | 101 | 60 |
| 29 | 39.4 | 60 | 39.5 | 100 | 60 | 39.6 | 101 | 60 | 40.1 | 102 | 60 |
| 33 | 43.3 | 60 | 43.4 | 100 | 60 | 43.4 | 100 | 60 | 43.7 | 101 | 60 |
| 37 | 45.6 | 60 | 45.6 | 100 | 60 | 46.0 | 101 | 60 | 45.9 | 101 | 60 |
| 41 | 46.0 | 60 | 46.5 | 101 | 60 | 46.4 | 101 | 60 | 46.7 | 102 | 60 |
| 45 | 48.1 | 60 | 48.1 | 100 | 60 | 48.0 | 100 | 60 | 48.6 | 101 | 60 |
| 49 | 48.0 | 60 | 48.3 | 101 | 60 | 47.8 | 100 | 60 | 48.7 | 102 | 60 |
| 53 | 48.4 | 59 | 48.2 | 100 | 60 | 48.2 | 100 | 60 | 48.9 | 101 | 60 |
| 57 | 48.6 | 59 | 48.6 | 100 | 60 | 48.5 | 100 | 59 | 49.3 | 101 | 60 |
| 61 | 50.5 | 59 | 50.0 | 99 | 60 | 49.9 | 99 | 59 | 50.3 | 100 | 60 |
| 65 | 49.7 | 59 | 49.3 | 99 | 60 | 49.7 | 100 | 59 | 49.5 | 100 | 60 |
| 69[a] | 49.9 | 49 | 49.2 | 99 | 50 | 49.6 | 99 | 49 | 46.9 | 94 | 50 |
| 73 | 50.0 | 49 | 49.4 | 99 | 50 | 49.8 | 100 | 47 | 44.9 | 90 | 50 |
| 77 | 50.2 | 49 | 48.7 | 97 | 49 | 49.0 | 98 | 47 | 46.3 | 92 | 50 |
| 81 | 50.2 | 49 | 48.9 | 97 | 48 | 49.3 | 98 | 46 | 45.8 | 91 | 50 |
| 85 | 50.5 | 49 | 48.6 | 96 | 48 | 49.2 | 97 | 46 | 46.5 | 92 | 48 |
| 89 | 50.8 | 48 | 48.3 | 95 | 48 | 49.8 | 98 | 45 | 46.6 | 92 | 47 |
| 93 | 50.1 | 48 | 46.7 | 93 | 47 | 48.1 | 96 | 44 | 45.0 | 90 | 47 |
| 97 | 48.7 | 48 | 45.1 | 93 | 44 | 46.8 | 96 | 42 | 44.9 | 92 | 44 |
| 101 | 48.6 | 47 | 44.9 | 92 | 41 | 46.5 | 96 | 39 | 43.5 | 90 | 43 |
| 104 | 48.4 | 46 | 45.0 | 93 | 40 | 47.0 | 97 | 39 | 44.0 | 91 | 42 |
| **Mean for weeks** | | | | | | | | | | | |
| 1-13 | 27.6 | | 27.6 | 100 | | 27.6 | 100 | | 28.0 | 101 | |
| 14-52 | 42.1 | | 42.3 | 100 | | 42.3 | 100 | | 42.6 | 101 | |
| 53-104 | 49.6 | | 47.9 | 97 | | 48.7 | 98 | | 46.6 | 94 | |

[a] Interim evaluation occurred during week 66.

**TABLE 13**
**Mean Body Weights and Survival of Female Mice in the 2-Year Dermal Study of Triethanolamine**

| Weeks on Study | 0 mg/kg | | 100 mg/kg | | | 300 mg/kg | | | 1,000 mg/kg | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Av. Wt. (g) | No. of Survivors | Av. Wt. (g) | Wt. (% of controls) | No. of Survivors | Av. Wt. (g) | Wt. (% of controls) | No. of Survivors | Av. Wt. (g) | Wt. (% of controls) | No. of Survivors |
| 1 | 17.6 | 60 | 17.4 | 99 | 60 | 17.6 | 100 | 60 | 17.4 | 99 | 60 |
| 2 | 19.4 | 59 | 19.4 | 100 | 59 | 19.7 | 102 | 60 | 19.4 | 100 | 60 |
| 3 | 21.1 | 59 | 21.1 | 100 | 59 | 21.0 | 100 | 60 | 21.0 | 100 | 60 |
| 4 | 21.6 | 59 | 21.8 | 101 | 59 | 22.1 | 102 | 60 | 22.1 | 102 | 60 |
| 5 | 22.8 | 59 | 23.0 | 101 | 59 | 23.1 | 101 | 60 | 23.2 | 102 | 60 |
| 6 | 23.5 | 59 | 23.4 | 100 | 59 | 23.4 | 100 | 60 | 23.9 | 102 | 60 |
| 7 | 24.9 | 59 | 24.4 | 98 | 59 | 24.9 | 100 | 60 | 25.1 | 101 | 60 |
| 8 | 25.6 | 59 | 25.6 | 100 | 59 | 26.0 | 102 | 60 | 25.9 | 101 | 60 |
| 9 | 26.4 | 59 | 26.2 | 99 | 59 | 26.6 | 101 | 60 | 26.5 | 100 | 60 |
| 10 | 26.7 | 59 | 26.6 | 100 | 59 | 27.0 | 101 | 60 | 26.7 | 100 | 60 |
| 11 | 27.2 | 59 | 26.9 | 99 | 59 | 27.3 | 100 | 60 | 27.4 | 101 | 60 |
| 12 | 27.7 | 59 | 27.7 | 100 | 59 | 28.1 | 101 | 60 | 28.0 | 101 | 60 |
| 13 | 28.5 | 59 | 28.1 | 99 | 59 | 29.0 | 102 | 60 | 28.6 | 100 | 60 |
| 17 | 30.8 | 59 | 30.8 | 100 | 59 | 30.8 | 100 | 60 | 30.7 | 100 | 60 |
| 21 | 32.7 | 59 | 32.8 | 100 | 59 | 32.8 | 100 | 60 | 32.5 | 99 | 60 |
| 25 | 34.1 | 59 | 34.1 | 100 | 59 | 34.6 | 102 | 60 | 34.6 | 102 | 60 |
| 29 | 35.7 | 58 | 35.9 | 101 | 59 | 35.8 | 100 | 60 | 36.1 | 101 | 60 |
| 33 | 38.9 | 58 | 38.8 | 100 | 59 | 39.2 | 101 | 60 | 39.3 | 101 | 60 |
| 37 | 41.9 | 58 | 41.1 | 98 | 59 | 41.3 | 99 | 60 | 41.8 | 100 | 60 |
| 41 | 42.7 | 58 | 42.4 | 99 | 59 | 42.6 | 100 | 60 | 42.8 | 100 | 60 |
| 45 | 45.0 | 57 | 44.6 | 99 | 59 | 44.6 | 99 | 60 | 45.3 | 101 | 60 |
| 49 | 46.2 | 57 | 45.4 | 98 | 59 | 45.8 | 99 | 59 | 46.1 | 100 | 59 |
| 53 | 46.4 | 56 | 45.2 | 97 | 59 | 46.3 | 100 | 59 | 46.1 | 99 | 59 |
| 57 | 46.8 | 56 | 45.8 | 98 | 59 | 46.5 | 99 | 59 | 47.2 | 101 | 59 |
| 61 | 49.6 | 56 | 48.2 | 97 | 58 | 48.9 | 99 | 59 | 49.3 | 99 | 58 |
| 65 | 49.3 | 56 | 47.8 | 97 | 58 | 48.5 | 98 | 58 | 48.9 | 99 | 58 |
| 69[a] | 48.7 | 46 | 47.9 | 98 | 48 | 49.2 | 101 | 48 | 48.6 | 100 | 48 |
| 73 | 49.4 | 45 | 48.4 | 98 | 48 | 49.8 | 101 | 48 | 48.2 | 98 | 48 |
| 77 | 49.8 | 43 | 48.4 | 97 | 48 | 49.1 | 99 | 48 | 48.2 | 97 | 47 |
| 81 | 50.0 | 43 | 48.5 | 97 | 47 | 49.0 | 98 | 47 | 49.1 | 98 | 45 |
| 85 | 50.6 | 42 | 49.5 | 98 | 46 | 49.9 | 99 | 46 | 50.0 | 99 | 44 |
| 89 | 51.6 | 42 | 49.2 | 95 | 46 | 51.1 | 99 | 44 | 51.0 | 99 | 44 |
| 93 | 50.5 | 42 | 48.7 | 96 | 45 | 50.0 | 99 | 43 | 49.2 | 97 | 44 |
| 97 | 49.6 | 42 | 47.8 | 96 | 43 | 49.3 | 99 | 41 | 47.9 | 97 | 41 |
| 101 | 49.3 | 39 | 46.9 | 95 | 41 | 47.6 | 97 | 40 | 46.4 | 94 | 39 |
| 104 | 49.2 | 39 | 46.7 | 95 | 40 | 48.2 | 98 | 38 | 46.1 | 94 | 37 |
| **Mean for weeks** | | | | | | | | | | | |
| 1-13 | 24.1 | | 24.0 | 100 | | 24.3 | 101 | | 24.2 | 100 | |
| 14-52 | 38.7 | | 38.4 | 99 | | 38.6 | 100 | | 38.8 | 100 | |
| 53-104 | 49.3 | | 47.8 | 97 | | 48.8 | 99 | | 48.3 | 98 | |

[a] Interim evaluation occurred during week 66.



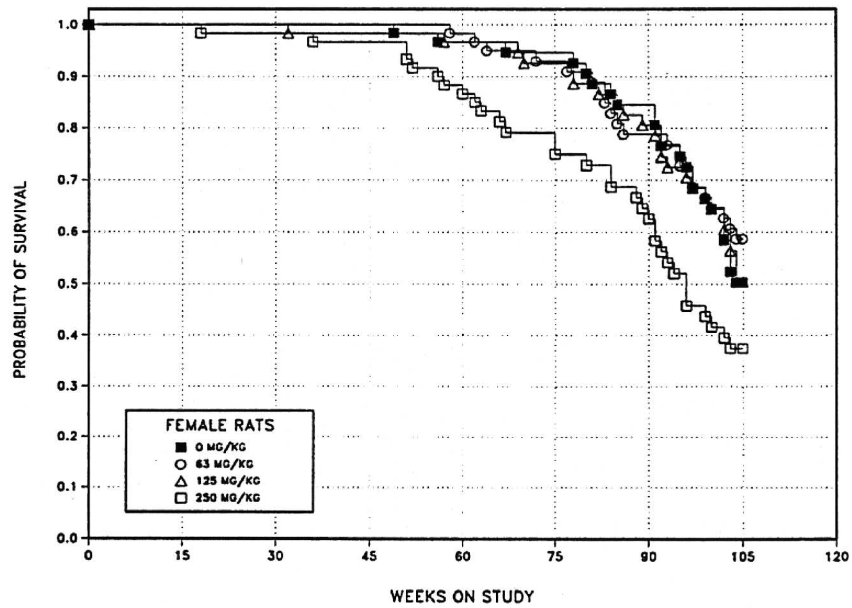




**FIGURE 4**
**Growth Curves for Male and Female Mice Administered Triethanolamine in Acetone by Dermal Application for 2 Years**

## *Pathology and Statistical Analyses*

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

*Skin:* Acanthosis and inflammation of the skin were observed at the site of application in male and female mice at the 15-month interim evaluation and at the end of the 2-year study (Tables 14, C5, and D5). In males in the 2,000 mg/kg group, the incidences of both lesions were significantly greater than those in the vehicle controls at both time points; however, the severity of acanthosis and inflammation did not increase with increasing dose.

After 2 years, the incidences of minimal to mild chronic inflammation at the site of application were generally greater in dosed males and females than in the vehicle controls (Table 14). Additionally, the incidences of thickened epidermis (acanthosis) and segmental atrophy of hair follicles and associated sebaceous glands were significantly greater in males in the 2,000 mg/kg group than in the vehicle controls.

The acanthosis in male mice was mild (thickness two to three times normal) and had a focal to segmental distribution. The minimal infiltrates of chronic inflammatory cells in the dermis often occurred in conjunction with the acanthosis. The adnexal atrophy was minimal to mild and usually occurred without concurrent acanthosis and dermal inflammation. It was characterized by an absence or reduced number of hair follicles and sebaceous glands in a distinct segment of the site of application; the hair follicles and sebaceous glands that were present appeared relatively normal to slightly hypertrophic. The incidences of skin neoplasms in dosed mice were similar to those in the vehicle controls at and away from the site of application.

*Liver:* The incidences of hepatocellular neoplasms in females receiving 1,000 mg/kg were significantly greater than those in the vehicle controls (Tables 15, C3, and D3). The historical incidences of these neoplasms in recent NTP feed studies range from 3% to 56% (Tables 15 and D4). The historical rates for dermal studies include only two other studies with an acetone vehicle; the incidences of hepatocellular neoplasms in females in these studies were 14% and 20%. While the greater neoplasm incidences in dosed mice were for benign (adenoma) rather than malignant (carcinoma) hepatocellular neoplasms, the number of females in the 1,000 mg/kg group with multiple adenomas was significantly greater than that in the vehicle controls. The incidences of eosinophilic foci in females in the 300 and 1,000 mg/kg groups were slightly greater than the incidence in the vehicle controls, although the difference was statistically significant only in the 300 mg/kg group (Table 15).

In males, the incidences of hepatocellular neoplasms in the 2,000 mg/kg group were significantly greater than those in the vehicle controls (Tables 15 and C3). The historical incidences of these neoplasms range from 10% to 68% (Tables 15 and C4). In the other dermal studies in the historical database with an acetone vehicle, the incidences of hepatocellular neoplasms in males were 18% and 46%. The number of males in the 2,000 mg/kg group with multiple adenomas was significantly greater than that in the vehicle controls. Additionally, the incidence of eosinophilic foci was significantly greater in males in the 2,000 mg/kg group than in the vehicle controls (Table 15). Hepatoblastomas, which do not commonly occur spontaneously, were observed in the livers of three males in the 2,000 mg/kg group.

The hepatocellular adenomas were well-demarcated nodular proliferations (Plate 3) that often occupied several lobules and caused compression of the surrounding parenchyma (Plate 4). There was loss of normal lobular architecture, and hepatic cords abruptly intersected with those of the surrounding tissue. Although the cellular morphology within neoplasms varied, generally the neoplastic cells were large and variably vacuolated, with abundant eosinophilic cytoplasm and large round nuclei. The eosinophilic foci were variably sized; the largest occupied several hepatic lobules, with limited compression of the adjacent parenchyma. The foci were composed of large cells as described for the adenomas.

**TABLE 14**
**Incidences of Nonneoplastic Lesions of the Skin at the Site of Application in Mice in the 2-Year Dermal Study of Triethanolamine**

| | 0 mg/kg | 200 mg/kg | 630 mg/kg | 2,000 mg/kg |
|---|---|---|---|---|
| **Male** | | | | |
| **15-Month Interim Evaluation** | | | | |
| Number Examined Microscopically | 10 | 10 | 10 | 10 |
| Acanthosis[a] | 0 | 1 (1.0)[b] | 1 (3.0) | 6** (1.7) |
| Inflammation, Chronic | 0 | 0 | 2 (2.0) | 5* (1.4) |
| **2-Year Study** | | | | |
| Number Examined Microscopically | 50 | 50 | 50 | 50 |
| Acanthosis | 2 (2.0) | 1 (1.0) | 6 (1.3) | 11** (1.9) |
| Inflammation, Chronic | 2 (1.5) | 0 | 7 (1.1) | 11** (1.6) |
| Ulcer | 1 (1.0) | 0 | 2 (2.0) | 2 (2.5) |
| Hair Follicle, Sebaceous Gland, Atrophy | 0 | 0 | 1 (1.0) | 15** (1.7) |
| | **0 mg/kg** | **100 mg/kg** | **300 mg/kg** | **1,000 mg/kg** |
| **Female** | | | | |
| **15-Month Interim Evaluation** | | | | |
| Number Examined Microscopically | 10 | 10 | 10 | 10 |
| Acanthosis | 0 | 1 (1.0) | 0 | 2 (1.5) |
| Inflammation, Chronic | 0 | 0 | 0 | 3 (1.0) |
| **2-Year Study** | | | | |
| Number Examined Microscopically | 50 | 50 | 50 | 50 |
| Acanthosis | 0 | 2 (2.0) | 1 (1.0) | 3 (1.3) |
| Inflammation, Chronic | 0 | 2 (1.5) | 2 (1.0) | 5* (1.4) |

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

**Table 15**
**Incidences of Neoplasms and Nonneoplastic Lesions of the Liver in Mice in the 2-Year Dermal Study of Triethanolamine**

| | 0 mg/kg | 200 mg/kg | 630 mg/kg | 2,000 mg/kg |
|---|---|---|---|---|
| **Male** | | | | |
| **15-Month Interim Evaluation** | | | | |
| Number Examined Microscopically | 10 | 10 | 10 | 10 |
| Basophilic Focus[a] | 0 | 1 | 1 | 0 |
| Clear Cell Focus | 0 | 1 | 0 | 0 |
| Eosinophilic Focus | 0 | 0 | 0 | 1 |
| Mixed Cell Focus | 0 | 0 | 0 | 2 |
| Karyomegaly | 2 | 1 | 1 | 2 |
| Oval Cell, Hyperplasia | 2 | 1 | 1 | 3 |
| Hepatocellular Adenoma | 1 | 2 | 1 | 4 |
| Hepatocellular Carcinoma | 1 | 2 | 0 | 1 |
| **2-Year Study** | | | | |
| Number Examined Microscopically | 50 | 50 | 50 | 50 |
| Basophilic Focus | 7 | 2 | 3 | 3 |
| Clear Cell Focus | 13 | 10 | 7 | 5 |
| Eosinophilic Focus | 10 | 17 | 11 | 23** |
| Karyomegaly | 11 | 17 | 9 | 16 |
| Oval Cell, Hyperplasia | 10 | 14 | 9 | 16 |
| Hepatocellular Adenoma | | | | |
| Overall rate[b] | 27/50 (54%) | 27/50 (54%) | 29/50 (58%) | 37/50 (74%) |
| Adjusted rate[c] | 54.0% | 62.7% | 67.4% | 78.6% |
| Terminal rate[d] | 23/46 (50%) | 24/40 (60%) | 25/39 (64%) | 31/41 (76%) |
| First incidence (days) | 367 | 665 | 607 | 572 |
| Logistic regression test[e] | P=0.012 | P=0.571 | P=0.359 | P=0.034 |
| Hepatocellular Adenoma, Multiple | 17 | 18 | 17 | 29* |
| Hepatocellular Carcinoma | | | | |
| Overall rate | 15/50 (30%) | 20/50 (40%) | 15/50 (30%) | 14/50 (28%) |
| Adjusted rate | 31.2% | 43.0% | 33.2% | 30.0% |
| Terminal rate | 13/46 (28%) | 14/40 (35%) | 9/39 (23%) | 9/41 (22%) |
| First incidence (days) | 678 | 537 | 507 | 572 |
| Logistic regression test | P=0.175N | P=0.207 | P=0.585 | P=0.494N |
| Hepatocellular Carcinoma, Multiple | 6 | 8 | 7 | 5 |
| Hepatoblastoma | 0 | 0 | 0 | 3 |
| Hepatocellular Adenoma, Hepatocellular Carcinoma, or Hepatoblastoma[f] | | | | |
| Overall rate | 31/50 (62%) | 34/50 (68%) | 33/50 (66%) | 42/50 (84%) |
| Adjusted rate | 62.0% | 72.2% | 73.3% | 85.7% |
| Terminal rate | 27/46 (59%) | 27/40 (68%) | 27/39 (69%) | 34/41 (83%) |
| First incidence (days) | 467 | 537 | 507 | 572 |
| Logistic regression test | P=0.009 | P=0.359 | P=0.377 | P=0.018 |

* Significantly different ($P \leq 0.05$) from the vehicle control group by the logistic regression test
** $P \leq 0.01$

**TABLE 15**
**Incidences of Neoplasms and Nonneoplastic Lesions of the Liver in Mice in the 2-Year Dermal Study of Triethanolamine** (continued)

| | 0 mg/kg | 100 mg/kg | 300 mg/kg | 1,000 mg/kg |
|---|---|---|---|---|
| **Female** | | | | |
| **15-Month Interim Evaluation** | | | | |
| Number Examined Microscopically | 10 | 10 | 10 | 10 |
| Basophilic Focus | 0 | 0 | 1 | 0 |
| Clear Cell Focus | 0 | 1 | 0 | 0 |
| Eosinophilic Focus | 2 | 0 | 0 | 1 |
| Hepatocellular Adenoma | 2 | 2 | 1 | 1 |
| **2-Year Study** | | | | |
| Number Examined Microscopically | 50 | 50 | 50 | 50 |
| Basophilic Focus | 0 | 2 | 1 | 1 |
| Clear Cell Focus | 1 | 0 | 0 | 1 |
| Eosinophilic Focus | 9 | 10 | 18* | 16 |
| Karyomegaly | 0 | 1 | 0 | 0 |
| Hepatocellular Adenoma | | | | |
| Overall rate | 22/50 (44%) | 22/50 (44%) | 24/50 (48%) | 40/50 (80%) |
| Adjusted rate | 54.9% | 53.6% | 58.3% | 95.2% |
| Terminal rate | 21/39 (54%) | 21/40 (53%) | 21/38 (55%) | 35/37 (95%) |
| First incidence (days) | 681 | 650 | 597 | 647 |
| Logistic regression test | P<0.001 | P=0.496N | P=0.480 | P<0.001 |
| Hepatocellular Adenoma, Multiple | 11 | 9 | 13 | 29** |
| Hepatocellular Carcinoma | | | | |
| Overall rate | 1/50 (2%) | 4/50 (8%) | 7/50 (14%) | 5/50 (10%) |
| Adjusted rate | 2.6% | 9.0% | 16.0% | 12.8% |
| Terminal rate | 1/39 (3%) | 2/40 (5%) | 4/38 (11%) | 4/37 (11%) |
| First incidence (days) | 729 (T) | 557 | 434 | 591 |
| Logistic regression test | P=0.204 | P=0.176 | P=0.024 | P=0.110 |
| Hepatocellular Adenoma or Carcinoma[g] | | | | |
| Overall rate | 23/50 (46%) | 26/50 (52%) | 28/50 (56%) | 41/50 (82%) |
| Adjusted rate | 57.4% | 60.2% | 64.7% | 95.3% |
| Terminal rate | 22/39 (56%) | 23/40 (58%) | 23/38 (61%) | 35/37 (95%) |
| First incidence (days) | 681 | 557 | 434 | 591 |
| Logistic regression test | P<0.001 | P=0.457 | P=0.276 | P<0.001 |

(T)Terminal sacrifice
[a] Number of animals with lesion
[b] Number of animals with neoplasm per number of animals with liver examined microscopically
[c] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[d] Observed incidence in animals surviving until the end of the study
[e] In the vehicle control column are the P values associated with the trend test. In the dosed group columns are the P values corresponding to the pairwise comparisons between the vehicle controls and that dosed group. The logistic regression test regards neoplasms in animals dying prior to terminal kill as nonfatal. For all tests, a negative trend or a lower incidence in a dose group is indicated by N.
[f] Historical incidence for 2-year NTP dermal studies with acetone vehicle control groups (mean ± standard deviation): 63/150 (42.0% ± 22.3%); range, 18%-62%. Historical incidence for 2-year NTP feed studies with untreated control groups: 509/1,316 (38.7% ± 13.9%); range, 10%-68%
[g] Historical incidence (dermal): 40/150 (26.7% ± 17.0%); range, 14%-46%. Historical incidence (feed): 260/1,312 (19.8% ± 12.8%); range, 3%-56%

Hepatoblastomas are uncommon neoplasms in mice; these neoplasms may occur spontaneously or may be chemically induced in the liver of several mouse strains (Turusov *et al.*, 1973; Nonoyama *et al.*, 1988), including the B6C3F$_1$ mouse used in NTP studies. It is considered to be a malignant neoplasm, and in NTP studies, its metastatic potential appears similar to that of hepatocellular carcinomas. Hepatoblastomas are easily diagnosed on hematoxylin- and eosin-stained sections because of their distinctive morphology and were typical in this study. The neoplasms were sharply demarcated from surrounding tissue (Plate 5) and were composed of deep basophilic-staining pleomorphic (small spindle to large ovoid) cells arranged in compact sheets, islands, or trabeculae (Plate 6). Cells generally contained a scant amount of eosinophilic cytoplasm and had round to oval nuclei. Two of the hepatoblastomas were less than 5 mm in diameter, while the third was 2 cm in diameter, with trabeculae and large, cystic, hemorrhagic areas and a thick fibrous capsule.

Hepatoblastomas almost always occur within an existing proliferative lesion, most often a hepatocellular carcinoma. In NTP studies, the diagnosis of hepatoblastoma is made whenever this distinctive lesion is observed. To avoid duplicate diagnoses, no separate diagnosis is made for the lesion within which the hepatoblastoma occurs. The cell of origin of the hepatoblastoma has not been clearly defined in rodents or humans but may be a very primordial cell (Abenoza *et al.*, 1987; Nonoyama *et al.*, 1988; Van Eyken *et al.*, 1990). To determine the significance of increases in the incidences of neoplasms that may be related to chemical treatment, the NTP generally performs statistical analyses on benign and malignant neoplasms of like histogenesis both independently and in combination. Although the biology of hepatoblastomas is not fully understood, the NTP considers this neoplasm to be part of the spectrum of liver neoplasms that occurs spontaneously and as a result of chemical treatment. Therefore, the NTP considers the combined analyses (hepatocellular carcinoma and hepatoblastoma; hepatocellular adenoma, hepatocellular carcinoma, and hepatoblastoma) the most important analyses in evaluating the carcinogenic potential of an agent on the liver.

The livers of many of the male mice in all groups, including the vehicle controls, had mild to moderate karyomegaly of hepatocytes and oval cell hyperplasia (Table 15). These lesions occurred with greater incidences and/or severities than spontaneous occurrences. Individual hepatocytes in periportal areas were variably, and often markedly, enlarged, including nuclear enlargement (karyomegaly). Enlarged cells had varying degrees of cytoplasmic vacuolization, and frequently the cytoplasm was invaginated into the nucleus. Near the portal triads, along sinusoidal channels, were increased numbers of small, dark, ovoid- to spindle-shaped cells that were presumed to be "oval cells" or bile duct epithelium. These changes are consistent with those described by Ward *et al.* (1994a,b) as occurring in animals with livers containing *Helicobacter hepaticus* bacterial organisms. A Warthin-Starry histologic staining procedure was performed on sections of liver from 12 affected males, three unaffected males, and four unaffected females. Bacterial organisms were identified in affected, but not in unaffected, livers. The organisms were generally thin, elongate (2 to 10 $\mu$m), often spiraled rods observed singly or in small clusters. The bacteria were between and at the periphery of hepatocytes, which is consistent with localization within bile canaliculi as described by Ward *et al.* (1994a,b). Frozen livers from four male mice with characteristic liver lesions were evaluated with a polymerase chain reaction (PCR)-based assay and culture (Fox *et al.*, 1998); all were confirmed to be infected with *H. hepaticus*. In a larger subsequent analysis of 44 male and female mice without characteristic liver lesions, *H. hepaticus*-specific DNA was amplified from the livers of 21 of 44 mice (47%) compared to 14 of 44 mice (32%) having *H. hepaticus* cultured from frozen liver. Similar PCR assay results were obtained in frozen liver from a smaller subset of these same mice at a different laboratory (Malarkey *et al.*, 1997; Appendix L).

*Hematopoietic System:* The incidence of malignant lymphoma (all types) was significantly greater in females administered 1,000 mg/kg than in the vehicle controls (0 mg/kg, 6/50; 100 mg/kg, 10/50; 300 mg/kg, 6/50; 1,000 mg/kg, 15/50; Table D3). Malignant lymphoma in mice, especially females, is a commonly occurring neoplasm with a variable incidence. These neoplasms occurred in 324 of 1,320 (24.5%) untreated female mice in NTP feed studies in the historical database; in the two other dermal studies with acetone as the vehicle, malignant lymphomas occurred in 22 of 100 vehicle control females. In this study, the incidences were not

increased in other dosed groups, and the incidence in the 300 mg/kg group was the same as in the vehicle control group. Also, the vehicle control incidence of 12% is well below the historical control incidences, while the incidence of 30% in the 1,000 mg/kg group is close to the average historical control incidence. Although male mice received triethanolamine at doses that were twice those administered to females, the incidences of malignant lymphoma in dosed and vehicle control males were similar (0 mg/kg, 4/50; 200 mg/kg, 1/50; 630 mg/kg, 9/50; 2,000 mg/kg, 1/50). Therefore, the increased incidence of malignant lymphoma in female mice in the 1,000 mg/kg group was not considered to be related to triethanolamine administration.

*Bone:* Osteosarcomas were observed in two female mice administered 1,000 mg/kg (Table D1). In one female, the osteosarcoma involved the right scapula, while in the other female, the lumbar vertebrae were involved. An additional osteosarcoma occurred in the inguinal skin of a female in the 300 mg/kg group; there was no evidence of a primary site in the bone of this mouse. These osteosarcomas were composed of variably sized and shaped spindle cells with multifocal areas of osteoid formation. Osteosarcoma is an uncommon neoplasm in mice, occurring in 7 of 1,320 untreated control females. These neoplasms are not considered to be related to triethanolamine administration because of their low incidences, the lack of statistical significance, and the lack of other information that would suggest an effect of triethanolamine on bone.

## GENETIC TOXICOLOGY

Triethanolamine (33 to 3,333 μg/plate) was negative for induction of mutations in *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537 when tested with or without S9 metabolic activation (Table E1; Mortelmans *et al.*, 1986). In cytogenetic tests with cultured Chinese hamster ovary cells, no induction of sister chromatid exchanges (Table E2) or chromosomal aberrations (Table E3) was observed with or without S9 (Galloway *et al.*, 1987). In the sister chromatid exchange test without S9, the first of two trials was negative. In the second trial, a significant increase in sister chromatid exchanges was observed at the highest dose tested (2,520 μg/mL), but the trend test was negative ($P \geq 0.025$), and the trial was concluded to be equivocal. Severe cytotoxicity limited the number of cells that could be scored at this high dose. Overall, the sister chromatid exchange test was considered to be negative. Cytotoxicity was also noted at the highest dose tested (4,030 μg/mL) in the chromosomal aberrations test without S9.

Triethanolamine administered by feeding or injection at doses up to 30,000 ppm did not induce sex-linked recessive lethal mutations in germ cells of male *Drosophila melanogaster* (Table E4; Yoon *et al.*, 1985). Results of an *in vivo* peripheral blood micronucleus test in mice were also negative (Table E5). In this test, blood samples were obtained from male and female mice after 13 weeks of dermal applications of 1,000 to 4,000 mg/kg triethanolamine. No significant increases in the frequencies of micronucleated normochromatic or polychromatic erythrocytes were observed at any dose tested.

# DISCUSSION AND CONCLUSIONS

Triethanolamine has use patterns that could lead to human exposure through a variety of routes. Clearly its use in cosmetics results in dermal exposure, but its presence in cutting fluids and in other industrial applications could also lead to inhalation of mists. The chemical is also approved for use in food packaging, potentially resulting in oral ingestion. Because of this, comparative 2-week studies were performed with triethanolamine administered to rats and mice at concentrations up to 80,000 ppm in drinking water, 2,000 mg/m$^3$ by whole body inhalation, and 3,370 mg/kg by dermal application (NTP, unpublished data). The results of these short-term studies gave little evidence of significant systemic toxicity by any route. Triethanolamine was toxic at the site of application, resulting in hemorrhage and necrosis of the glandular stomach of rats in the drinking water study, inflammation of the laryngeal submucosa in rats and mice in the inhalation studies, and inflammation of the skin of rats and mice in the dermal studies. Poor palatability led to the deaths of rats receiving 80,000 ppm triethanolamine in drinking water.

The dermal route of exposure was chosen for further studies because of the predominant potential for dermal exposure to humans through the use of cosmetics. Studies of absorption and metabolism of triethanolamine have indicated quite extensive dermal absorption of doses similar to those used in the 13-week studies, with little evidence of significant metabolism prior to excretion in urine and feces (Melnick and Tomaszewski, 1990). Thus, dermal studies were expected to provide a systemic challenge and yield information applicable to exposure by other routes.

In the 13-week rat study, topical application of 2,000 mg triethanolamine per kilogram body weight resulted in a significant decrease in body weight gain, and grossly visible crusts at the site of application were noted in males and females administered 1,000 or 2,000 mg/kg. Hematologic changes were consistent with the presence of skin inflammation in rats in the 2,000 mg/kg groups, and clinical chemistry findings of very mild but generally dose-related increases in serum alanine and aspartate aminotransferase activities were suggestive of liver injury. However, sorbitol dehydrogenase activity, which is generally considered to be a better gauge of liver damage, was not increased, and histopathology revealed no evidence of hepatic injury. Aspartate aminotransferase has a wider tissue distribution than sorbitol dehydrogenase, and increased serum activity could be related to minor injury at another site, such as the muscle, rather than to hepatotoxicity. Additionally, some compounds can cause increases in alanine aminotransferase activity in the liver or serum without causing hepatic injury.

Kidney weights increased with increasing dose in male and female rats in the 13-week study. Dosed males had decreased urinary protein excretion which likely reflected a change in renal function or an increase in protein reabsorption, as serum protein concentrations were not affected. Although these findings suggest the possibility of protein droplet accumulation or some other form of renal dysfunction or injury, no evidence of hyaline droplet nephropathy or other histopathologic changes that might account for the weight changes was noted.

Lesions at the site of application in rats in the 13-week study ranged from no discernable change, through minimal to mild epidermal thickening (acanthosis), to chronic active inflammation, erosion, and ulceration. The dermis was also thickened with inflammation and fibrosis at the higher doses. There was no histologic evidence to suggest the development of skin sensitization or contact dermatitis. This does not, however, rule out the possibility that triethanolamine might cause contact sensitization in a more sensitive animal model, such as the guinea pig. Doses selected for the 2-year study were lower than those that caused inflammation in the 13-week study.

The findings in the 13-week mouse study were similar to those in the rat study. Clinical pathology and histopathology evaluations provided no evidence of significant systemic toxicity, although liver and kidney

weights were increased in the 4,000 mg/kg groups. Dose-related decreases in serum sorbitol dehydrogenase activities occurred in male and female mice. The cause of this change, and any possible biological relevance it may have, are unclear. Doses selected for the 2-year mouse study were lower than those that caused inflammation at the site of application in the 13-week study.

Although the results of the 13-week rat study led to the selection of doses for female rats in the 2-year study that were twice those administered to males, the females were clearly more sensitive to triethanolamine administration, as shown by the much greater incidences and severities of inflammation and irritation at the site of application in females compared to males in the 2-year study. Ulceration occurred in about half the female rats receiving 125 or 250 mg/kg, while only 5 of 50 males receiving 125 mg/kg had similar lesions. The survival rate of female rats receiving 250 mg/kg was less than that of the other groups, although the mean body weight of this group was only slightly decreased during the study, and this decrease was observed only around week 90. There were no skin neoplasms in male or female rats at or away from the site of application that were considered to be related to triethanolamine administration.

Histopathologic findings which were evaluated to determine their relationship with triethanolamine exposure included renal tubule adenomas in male rats and thyroid gland C-cell adenomas and carcinomas and uterine stromal polyps in female rats. The increased incidences of thyroid gland C-cell neoplasms and uterine stromal polyps were not considered to be related to triethanolamine administration. The evidence for a relationship between the renal tubule neoplasms in male rats and triethanolamine administration was considered equivocal. The total number of male rats identified in the combined single and step-section evaluations as having proliferative lesions (hyperplasia and adenoma) of the renal tubule epithelium was 10/50 (vehicle controls), 8/50 (32 mg/kg), 11/49 (63 mg/kg), and 8/50 (125 mg/kg). Although the proliferative lesions were observed only microscopically, those that were identified as adenomas were clearly larger lesions; these appeared in one vehicle control male, two males in the 32 mg/kg group, six males in the 63 mg/kg group, and four males in the 125 mg/kg group. Four of the six adenomas in the 63 mg/kg group were noted during the standard histopathologic evaluation, and thus this incidence may be compared to historical control data. The 8% incidence in the 63 mg/kg group exceeds the historical mean (0.8%) and range (0%-6%) observed in previous untreated control groups from feed studies. However, the lack of both a clear dose response and an increase in incidences of total proliferative lesions in dosed rats leaves doubt that this result could be attributed to triethanolamine administration with certainty. Other examples of the use of an extended evaluation of the kidney and their interpretation have been discussed by Eustis *et al.* (1994).

In a previous carcinogenicity study in which triethanolamine was administered in drinking water at concentrations of 1% and 2% to groups of 47 to 50 F344/DuCrj rats (Maekawa *et al.*, 1986), two renal tubule adenomas were observed in females in the 2% group; none occurred in the controls or in the 1% group. This finding was discounted by the authors because renal toxicity was observed in females in the 2% group. Doses were halved for females after week 68 because of toxicity. The total triethanolamine intake during the study was reported to be 119 or 232 mg (actually grams) for female rats. For comparison, assuming 100% absorption of material from the skin and average body weights of 350 g for males and 200 g for females, rats in the 125 (male) and 250 mg/kg (female) groups in the current studies would have received total doses of approximately 23 g for males and 26 g for females. Thus, the lack of kidney toxicity in the current study is consistent with the findings of Maekawa *et al.* (1986). These authors also reported increased incidences of hepatic neoplasms in males and uterine endometrial sarcoma in females. However, these findings were not attributed to triethanolamine administration because in comparison to historical incidences, the neoplasm trends reflected low incidences in the control groups rather than increased incidences in the exposed groups.

In the current 2-year mouse study, the doses were much greater than those administered to rats in relation to body weight. Inflammation and acanthosis of the skin were seen in the mouse study but were much less severe than the lesions in dosed rats, and there was little evidence of progression of the lesions. Treatment-related skin neoplasms did not occur at or away from the site of application. Survival rates were 74% or greater in all groups, and possible treatment-related effects on body weights were observed only in

males in the 2,000 mg/kg group after week 65. The maximum mean body weight of males and females was approximately 50 g, which is moderately heavy but is consistent with other recent studies in which mice were housed individually. It is likely that male and female mice could have tolerated somewhat higher doses, but the selection of doses was appropriate, based on the findings of the 13-week studies.

The incidences of proliferative lesions of the liver were increased in male and female mice receiving triethanolamine for 2 years. In females, the incidences of hepatocellular carcinoma and eosinophilic foci were significantly greater in the 300 mg/kg group and the incidences of hepatocellular adenoma and multiple adenomas were significantly greater in the 1,000 mg/kg group than in the vehicle controls. In male and female mice, the combined incidences of hepatocellular neoplasms showed a positive, dose-related trend and were significantly greater in males in the 2,000 mg/kg group and females in the 1,000 mg/kg group than in the vehicle controls. The incidences of hepatocellular neoplasms in dosed and vehicle control females exceeded the historical control range for untreated controls. In males, increased incidences were limited to hepatocellular adenomas, multiple adenomas, and eosinophilic foci in animals receiving 2,000 mg/kg. In addition, three males in this group each had a hepatoblastoma, a rare and atypical form of hepatocellular carcinoma. However, the incidence of hepatocellular carcinoma was not increased in this group.

Based on retrospective analyses, *Helicobacter hepaticus* was determined to have infected mice in 12 recent NTP 2-year studies (Appendix L). Of the 12 studies, mice (primarily males) from nine studies, including the current study of triethanolamine, had *H. hepaticus*-associated hepatitis. Qualitatively, the hepatitis and the silver-staining organisms within the liver were similar among the nine studies. In studies from which adequately preserved (frozen) liver tissue was available, including the triethanolamine study, an organism compatible with *H. hepaticus* was identified with assays based on polymerase chain reaction (PCR) (Malarkey *et al.*, 1997; Fox *et al.*, 1998). In general, efforts to identify *H. hepaticus* from tissue that had been fixed in formalin for longer than a week were not successful (Malarkey *et al.*, 1997). Because of the presence of the typical liver lesions, silver-staining helical organisms, and confirmation with PCR-based assays and culture, mice from the current study of triethanolamine were determined to be infected with *H. hepaticus*.

Increases in the incidences of hepatocellular neoplasms in male mice have been shown to be associated with *H. hepaticus* infection when hepatitis is also present (Ward *et al.*, 1994a; Fox *et al.*, 1996; Appendix L). Additionally, in NTP studies in which the *H. hepaticus*-associated hepatitis was observed, there was an increased incidence of hemangiosarcoma of the liver in male mice (Appendix L). Because of the former association, interpretation of the increased incidences of hepatocellular neoplasms in male mice in the triethanolamine study was confounded. Other findings in this study were not considered to have been significantly impacted by the infection with *H. hepaticus* or its associated hepatitis.

In female mice, there were also significantly increased incidences of hepatocellular neoplasms. The association of triethanolamine with liver neoplasms in female mice is more certain, and NTP staff originally proposed that this constituted some evidence of carcinogenicity. The Technical Reports Review Subcommittee considered the female mouse study to be inadequate, however, because of uncertainty about the potential for *H. hepaticus* infection to influence the liver neoplasm incidence (see pages 15 and 16).

As mentioned earlier, there have been several other carcinogenicity studies of triethanolamine in mice. Konishi *et al.* (1992) found that triethanolamine was not carcinogenic or toxic in B6C3F$_1$ mice receiving 1% or 2% in drinking water for 82 weeks. Incidences of liver neoplasms were reported, and the only suggestive finding was a nonsignificant increase in the incidences of hyperplastic nodules in female mice (vehicle controls, 4%; 1% group, 8%; 2% group, 12%). Whether treatment-related liver neoplasia would have developed if the study had progressed for 2 years is unknown. There was no evidence of increased incidences of liver neoplasms at 15 months in the present study, although the doses used by Konishi *et al.* likely resulted in a greater total exposure to triethanolamine than occurred in this study.

Hoshino and Tanooka (1978) reported increased incidences of malignant lymphoma in female ICR-JCL mice receiving a relatively low dose of 0.03% or 0.3% triethanolamine in feed in a lifetime study.

Other studies with this strain have reported much greater control incidences of malignant lymphoma (Konishi *et al.*, 1992) than was found in the Hoshino and Tanooka study, and this may account for these findings. Incidences of malignant lymphoma, although not thymic lymphoma as reported by Hoshino and Tanooka, were also increased in the present study. This was also attributed to a lower than expected vehicle control incidence of this rather common and variable neoplasm.

The results of a variety of *in vitro* and *in vivo* assays for genetic toxicity of triethanolamine were negative. Potential mechanisms accounting for the increased incidence of liver neoplasms in female mice will require further study.

## CONCLUSIONS

Under the conditions of these dermal studies, there was *equivocal evidence of carcinogenic activity** of triethanolamine in male F344/N rats based on a marginal increase in the incidences of renal tubule cell adenoma. There was *no evidence of carcinogenic activity* in female F344/N rats receiving 63, 125, or 250 mg triethanolamine per kilogram body weight. The study in male and female B6C3F$_1$ mice was considered *inadequate*, because the presence of a *Helicobacter hepaticus* infection complicated interpretation of the relationship between triethanolamine administration and liver neoplasms in these animals.

Dosed rats and mice had varying degrees of acanthosis and inflammation, dosed rats had ulceration, and dosed female rats had epidermal erosion at the site of skin application.

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* Explanation of Levels of Evidence of Carcinogenic Activity is on page 11. A summary of the Technical Reports Review Subcommittee comments and the public discussion on this Technical Report appears on page 14.

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


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**Table A1**
**Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Dermal Study of Triethanolamine[a]**

| | 0 mg/kg | 32 mg/kg | 63 mg/kg | 125 mg/kg |
|---|---|---|---|---|
| **Disposition Summary** | | | | |
| Animals initially in study | 60 | 60 | 60 | 60 |
| ***15-Month interim evaluation*** | 10 | 10 | 10 | 10 |
| Early deaths | | | | |
| Accidental deaths | 2 | | | |
| Moribund | 18 | 27 | 25 | 23 |
| Natural deaths | 9 | 12 | 6 | 8 |
| Survivors | | | | |
| Terminal sacrifice | 21 | 11 | 18 | 19 |
| Missexed | | | 1 | |
| Animals examined microscopically | 60 | 60 | 59 | 60 |
| ***15-Month Interim Evaluation*** | | | | |
| **Endocrine System** | | | | |
| Adrenal medulla | (10) | (10) | (10) | (10) |
| Pheochromocytoma benign | | | 1 (10%) | |
| Pituitary gland | (10) | (10) | (10) | (10) |
| Pars distalis, adenoma | 3 (30%) | 3 (30%) | 5 (50%) | 2 (20%) |
| Thyroid gland | (10) | (10) | (10) | (10) |
| C-cell, adenoma | 1 (10%) | | 1 (10%) | |
| **Genital System** | | | | |
| Epididymis | (10) | (10) | (10) | (10) |
| Prostate | (10) | (10) | (10) | (10) |
| Testes | (10) | (10) | (10) | (10) |
| Bilateral, interstitial cell, adenoma | 1 (10%) | 3 (30%) | 1 (10%) | |
| Interstitial cell, adenoma | 2 (20%) | 4 (40%) | 3 (30%) | 4 (40%) |
| **Integumentary System** | | | | |
| Skin | (10) | (10) | (10) | (10) |
| Subcutaneous tissue, fibroma | | 1 (10%) | | |
| **Systemic Lesions** | | | | |
| Multiple organs[b] | (10) | (10) | (10) | (10) |
| Leukemia mononuclear | 1 (10%) | | | |
| Mesothelioma NOS | 1 (10%) | | 1 (10%) | 1 (10%) |

***Systems Examined with No Neoplasms Observed***
**Alimentary System**
**Cardiovascular System**
**General Body System**
**Hematopoietic System**
**Musculoskeletal System**
**Nervous System**
**Respiratory System**
**Special Senses System**
**Urinary System**

**TABLE A1**
**Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Dermal Study of Triethanolamine** (continued)

| | 0 mg/kg | 32 mg/kg | 63 mg/kg | 125 mg/kg |
|---|---|---|---|---|
| ***2-Year Study*** | | | | |
| **Alimentary System** | | | | |
| Intestine large, colon | (50) | (50) | (49) | (50) |
| Leiomyosarcoma | | 1 (2%) | | |
| Intestine small, duodenum | (50) | (50) | (49) | (50) |
| Leiomyosarcoma, metastatic, intestine large, colon | | 1 (2%) | | |
| Leiomyosarcoma, metastatic, stomach, glandular | | | 1 (2%) | |
| Intestine small, jejunum | (50) | (50) | (49) | (50) |
| Fibrous histiocytoma, metastatic, spleen | | | | 1 (2%) |
| Mast cell tumor malignant | | | | 1 (2%) |
| Intestine small, ileum | (50) | (50) | (49) | (50) |
| Fibrous histiocytoma, metastatic, spleen | | | | 1 (2%) |
| Liver | (50) | (50) | (49) | (50) |
| Hepatocellular carcinoma | | | 1 (2%) | |
| Hepatocellular adenoma | 3 (6%) | | | 1 (2%) |
| Leiomyosarcoma, metastatic, intestine large, colon | | 1 (2%) | | |
| Leiomyosarcoma, metastatic, stomach, glandular | | | 1 (2%) | |
| Schwannoma malignant, metastatic, skin | | 1 (2%) | | |
| Mesentery | (9) | (9) | (10) | (5) |
| Leiomyosarcoma, metastatic, intestine large, colon | | 1 (11%) | | |
| Leiomyosarcoma, metastatic, stomach, glandular | | | 1 (10%) | |
| Pancreas | (50) | (50) | (49) | (50) |
| Leiomyosarcoma, metastatic, intestine large, colon | | 1 (2%) | | |
| Leiomyosarcoma, metastatic, stomach, glandular | | | 1 (2%) | |
| Salivary glands | (50) | (50) | (48) | (50) |
| Neurofibrosarcoma, metastatic, skin | | 1 (2%) | | |
| Schwannoma malignant, metastatic, skin | | 1 (2%) | | |
| Stomach, forestomach | (50) | (50) | (49) | (50) |
| Squamous cell papilloma | 1 (2%) | 1 (2%) | 1 (2%) | |
| Stomach, glandular | (50) | (50) | (49) | (50) |
| Leiomyosarcoma | | | 1 (2%) | |
| Leiomyosarcoma, metastatic, intestine large, colon | | 1 (2%) | | |
| Tongue | (1) | | | |
| Squamous cell papilloma | 1 (100%) | | | |
| **Cardiovascular System** | | | | |
| Blood vessel | (50) | (50) | (49) | (49) |
| Heart | (50) | (50) | (49) | (50) |

**Table A1**
**Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Dermal Study of Triethanolamine** (continued)

| | 0 mg/kg | 32 mg/kg | 63 mg/kg | 125 mg/kg |
|---|---|---|---|---|
| ***2-Year Study*** (continued) | | | | |
| **Endocrine System** | | | | |
| Adrenal cortex | (50) | (50) | (49) | (50) |
| Adrenal medulla | (50) | (50) | (49) | (50) |
| Pheochromocytoma complex | | | 1 (2%) | |
| Pheochromocytoma benign | 2 (4%) | 8 (16%) | 4 (8%) | 3 (6%) |
| Bilateral, pheochromocytoma benign | 1 (2%) | | | |
| Islets, pancreatic | (50) | (50) | (49) | (50) |
| Adenoma | 1 (2%) | 3 (6%) | 3 (6%) | 5 (10%) |
| Parathyroid gland | (49) | (47) | (44) | (47) |
| Adenoma | | | | 1 (2%) |
| Pituitary gland | (50) | (50) | (48) | (50) |
| Pars distalis, adenoma | 34 (68%) | 37 (74%) | 30 (63%) | 37 (74%) |
| Pars distalis, adenoma, multiple | 1 (2%) | 1 (2%) | 2 (4%) | 4 (8%) |
| Thyroid gland | (50) | (50) | (49) | (50) |
| Neurofibrosarcoma, metastatic, skin | | 1 (2%) | | |
| Bilateral, C-cell, adenoma | 1 (2%) | | | |
| C-cell, adenoma | 5 (10%) | 4 (8%) | 7 (14%) | 6 (12%) |
| C-cell, carcinoma | | 1 (2%) | 1 (2%) | |
| Follicular cell, adenoma | | | 1 (2%) | |
| Follicular cell, carcinoma | | 1 (2%) | | |
| **General Body System** | | | | |
| None | | | | |
| **Genital System** | | | | |
| Epididymis | (50) | (50) | (49) | (50) |
| Preputial gland | (50) | (50) | (48) | (50) |
| Adenoma | | | 1 (2%) | 1 (2%) |
| Carcinoma | 1 (2%) | 1 (2%) | | |
| Fibrosarcoma | | 1 (2%) | | |
| Prostate | (50) | (49) | (49) | (50) |
| Adenocarcinoma | 1 (2%) | 1 (2%) | | |
| Sarcoma | | 1 (2%) | | |
| Seminal vesicle | (50) | (50) | (49) | (50) |
| Testes | (50) | (50) | (49) | (50) |
| Bilateral, interstitial cell, adenoma | 15 (30%) | 11 (22%) | 15 (31%) | 9 (18%) |
| Interstitial cell, adenoma | 16 (32%) | 22 (44%) | 18 (37%) | 16 (32%) |
| **Hematopoietic System** | | | | |
| Bone marrow | (50) | (50) | (49) | (50) |
| Lymph node | (14) | (10) | (16) | (9) |
| Deep cervical, carcinoma, metastatic, thyroid gland | | | 1 (6%) | |
| Lymph node, mandibular | (50) | (50) | (49) | (50) |
| Schwannoma malignant, metastatic, skin | | 1 (2%) | | |
| Lymph node, mesenteric | (50) | (50) | (49) | (49) |
| Spleen | (50) | (50) | (49) | (50) |
| Fibrous histiocytoma | | | | 1 (2%) |
| Thymus | (46) | (49) | (48) | (49) |

**Table A1**
**Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Dermal Study of Triethanolamine** (continued)

| | 0 mg/kg | 32 mg/kg | 63 mg/kg | 125 mg/kg |
|---|---|---|---|---|
| ***2-Year Study*** (continued) | | | | |
| **Integumentary System** | | | | |
| Mammary gland | (48) | (43) | (45) | (45) |
| Carcinoma | 1 (2%) | 1 (2%) | | |
| Fibroadenoma | 1 (2%) | | | |
| Skin | (50) | (50) | (49) | (50) |
| Basal cell adenoma | | 1 (2%) | | |
| Keratoacanthoma | 1 (2%) | | | |
| Abdominal, ventral, keratoacanthoma | | | | 1 (2%) |
| Dorsal, keratoacanthoma | | | 1 (2%) | |
| Face, basosquamous tumor malignant | | 1 (2%) | | |
| Face, squamous cell papilloma | 2 (4%) | | 1 (2%) | |
| Head, basosquamous tumor benign | | | | 1 (2%) |
| Hindlimb, subcutaneous tissue, fibroma | 1 (2%) | | | |
| Inguinal, keratoacanthoma | 1 (2%) | | | |
| Inguinal, subcutaneous tissue, fibrosarcoma | | | 1 (2%) | |
| Inguinal, subcutaneous tissue, sarcoma | | | | 1 (2%) |
| Neck, subcutaneous tissue, schwannoma malignant | | 1 (2%) | | |
| Pinna, sarcoma | | | | 1 (2%) |
| Pinna, squamous cell papilloma | 1 (2%) | | | |
| Site of application-mass, basal cell adenoma | 1 (2%) | | | |
| Site of application-mass, keratoacanthoma | | | | 1 (2%) |
| Subcutaneous tissue, fibroma | 1 (2%) | | | |
| Subcutaneous tissue, fibrous histiocytoma, metastatic, spleen | | | | 1 (2%) |
| Subcutaneous tissue, liposarcoma | | 1 (2%) | | |
| Subcutaneous tissue, neurofibrosarcoma | | 1 (2%) | | |
| Subcutaneous tissue, sarcoma | 1 (2%) | | | |
| Subcutaneous tissue, ventral, fibroma | | | 1 (2%) | |
| Tail, fibrosarcoma | 1 (2%) | | | |
| Thoracic, keratoacanthoma | 2 (4%) | | 1 (2%) | |
| Thoracic, subcutaneous tissue, fibroma | | 1 (2%) | 1 (2%) | |
| Ventral, keratoacanthoma | 1 (2%) | | | |
| **Musculoskeletal System** | | | | |
| Skeletal muscle | (1) | (1) | (1) | (1) |
| Neurofibrosarcoma, metastatic, skin | | 1 (100%) | | |
| **Nervous System** | | | | |
| Brain | (50) | (50) | (48) | (50) |
| Astrocytoma NOS | | | | 1 (2%) |
| Spinal cord | (2) | | (2) | |

**Table A1**
**Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Dermal Study of Triethanolamine** (continued)

| | 0 mg/kg | 32 mg/kg | 63 mg/kg | 125 mg/kg |
|---|---|---|---|---|
| ***2-Year Study*** (continued) | | | | |
| **Respiratory System** | | | | |
| Lung | (50) | (50) | (49) | (50) |
| Carcinoma, metastatic, thyroid gland | | 1 (2%) | | |
| Carcinoma, metastatic, uncertain primary site | | 1 (2%) | | |
| Schwannoma malignant, metastatic, skin | | 1 (2%) | | |
| Nose | (50) | (50) | (49) | (50) |
| Squamous cell carcinoma | 1 (2%) | | | |
| **Special Senses System** | | | | |
| Ear | (1) | (2) | (2) | (1) |
| Zymbal's gland | | (2) | (2) | (1) |
| Carcinoma | | 2 (100%) | 1 (50%) | 1 (100%) |
| **Urinary System** | | | | |
| Kidney | (50) | (50) | (49) | (50) |
| Hemangiosarcoma | | | 1 (2%) | |
| Leiomyosarcoma, metastatic, intestine large, colon | | 1 (2%) | | |
| Renal tubule, adenoma | | 1 (2%) | 4 (8%) | 2 (4%) |
| Urinary bladder | (50) | (50) | (48) | (49) |
| **Systemic Lesions** | | | | |
| Multiple organs | (50) | (50) | (49) | (50) |
| Leukemia mononuclear | 24 (48%) | 16 (32%) | 21 (43%) | 22 (44%) |
| Mesothelioma NOS | 2 (4%) | | 1 (2%) | 1 (2%) |

**Table A1**
**Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Dermal Study of Triethanolamine** (continued)

| | 0 mg/kg | 32 mg/kg | 63 mg/kg | 125 mg/kg |
|---|---|---|---|---|
| **Neoplasm Summary** | | | | |
| Total animals with primary neoplasms[c] | | | | |
| 15-Month interim evaluation | 6 | 9 | 9 | 5 |
| 2-Year study | 47 | 49 | 48 | 50 |
| Total primary neoplasms | | | | |
| 15-Month interim evaluation | 9 | 11 | 12 | 7 |
| 2-Year study | 125 | 120 | 120 | 117 |
| Total animals with benign neoplasms | | | | |
| 15-Month interim evaluation | 5 | 9 | 9 | 5 |
| 2-Year study | 44 | 49 | 47 | 48 |
| Total benign neoplasms | | | | |
| 15-Month interim evaluation | 7 | 11 | 11 | 6 |
| 2-Year study | 93 | 90 | 91 | 88 |
| Total animals with malignant neoplasms | | | | |
| 15-Month interim evaluation | 1 | | | |
| 2-Year study | 26 | 23 | 27 | 26 |
| Total malignant neoplasms | | | | |
| 15-Month interim evaluation | 1 | | | |
| 2-Year study | 30 | 30 | 28 | 27 |
| Total animals with metastatic neoplasms | | | | |
| 2-Year study | | 5 | 2 | 1 |
| Total metastatic neoplasms | | | | |
| 2-Year study | | 15 | 5 | 3 |
| Total animals with malignant neoplasms of uncertain primary site | | | | |
| 2-Year study | | 1 | | |
| Total animals with uncertain neoplasms-benign or malignant | | | | |
| 15-Month interim evaluation | 1 | | 1 | 1 |
| 2-Year study | 2 | | 1 | 2 |
| Total uncertain neoplasms | | | | |
| 15-Month interim evaluation | 2 | | 1 | 2 |
| 2-Year study | 14 | | 5 | 10 |

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

**Table A2**
**Individual Animal Tumor Pathology of Male Rats in the 2-Year Dermal Study of Triethanolamine: 0 mg/kg**

| Number of Days on Study | 012 | 452 | 476 | 535 | 536 | 538 | 550 | 554 | 554 | 577 | 586 | 589 | 591 | 609 | 618 | 621 | 631 | 642 | 654 | 656 | 670 | 670 | 670 | 702 | 705 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 044 | 038 | 053 | 049 | 040 | 005 | 018 | 007 | 054 | 008 | 034 | 047 | 041 | 056 | 057 | 002 | 001 | 037 | 029 | 027 | 016 | 023 | 059 | 052 | 020 |
| **Alimentary System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Esophagus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine large, colon | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine large, rectum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine large, cecum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine small, duodenum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine small, jejunum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine small, ileum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Liver | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Hepatocellular adenoma | | | | | | | X | | | | | | | | | | | X | | | | | | | |
| Mesentery | | | | | | | | + | + | | | | | | | | | | + | | + | | | + | |
| Pancreas | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Salivary glands | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Stomach, forestomach | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Squamous cell papilloma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Stomach, glandular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Tongue | | | | | | | | | | | | | | | | | | | | | | | | | |
| Squamous cell papilloma | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Cardiovascular System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Blood vessel | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Heart | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Endocrine System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Adrenal cortex | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Adrenal medulla | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Pheochromocytoma benign | | | | | | | | | | | | | | | | | | | | | | | | X | |
| Bilateral, pheochromocytoma benign | | | | | | | | | | | | | | | | | | | | | | | | | |
| Islets, pancreatic | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Adenoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Parathyroid gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + |
| Pituitary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Pars distalis, adenoma | | | | | X | | X | X | | X | | X | | X | X | X | X | | | X | X | X | X | X | X |
| Pars distalis, adenoma, multiple | | | | | | | | | | | | | X | | | | | | | | | | | | |
| Thyroid gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Bilateral, C-cell, adenoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| C-cell, adenoma | | | | | | | | | | | | | X | | | | | | | | | | | | |
| **General Body System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Tissue NOS | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Genital System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Epididymis | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Penis | | | | | | | | | | | | | | | | | | | | | | | | + | |
| Preputial gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Prostate | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Adenocarcinoma | | | | | | | | | | | | | | | | | | | | | | | | | |

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

**TABLE A2**
**Individual Animal Tumor Pathology of Male Rats in the 2-Year Dermal Study of Triethanolamine: 0 mg/kg**
(continued)

| **Number of Days on Study** | 705 | 705 | 710 | 727 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 730 | 730 | 730 | 730 | 730 | 730 | 730 | 730 | 731 | 731 | 731 | 731 | 731 | 731 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 032 | 035 | 026 | 012 | 011 | 013 | 022 | 033 | 039 | 042 | 055 | 003 | 010 | 015 | 021 | 031 | 045 | 046 | 050 | 004 | 006 | 024 | 030 | 043 | 060 | Total Tissues/ Tumors |
| **Alimentary System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Esophagus | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Intestine large, colon | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Intestine large, rectum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Intestine large, cecum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Intestine small, duodenum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Intestine small, jejunum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Intestine small, ileum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Liver | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Hepatocellular adenoma | X | | | | | | | | | | | | | | | | | | | | | | | | | 3 |
| Mesentery | + | | | | | | | | + | | | | | | + | | | + | | | | | | | | 9 |
| Pancreas | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Salivary glands | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Stomach, forestomach | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Squamous cell papilloma | | | | | | | | | | | | | | | | | | | | | | | | | X | 1 |
| Stomach, glandular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Tongue | | | | | | | | | | | | | | | | | | | | | | + | | | | 1 |
| Squamous cell papilloma | | | | | | | | | | | | | | | | | | | | | | X | | | | 1 |
| **Cardiovascular System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Blood vessel | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Heart | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Endocrine System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Adrenal cortex | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Adrenal medulla | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Pheochromocytoma benign | | X | | | | | | | | | | | | | | | | | | | | | | | | 2 |
| Bilateral, pheochromocytoma benign | | | | | | | | | | | | | | | | | X | | | | | | | | | 1 |
| Islets, pancreatic | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Adenoma | | | | | | | | | | | | | | X | | | | | | | | | | | | 1 |
| Parathyroid gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Pituitary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Pars distalis, adenoma | X | X | X | | X | | | X | X | X | X | | X | X | X | X | | X | X | | X | X | X | X | X | 34 |
| Pars distalis, adenoma, multiple | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Thyroid gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Bilateral, C-cell, adenoma | | | | | | | | | | | | | X | | | | | | | | | | | | | 1 |
| C-cell, adenoma | | | | | X | | X | X | | | | | | X | | | | | | | | | | | | 5 |
| **General Body System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Tissue NOS | | | | | | | | | | | + | | | | | | | | | | | | | | | 1 |
| **Genital System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Epididymis | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Penis | + | | | | | | | | | | | | | | | | | | | | | | | | | 2 |
| Preputial gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Carcinoma | | X | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Prostate | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Adenocarcinoma | | | | | | | | | | | | | | | | | | | | | | | | | X | 1 |

**TABLE A2**
**Individual Animal Tumor Pathology of Male Rats in the 2-Year Dermal Study of Triethanolamine: 0 mg/kg**
(continued)

| | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Number of Days on Study** | 0<br>1<br>2 | 4<br>5<br>2 | 4<br>7<br>6 | 5<br>3<br>5 | 5<br>3<br>6 | 5<br>3<br>8 | 5<br>5<br>0 | 5<br>5<br>4 | 5<br>5<br>4 | 5<br>7<br>7 | 5<br>8<br>6 | 5<br>8<br>9 | 5<br>9<br>1 | 6<br>0<br>9 | 6<br>1<br>8 | 6<br>2<br>1 | 6<br>3<br>1 | 6<br>4<br>2 | 6<br>5<br>4 | 6<br>5<br>6 | 6<br>7<br>0 | 6<br>7<br>0 | 6<br>7<br>0 | 7<br>0<br>2 | 7<br>0<br>5 |
| **Carcass ID Number** | 0<br>4<br>4 | 0<br>3<br>8 | 0<br>5<br>3 | 0<br>4<br>9 | 0<br>4<br>0 | 0<br>0<br>5 | 0<br>1<br>8 | 0<br>0<br>7 | 0<br>5<br>4 | 0<br>0<br>8 | 0<br>3<br>4 | 0<br>4<br>7 | 0<br>4<br>1 | 0<br>5<br>6 | 0<br>5<br>7 | 0<br>0<br>2 | 0<br>0<br>1 | 0<br>3<br>7 | 0<br>2<br>9 | 0<br>2<br>7 | 0<br>1<br>6 | 0<br>2<br>3 | 0<br>5<br>9 | 0<br>5<br>2 | 0<br>2<br>0 |
| **Genital System** (continued) | | | | | | | | | | | | | | | | | | | | | | | | | |
| Seminal vesicle | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Testes | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Bilateral, interstitial cell, adenoma | | | | | | | | | | | | | X | | | | | X | | X | X | | | | |
| Interstitial cell, adenoma | | | | | | X | X | | | | X | | | X | | X | X | | | | | | X | X | X |
| **Hematopoietic System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone marrow | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Lymph node | | + | | | | + | + | | + | | + | | | | | | | + | + | | + | | | | + |
| Lymph node, mandibular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Lymph node, mesenteric | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Spleen | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Thymus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | M | M | M | + |
| **Integumentary System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Mammary gland | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Fibroadenoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Skin | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Keratoacanthoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Face, squamous cell papilloma | | | | | | | X | | | | | | | | | | | X | | | | | | | |
| Hindlimb, subcutaneous tissue, fibroma | | | | | | | | | | | X | | | | | | | | | | | | | | |
| Inguinal, keratoacanthoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Pinna, squamous cell papilloma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Site of application-mass, basal cell, adenoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Subcutaneous tissue, fibroma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Subcutaneous tissue, sarcoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Tail, fibrosarcoma | | | | | | | | | | | | | | | | | | X | | | | | | | |
| Thoracic, keratoacanthoma | | | | | | | | | | | | | | | | | | | | | X | | | | |
| Ventral, keratoacanthoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Musculoskeletal System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Skeletal muscle | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Nervous System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Brain | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Peripheral nerve | + | | | | | | | | | | | | | | | | | | | + | | | | | |
| Spinal cord | + | | | | | | | | | | | | | | | | | | | + | | | | | |
| **Respiratory System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lung | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Nose | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Squamous cell carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Trachea | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |

**TABLE A2**
**Individual Animal Tumor Pathology of Male Rats in the 2-Year Dermal Study of Triethanolamine: 0 mg/kg**
(continued)

| **Number of Days on Study** | 705 | 705 | 710 | 727 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 730 | 730 | 730 | 730 | 730 | 730 | 730 | 730 | 731 | 731 | 731 | 731 | 731 | 731 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 032 | 035 | 026 | 012 | 011 | 013 | 022 | 033 | 039 | 042 | 055 | 003 | 010 | 015 | 021 | 031 | 045 | 046 | 050 | 004 | 006 | 024 | 030 | 043 | 060 | Total Tissues/ Tumors |
| **Genital System** (continued) | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Seminal vesicle | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Testes | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Bilateral, interstitial cell, adenoma | | | | | X | X | X | X | | | | X | | X | | | X | X | | | X | X | | X | | 15 |
| Interstitial cell, adenoma | | | X | X | | | | | | | X | | | | X | | | | X | X | | | X | | | 16 |
| **Hematopoietic System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone marrow | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Lymph node | | | | | + | | | | | | | | | | | + | | + | | | | + | | | + | 14 |
| Lymph node, mandibular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Lymph node, mesenteric | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Spleen | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Thymus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | M | 46 |
| **Integumentary System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Mammary gland | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 48 |
| Carcinoma | | | | | | | | | | | | | | X | | | | | | | | | | | | 1 |
| Fibroadenoma | | | | | | | | | | X | | | | | | | | | | | | | | | | 1 |
| Skin | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Keratoacanthoma | | | | | | | | | | | | | | X | | | | | | | | | | | | 1 |
| Face, squamous cell papilloma | | | | | | | | | | | | | | | | | | | | | | | | | | 2 |
| Hindlimb, subcutaneous tissue, fibroma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Inguinal, keratoacanthoma | | | | | | | | | | | | | | | | | | | | | | | | X | | 1 |
| Pinna, squamous cell papilloma | | | | | | | | | | | | | | | | | | | | | | | X | | | 1 |
| Site of application-mass, basal cell, adenoma | | | | | | | | X | | | | | | | | | | | | | | | | | | 1 |
| Subcutaneous tissue, fibroma | | | | X | | | | | | | | | | | | | | | | | | | | | | 1 |
| Subcutaneous tissue, sarcoma | | | | | | | | | | | | X | | | | | | | | | | | | | | 1 |
| Tail, fibrosarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Thoracic, keratoacanthoma | | | | | | | | | | | | | | | | | | | | | | | X | | | 2 |
| Ventral, keratoacanthoma | | | | | | | | | | | | | | | X | | | | | | | | | | | 1 |
| **Musculoskeletal System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Skeletal muscle | + | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| **Nervous System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Brain | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Peripheral nerve | | | | | | | | | | | | | | | | | | | | | | | | | | 2 |
| Spinal cord | | | | | | | | | | | | | | | | | | | | | | | | | | 2 |
| **Respiratory System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lung | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Nose | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Squamous cell carcinoma | | | | | | | | | | | | | | | | | | | | X | | | | | | 1 |
| Trachea | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |

**TABLE A2**
**Individual Animal Tumor Pathology of Male Rats in the 2-Year Dermal Study of Triethanolamine: 0 mg/kg**
(continued)

| **Number of Days on Study** | 012 | 452 | 476 | 535 | 536 | 538 | 550 | 554 | 554 | 577 | 586 | 589 | 591 | 609 | 618 | 621 | 631 | 642 | 654 | 656 | 670 | 670 | 670 | 702 | 705 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 044 | 038 | 053 | 049 | 040 | 005 | 018 | 007 | 054 | 008 | 034 | 047 | 041 | 056 | 057 | 002 | 001 | 037 | 029 | 027 | 016 | 023 | 059 | 052 | 020 |
| **Special Senses System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Ear | | | | | | | | | | | | | | | | | | | | | | | | | |
| Eye | + | | | | | | | | | | | | | | | | | | | | + | | | | |
| **Urinary System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Kidney | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Urinary bladder | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Systemic Lesions** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Multiple organs | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Leukemia mononuclear | | X | | | | X | X | | X | | X | | | | | X | | X | X | | X | | | | X |
| Mesothelioma NOS | | | | | | | | | | | | | | | | | X | | | | | | | | |

**Table A2**
**Individual Animal Tumor Pathology of Male Rats in the 2-Year Dermal Study of Triethanolamine: 0 mg/kg**
(continued)

| Number of Days on Study | 705 | 705 | 710 | 727 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 730 | 730 | 730 | 730 | 730 | 730 | 730 | 730 | 731 | 731 | 731 | 731 | 731 | 731 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 032 | 035 | 026 | 012 | 011 | 013 | 022 | 033 | 039 | 042 | 055 | 003 | 010 | 015 | 021 | 031 | 045 | 046 | 050 | 004 | 006 | 024 | 030 | 043 | 060 | Total Tissues/ Tumors |
| **Special Senses System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Ear | | | | | | | | | | | | | | | | | | | | | | | | | + | 1 |
| Eye | | | | | | | | | | | | | | | | | | | | | | | | | | 2 |
| **Urinary System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Kidney | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Urinary bladder | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Systemic Lesions** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Multiple organs | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Leukemia mononuclear | X | | | | X | | X | | X | X | | X | | | | X | | X | X | X | X | X | X | | X | 24 |
| Mesothelioma NOS | X | | | | | | | | | | | | | | | | | | | | | | | | | 2 |

**TABLE A2**
**Individual Animal Tumor Pathology of Male Rats in the 2-Year Dermal Study of Triethanolamine: 32 mg/kg**

| Number of Days on Study | 416 | 420 | 443 | 467 | 484 | 507 | 549 | 558 | 558 | 564 | 572 | 573 | 578 | 599 | 604 | 606 | 608 | 613 | 619 | 620 | 621 | 631 | 634 | 635 | 649 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 116 | 086 | 069 | 099 | 101 | 074 | 089 | 068 | 105 | 092 | 096 | 097 | 064 | 082 | 077 | 115 | 065 | 107 | 091 | 067 | 094 | 120 | 114 | 095 | 066 |
| **Alimentary System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Esophagus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine large, colon | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Leiomyosarcoma | | | | | | | | | | | | | X | | | | | | | | | | | | |
| Intestine large, rectum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine large, cecum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine small, duodenum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Leiomyosarcoma, metastatic, intestine large, colon | | | | | | | | | | | | | X | | | | | | | | | | | | |
| Intestine small, jejunum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine small, ileum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Liver | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Leiomyosarcoma, metastatic, intestine large, colon | | | | | | | | | | | | | X | | | | | | | | | | | | |
| Schwannoma malignant, metastatic, skin | | | | | | | | | | | | | | | | | | | | | | | | | |
| Mesentery | | | | + | | | | | | + | | | + | | | | | | | | + | | | | |
| Leiomyosarcoma, metastatic, intestine large, colon | | | | | | | | | | | | | X | | | | | | | | | | | | |
| Pancreas | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Leiomyosarcoma, metastatic, intestine large, colon | | | | | | | | | | | | | X | | | | | | | | | | | | |
| Salivary glands | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Neurofibrosarcoma, metastatic, skin | | | | | | | | | | | | | | | | | | | | | | | | X | |
| Schwannoma malignant, metastatic, skin | | | | | | | | | | | | | | | | | | | | | | | | | |
| Stomach, forestomach | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Squamous cell papilloma | | | | | | | | | | | | | | | | | | | X | | | | | | |
| Stomach, glandular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Leiomyosarcoma, metastatic, intestine large, colon | | | | | | | | | | | | | X | | | | | | | | | | | | |
| Tooth | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Cardiovascular System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Blood vessel | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Heart | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Endocrine System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Adrenal cortex | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Adrenal medulla | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Pheochromocytoma benign | | | | | | | | | | | | X | | | | | | | X | | | X | | | |
| Islets, pancreatic | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Adenoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Parathyroid gland | + | + | + | + | + | + | + | + | + | + | + | + | + | M | + | + | + | + | M | + | M | + | + | + | + |
| Pituitary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Pars distalis, adenoma | X | | X | X | X | X | X | X | X | | X | X | | X | X | X | | X | X | X | X | X | X | X | X |
| Pars distalis, adenoma, multiple | | | | | | | | | | | | | | | | | | | | | | | | | |
| Thyroid gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Neurofibrosarcoma, metastatic, skin | | | | | | | | | | | | | | | | | | | | | | | | X | |
| C-cell, adenoma | | | | | | | | | | | | X | | | | | X | | | | | | | | X |
| C-cell, carcinoma | | | | | | | | X | | | | | | | | | | | | | | | | | |
| Follicular cell, carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | |

**TABLE A2**
**Individual Animal Tumor Pathology of Male Rats in the 2-Year Dermal Study of Triethanolamine: 32 mg/kg**
(continued)

| | | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Number of Days on Study** | 667 | 674 | 684 | 690 | 694 | 702 | 710 | 718 | 719 | 719 | 724 | 724 | 726 | 727 | 729 | 730 | 730 | 730 | 730 | 730 | 730 | 731 | 731 | 731 | 731 | |
| **Carcass ID Number** | 071 | 083 | 063 | 113 | 076 | 072 | 079 | 062 | 104 | 110 | 106 | 119 | 109 | 093 | 100 | 061 | 084 | 085 | 088 | 102 | 112 | 073 | 081 | 117 | 118 | Total Tissues/ Tumors |
| **Alimentary System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Esophagus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Intestine large, colon | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Leiomyosarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Intestine large, rectum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Intestine large, cecum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Intestine small, duodenum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Leiomyosarcoma, metastatic, intestine large, colon | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Intestine small, jejunum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Intestine small, ileum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Liver | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Leiomyosarcoma, metastatic, intestine large, colon | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Schwannoma malignant, metastatic, skin | X | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Mesentery | | | + | | + | + | + | | | | | | | | | | | | | | | | + | | | 9 |
| Leiomyosarcoma, metastatic, intestine large, colon | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Pancreas | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Leiomyosarcoma, metastatic, intestine large, colon | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Salivary glands | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Neurofibrosarcoma, metastatic, skin | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Schwannoma malignant, metastatic, skin | X | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Stomach, forestomach | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Squamous cell papilloma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Stomach, glandular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Leiomyosarcoma, metastatic, intestine large, colon | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Tooth | | | | | | | | | | | | | | + | | | | | | | | | | | | 1 |
| **Cardiovascular System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Blood vessel | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Heart | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Endocrine System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Adrenal cortex | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Adrenal medulla | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Pheochromocytoma benign | | | | | | X | | | | | | | | | | | | X | | X | | | X | X | | 8 |
| Islets, pancreatic | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Adenoma | X | | | | | X | | | | | | | | | | X | | | | | | | | | | 3 |
| Parathyroid gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 47 |
| Pituitary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Pars distalis, adenoma | X | X | X | X | X | X | | | X | X | | X | | X | X | X | X | | X | X | | X | | | | 37 |
| Pars distalis, adenoma, multiple | | | | | | | | | | | | | | | | | | | | | | | X | | | 1 |
| Thyroid gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Neurofibrosarcoma, metastatic, skin | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| C-cell, adenoma | | | | | | | | | | | | | | | | | | | | | | | X | | | 4 |
| C-cell, carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Follicular cell, carcinoma | | | X | | | | | | | | | | | | | | | | | | | | | | | 1 |

**Table A2**
**Individual Animal Tumor Pathology of Male Rats in the 2-Year Dermal Study of Triethanolamine: 32 mg/kg**
(continued)

| Number of Days on Study | 416 | 420 | 443 | 467 | 484 | 507 | 549 | 558 | 558 | 564 | 572 | 573 | 578 | 599 | 604 | 606 | 608 | 613 | 619 | 620 | 621 | 631 | 634 | 635 | 649 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 116 | 086 | 069 | 099 | 101 | 074 | 089 | 068 | 105 | 092 | 096 | 097 | 064 | 082 | 077 | 115 | 065 | 107 | 091 | 067 | 094 | 120 | 114 | 095 | 066 |
| **General Body System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| None | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Genital System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Epididymis | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Penis | | | | | | | | | | | | | | | | | | | | | | | | | |
| Preputial gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Fibrosarcoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Prostate | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Adenocarcinoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Sarcoma | | | | | | | | | | | | | | | | | | | | | X | | | | |
| Seminal vesicle | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Testes | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Bilateral, interstitial cell, adenoma | | | | | | | | | | | | | | | | | | | X | | | | | X | |
| Interstitial cell, adenoma | | | | | | | | X | | X | | X | X | | | | X | X | | | X | | | | X |
| **Hematopoietic System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone marrow | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Lymph node | | | | | | | | | | + | | | | | | | + | | | | + | | + | | + |
| Lymph node, mandibular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Schwannoma malignant, metastatic, skin | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lymph node, mesenteric | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Spleen | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Thymus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Integumentary System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Mammary gland | + | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Skin | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Basal cell adenoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Face, basosquamous tumor malignant | | | | | | | | | | | | | | | | | | | | | | | | | |
| Neck, subcutaneous tissue, schwannoma malignant | | | | | | | | | | | | | | | | | | | | | | | | | |
| Subcutaneous tissue, liposarcoma | | | | X | | | | | | | | | | | | | | | | | | | | | |
| Subcutaneous tissue, neurofibrosarcoma | | | | | | | | | | | | | | | | | | | | | | | | X | |
| Thoracic, subcutaneous tissue, fibroma | | | | | | | | | | | | | | | | | | X | | | | | | | |
| **Musculoskeletal System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Skeletal muscle | | | | | | | | | | | | | | | | | | | | | | | | + | |
| Neurofibrosarcoma, metastatic, skin | | | | | | | | | | | | | | | | | | | | | | | | X | |
| **Nervous System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Brain | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |

**TABLE A2**
**Individual Animal Tumor Pathology of Male Rats in the 2-Year Dermal Study of Triethanolamine: 32 mg/kg**
(continued)

| **Number of Days on Study** | 667 | 674 | 684 | 690 | 694 | 702 | 710 | 718 | 719 | 719 | 724 | 724 | 726 | 727 | 729 | 730 | 730 | 730 | 730 | 730 | 730 | 731 | 731 | 731 | 731 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 071 | 083 | 063 | 113 | 076 | 072 | 079 | 062 | 104 | 110 | 106 | 119 | 109 | 093 | 100 | 061 | 084 | 085 | 088 | 102 | 112 | 073 | 081 | 117 | 118 | Total Tissues/ Tumors |
| **General Body System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| None | | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Genital System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Epididymis | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Penis | + | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Preputial gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Carcinoma | | | | | | | | | | X | | | | | | | | | | | | | | | | 1 |
| Fibrosarcoma | | | X | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Prostate | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | M | + | + | + | + | 49 |
| Adenocarcinoma | | | | | | | X | | | | | | | | | | | | | | | | | | | 1 |
| Sarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Seminal vesicle | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Testes | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Bilateral, interstitial cell, adenoma | | | | X | | | | | | | X | | | | | | | X | X | X | X | X | X | | X | 11 |
| Interstitial cell, adenoma | X | X | X | | | | X | X | X | X | | X | X | X | X | X | X | | | | | | | X | | 22 |
| **Hematopoietic System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone marrow | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Lymph node | | + | | | | + | | | + | | + | | + | | | | | | | | | | | | | 10 |
| Lymph node, mandibular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Schwannoma malignant, metastatic, skin | X | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Lymph node, mesenteric | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Spleen | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Thymus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | M | + | + | + | + | 49 |
| **Integumentary System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Mammary gland | M | + | + | M | + | + | + | + | + | + | + | M | + | + | + | + | + | M | + | M | M | + | + | + | + | 43 |
| Carcinoma | | | | | | | | | | | | | | X | | | | | | | | | | | | 1 |
| Skin | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Basal cell adenoma | | | | | | | | | | | | X | | | | | | | | | | | | | | 1 |
| Face, basosquamous tumor malignant | | | | | | | | | | | X | | | | | | | | | | | | | | | 1 |
| Neck, subcutaneous tissue, schwannoma malignant | X | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Subcutaneous tissue, liposarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Subcutaneous tissue, neurofibrosarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Thoracic, subcutaneous tissue, fibroma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| **Musculoskeletal System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Skeletal muscle | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Neurofibrosarcoma, metastatic, skin | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| **Nervous System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Brain | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |

**Table A2**
**Individual Animal Tumor Pathology of Male Rats in the 2-Year Dermal Study of Triethanolamine: 32 mg/kg**
(continued)

| **Number of Days on Study** | 416 | 420 | 443 | 467 | 484 | 507 | 549 | 558 | 558 | 564 | 572 | 573 | 578 | 594 | 604 | 606 | 608 | 613 | 619 | 620 | 621 | 631 | 634 | 635 | 649 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 116 | 086 | 069 | 099 | 101 | 074 | 089 | 068 | 105 | 092 | 096 | 097 | 064 | 082 | 077 | 115 | 065 | 107 | 091 | 067 | 094 | 120 | 114 | 095 | 066 |
| **Respiratory System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lung | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Carcinoma, metastatic, thyroid gland | | | | | | | | X | | | | | | | | | | | | | | | | | |
| Carcinoma, metastatic, uncertain primary site | | | | | | | | | | | | | | | | X | | | | | | | | | |
| Schwannoma malignant, metastatic, skin | | | | | | | | | | | | | | | | | | | | | | | | | |
| Nose | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Trachea | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Special Senses System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Ear | | | | | | | | | | | | | | | | | | | | | | | | | |
| Zymbal's gland | | | | | | | | | + | | | | | | | | | | | | | | | | |
| Carcinoma | | | | | | | | | X | | | | | | | | | | | | | | | | |
| **Urinary System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Kidney | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Leiomyosarcoma, metastatic, intestine large, colon | | | | | | | | | | | | | X | | | | | | | | | | | | |
| Renal tubule, adenoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Urinary bladder | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Systemic Lesions** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Multiple organs | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Leukemia mononuclear | | | | | | | | | X | X | | | | | | | X | | | | X | | X | | X |

**TABLE A2**
**Individual Animal Tumor Pathology of Male Rats in the 2-Year Dermal Study of Triethanolamine: 32 mg/kg**
(continued)

| **Number of Days on Study** | 667 | 677 | 684 | 690 | 694 | 702 | 710 | 718 | 719 | 719 | 724 | 724 | 726 | 727 | 729 | 730 | 730 | 730 | 730 | 730 | 730 | 731 | 731 | 731 | 731 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 071 | 083 | 063 | 113 | 076 | 072 | 079 | 062 | 104 | 110 | 106 | 119 | 109 | 093 | 100 | 061 | 084 | 085 | 088 | 102 | 112 | 073 | 081 | 117 | 118 | Total Tissues/ Tumors |
| **Respiratory System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lung | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Carcinoma, metastatic, thyroid gland | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Carcinoma, metastatic, uncertain primary site | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Schwannoma malignant, metastatic, skin | X | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Nose | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Trachea | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Special Senses System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Ear | | | | | | | | + | + | | | | | | | | | | | | | | | | | 2 |
| Zymbal's gland | | | | | | + | | | | | | | | | | | | | | | | | | | | 2 |
| Carcinoma | | | | | | X | | | | | | | | | | | | | | | | | | | | 2 |
| **Urinary System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Kidney | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Leiomyosarcoma, metastatic, intestine large, colon | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Renal tubule, adenoma | | | | | | | | X | | | | | | | | | | | | | | | | | | 1 |
| Urinary bladder | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Systemic Lesions** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Multiple organs | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Leukemia mononuclear | | X | | X | | X | X | | X | X | X | | X | | | | X | | | | X | | | | | 16 |

**TABLE A2**
**Individual Animal Tumor Pathology of Male Rats in the 2-Year Dermal Study of Triethanolamine: 63 mg/kg**

| Number of Days on Study | 353 | 365 | 379 | 431 | 500 | 522 | 562 | 574 | 575 | 579 | 584 | 586 | 616 | 617 | 623 | 631 | 631 | 634 | 642 | 649 | 652 | 702 | 702 | 710 | 710 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 148 | 161 | 131 | 144 | 134 | 166 | 165 | 138 | 168 | 129 | 146 | 180 | 177 | 157 | 162 | 159 | 169 | 128 | 143 | 149 | 151 | 147 | 173 | 163 | 170 |
| **Alimentary System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Esophagus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine large, colon | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine large, rectum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine large, cecum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine small, duodenum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Leiomyosarcoma, metastatic, stomach, glandular | | | X | | | | | | | | | | | | | | | | | | | | | | |
| Intestine small, jejunum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine small, ileum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Liver | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Hepatocellular carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Leiomyosarcoma, metastatic, stomach, glandular | | | X | | | | | | | | | | | | | | | | | | | | | | |
| Mesentery | | | + | | | | + | | | + | | | | | | | + | | + | + | | + | | | |
| Leiomyosarcoma, metastatic, stomach, glandular | | | X | | | | | | | | | | | | | | | | | | | | | | |
| Pancreas | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Leiomyosarcoma, metastatic, stomach, glandular | | | X | | | | | | | | | | | | | | | | | | | | | | |
| Salivary glands | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | M | + |
| Stomach, forestomach | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Squamous cell papilloma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Stomach, glandular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Leiomyosarcoma | | | X | | | | | | | | | | | | | | | | | | | | | | |
| **Cardiovascular System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Blood vessel | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Heart | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Endocrine System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Adrenal cortex | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Adrenal medulla | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Pheochromocytoma complex | | | | | | | | | | | X | | | | | | | | | | | | | | |
| Pheochromocytoma benign | | | | | | | | | | | | X | | | | | | | | | | | | | X |
| Islets, pancreatic | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Adenoma | | | | | | | | | | | | | | | | | | | | | | | | | X |
| Parathyroid gland | + | + | + | + | + | + | + | + | + | + | M | M | M | + | + | + | + | M | + | + | + | + | + | + | + |
| Pituitary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Pars distalis, adenoma | | | X | X | | | | X | X | | X | X | X | X | X | X | | | | X | X | | | X | X |
| Pars distalis, adenoma, multiple | | | | | | | | | | X | | | | | | | | | | | | | X | | |
| Thyroid gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| C-cell, adenoma | | | | | | | | | | | X | | X | | | | X | X | | X | | | | | |
| C-cell, carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Follicular cell, adenoma | | | | | | | | | | | | | | X | | | | | | | | | | | |

**TABLE A2**
**Individual Animal Tumor Pathology of Male Rats in the 2-Year dermal Study of Triethanolamine: 63 mg/kg**
(continued)

| Number of Days on Study | 710 | 719 | 722 | 724 | 724 | 724 | 729 | 729 | 729 | 729 | 730 | 730 | 730 | 730 | 730 | 730 | 730 | 731 | 731 | 731 | 731 | 731 | 731 | 731 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 178 | 136 | 132 | 121 | 122 | 150 | 145 | 156 | 167 | 174 | 125 | 127 | 139 | 154 | 160 | 171 | 175 | 123 | 124 | 130 | 140 | 153 | 172 | 176 | Total Tissues/ Tumors |
| **Alimentary System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Esophagus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Intestine large, colon | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Intestine large, rectum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Intestine large, cecum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Intestine small, duodenum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Leiomyosarcoma, metastatic, stomach, glandular | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Intestine small, jejunum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Intestine small, ileum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Liver | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Hepatocellular carcinoma | | | X | | | | | | | | | | | | | | | | | | | | | | 1 |
| Leiomyosarcoma, metastatic, stomach, glandular | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Mesentery | | | | + | | | | | | + | | | | | | | | | + | | | | | | 10 |
| Leiomyosarcoma, metastatic, stomach, glandular | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Pancreas | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Leiomyosarcoma, metastatic, stomach, glandular | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Salivary glands | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 48 |
| Stomach, forestomach | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Squamous cell papilloma | | | | | | | | | | X | | | | | | | | | | | | | | | 1 |
| Stomach, glandular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Leiomyosarcoma | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| **Cardiovascular System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Blood vessel | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Heart | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| **Endocrine System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Adrenal cortex | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Adrenal medulla | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Pheochromocytoma complex | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Pheochromocytoma benign | | | | | | | | X | X | | | | | | | | | | | | | | | | 4 |
| Islets, pancreatic | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Adenoma | | | | | | | X | | | X | | | | | | | | | | | | | | | 3 |
| Parathyroid gland | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 44 |
| Pituitary gland | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 48 |
| Pars distalis, adenoma | X | X | X | | X | X | | X | | X | X | X | | | X | X | X | X | | X | X | X | | | 30 |
| Pars distalis, adenoma, multiple | | | | | | | | | | | | | | | | | | | | | | | | | 2 |
| Thyroid gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| C-cell, adenoma | | | | | | | | | | | X | | | | | | | | | | X | | | | 7 |
| C-cell, carcinoma | | | X | | | | | | | | | | | | | | | | | | | | | | 1 |
| Follicular cell, adenoma | | | | | | | | | | | | | | | | | | | | | | | | | 1 |

**TABLE A2**
**Individual Animal Tumor Pathology of Male Rats in the 2-Year Dermal Study of Triethanolamine: 63 mg/kg**
(continued)

| | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Number of Days on Study** | 3<br>5<br>3 | 3<br>6<br>5 | 3<br>7<br>9 | 4<br>3<br>1 | 5<br>0<br>0 | 5<br>2<br>2 | 5<br>6<br>2 | 5<br>7<br>4 | 5<br>7<br>5 | 5<br>7<br>9 | 5<br>8<br>4 | 5<br>8<br>6 | 6<br>1<br>6 | 6<br>1<br>7 | 6<br>2<br>3 | 6<br>3<br>1 | 6<br>3<br>1 | 6<br>3<br>4 | 6<br>4<br>2 | 6<br>4<br>9 | 6<br>5<br>2 | 7<br>0<br>2 | 7<br>0<br>2 | 7<br>1<br>0 | 7<br>1<br>0 |
| **Carcass ID Number** | 1<br>4<br>8 | 1<br>6<br>1 | 1<br>3<br>1 | 1<br>4<br>4 | 1<br>3<br>4 | 1<br>6<br>6 | 1<br>6<br>5 | 1<br>3<br>8 | 1<br>6<br>8 | 1<br>2<br>9 | 1<br>4<br>6 | 1<br>8<br>0 | 1<br>7<br>7 | 1<br>5<br>7 | 1<br>6<br>2 | 1<br>5<br>9 | 1<br>6<br>9 | 1<br>2<br>8 | 1<br>4<br>3 | 1<br>4<br>9 | 1<br>5<br>1 | 1<br>4<br>7 | 1<br>7<br>3 | 1<br>6<br>3 | 1<br>7<br>0 |
| **General Body System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| None | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Genital System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Epididymis | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Preputial gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Adenoma | X | | | | | | | | | | | | | | | | | | | | | | | | |
| Prostate | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Seminal vesicle | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Testes | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Bilateral, interstitial cell, adenoma | | | | | | X | X | | | | | X | X | | | | | X | X | | | | | | |
| Interstitial cell, adenoma | X | | | | | | | | X | X | | | | X | | X | | | | X | | X | X | | X |
| **Hematopoietic System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone marrow | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Lymph node | | | + | | + | | + | | | + | | | + | | | | + | + | | | | + | | | |
| Deep cervical, carcinoma, metastatic, thyroid gland | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lymph node, mandibular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Lymph node, mesenteric | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Spleen | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Thymus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + |
| **Integumentary System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Mammary gland | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | M | + | + | + | M | + | + | + | + | + |
| Skin | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Dorsal, keratoacanthoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Face, squamous cell papilloma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Inguinal, subcutaneous tissue, fibrosarcoma | | | | X | | | | | | | | | | | | | | | | | | | | | |
| Subcutaneous tissue, ventral, fibroma | | | | | | | | | | | | | | X | | | | | | | | | | | |
| Thoracic, keratoacanthoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Thoracic, subcutaneous tissue, fibroma | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Musculoskeletal System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Skeletal muscle | | | | | | | | | | + | | | | | | | | | | | | | | | |
| **Nervous System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Brain | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | M | + |
| Peripheral nerve | | | | | | | | + | | + | | | | | | | | | | | | | | | |
| Spinal cord | | | | | | | | + | | + | | | | | | | | | | | | | | | |
| **Respiratory System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lung | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Nose | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Trachea | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |

**TABLE A2**
**Individual Animal Tumor Pathology of Male Rats in the 2-Year Dermal Study of Triethanolamine: 63 mg/kg**
(continued)

| Number of Days on Study | 710 | 719 | 722 | 724 | 724 | 724 | 729 | 729 | 729 | 729 | 730 | 730 | 730 | 730 | 730 | 730 | 730 | 731 | 731 | 731 | 731 | 731 | 731 | 731 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 178 | 136 | 132 | 121 | 122 | 150 | 145 | 156 | 167 | 174 | 125 | 127 | 139 | 154 | 160 | 171 | 175 | 123 | 124 | 130 | 140 | 153 | 172 | 176 | Total Tissues/ Tumors |
| **General Body System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| None | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Genital System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Epididymis | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Preputial gland | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 48 |
| Adenoma | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Prostate | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Seminal vesicle | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Testes | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Bilateral, interstitial cell, adenoma | | | | | | | X | | | | | | X | X | X | | X | X | X | X | | | | X | 15 |
| Interstitial cell, adenoma | | X | X | X | X | X | | X | | | | X | | | | | | | | | | X | X | | 18 |
| **Hematopoietic System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone marrow | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Lymph node | | + | + | + | + | + | + | | | | | | | | | + | | + | | | | | | | 16 |
| Deep cervical, carcinoma, metastatic, thyroid gland | | | X | | | | | | | | | | | | | | | | | | | | | | 1 |
| Lymph node, mandibular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Lymph node, mesenteric | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Spleen | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Thymus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 48 |
| **Integumentary System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Mammary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | M | 45 |
| Skin | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Dorsal, keratoacanthoma | | | | | | | | | X | | | | | | | | | | | | | | | | 1 |
| Face, squamous cell papilloma | | | | | | | | | | | | | | | | | | | | X | | | | | 1 |
| Inguinal, subcutaneous tissue, fibrosarcoma | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Subcutaneous tissue, ventral, fibroma | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Thoracic, keratoacanthoma | | | | | | | | | | | | | | | | | | | | X | | | | | 1 |
| Thoracic, subcutaneous tissue, fibroma | | | | | | | | | | | | | | | | | | | | X | | | | | 1 |
| **Musculoskeletal System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Skeletal muscle | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| **Nervous System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Brain | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 48 |
| Peripheral nerve | | | | | | | | | | | | | | | | | | | | | | | | | 2 |
| Spinal cord | | | | | | | | | | | | | | | | | | | | | | | | | 2 |
| **Respiratory System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lung | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Nose | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Trachea | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |

**Table A2**
**Individual Animal Tumor Pathology of Male Rats in the 2-Year Dermal Study of Triethanolamine: 63 mg/kg**
(continued)

| | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 3 | 3 | 3 | 4 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 7 | 7 | 7 | 7 |
| **Number of Days on Study** | 5 | 6 | 7 | 3 | 0 | 2 | 6 | 7 | 7 | 7 | 8 | 8 | 1 | 1 | 2 | 3 | 3 | 3 | 4 | 4 | 5 | 0 | 0 | 1 | 1 |
| | 3 | 5 | 9 | 1 | 0 | 2 | 2 | 4 | 5 | 9 | 4 | 6 | 6 | 7 | 3 | 1 | 1 | 4 | 2 | 9 | 2 | 2 | 2 | 0 | 0 |
| | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| **Carcass ID Number** | 4 | 6 | 3 | 4 | 3 | 6 | 6 | 3 | 6 | 2 | 4 | 8 | 7 | 5 | 6 | 5 | 6 | 2 | 4 | 4 | 5 | 4 | 7 | 6 | 7 |
| | 8 | 1 | 1 | 4 | 4 | 6 | 5 | 8 | 8 | 9 | 6 | 0 | 7 | 7 | 2 | 9 | 9 | 8 | 3 | 9 | 1 | 7 | 3 | 3 | 0 |
| **Special Senses System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Ear | | | | | | | | | | + | | | | | | | + | | | | | | | | |
| Eye | | | | | | | | | | | + | | | | | | | | | | | | | | |
| Zymbal's gland | | | | | + | | | | | | | | | | | | | | | | + | | | | |
| Carcinoma | | | | | | | | | | | | | | | | | | | | | X | | | | |
| **Urinary System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Kidney | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Hemangiosarcoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Renal tubule, adenoma | | | | | | | | | | | | | | | | | | | | X | X | | | X | |
| Urinary bladder | + | + | + | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + |
| **Systemic Lesions** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Multiple organs | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Leukemia mononuclear | | | | | X | X | X | X | | X | | | X | | | | X | X | | | | X | | | |
| Mesothelioma NOS | | | | | | | | | | | | | | | | | | | | X | | | | | |

**Table A2**
**Individual Animal Tumor Pathology of Male Rats in the 2-Year Dermal Study of Triethanolamine: 63 mg/kg**
(continued)

| Number of Days on Study | 710 | 719 | 722 | 724 | 724 | 724 | 729 | 729 | 729 | 729 | 730 | 730 | 730 | 730 | 730 | 730 | 730 | 731 | 731 | 731 | 731 | 731 | 731 | 731 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 178 | 136 | 132 | 121 | 122 | 150 | 145 | 156 | 167 | 174 | 125 | 127 | 139 | 154 | 160 | 171 | 175 | 123 | 124 | 130 | 140 | 153 | 172 | 176 | Total Tissues/ Tumors |
| **Special Senses System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Ear | | | | | | | | | | | | | | | | | | | | | | | | | 2 |
| Eye | | | | | | | | | | | | | | | | | | | | | + | + | | | 3 |
| Zymbal's gland | | | | | | | | | | | | | | | | | | | | | | | | | 2 |
| Carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| **Urinary System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Kidney | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Hemangiosarcoma | | | | | | | | | X | | | | | | | | | | | | | | | | 1 |
| Renal tubule, adenoma | | | | | | | | | | | | | | | | | | X | | | | | | | 4 |
| Urinary bladder | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 48 |
| **Systemic Lesions** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Multiple organs | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Leukemia mononuclear | | X | | X | X | X | X | | | X | | | X | | | X | | X | X | | | X | | X | 21 |
| Mesothelioma NOS | | | | | | | | | | | | | | | | | | | | | | | | | 1 |

**TABLE A2**
**Individual Animal Tumor Pathology of Male Rats in the 2-Year Dermal Study of Triethanolamine: 125 mg/kg**

| **Number of Days on Study** | 404 | 424 | 444 | 459 | 502 | 502 | 535 | 543 | 546 | 558 | 558 | 562 | 563 | 572 | 572 | 579 | 617 | 642 | 642 | 645 | 649 | 664 | 665 | 667 | 670 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 225 | 206 | 224 | 198 | 182 | 210 | 236 | 227 | 219 | 187 | 199 | 226 | 203 | 232 | 233 | 230 | 202 | 190 | 200 | 240 | 215 | 183 | 229 | 186 | 209 |
| **Alimentary System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Esophagus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine large, colon | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine large, rectum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine large, cecum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine small, duodenum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine small, jejunum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Fibrous histiocytoma, metastatic, spleen | | | X | | | | | | | | | | | | | | | | | | | | | | |
| Mast cell tumor malignant | | | | | | | | | | | | | | | | | | | | | | | | | |
| Intestine small, ileum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Fibrous histiocytoma, metastatic, spleen | | | X | | | | | | | | | | | | | | | | | | | | | | |
| Liver | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Hepatocellular adenoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Mesentery | | | | | | | + | + | | | + | | | | | | | | | | | | | | |
| Pancreas | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Salivary glands | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Stomach, forestomach | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Stomach, glandular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Cardiovascular System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Blood vessel | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Heart | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Endocrine System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Adrenal cortex | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Adrenal medulla | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Pheochromocytoma benign | | | | | | | | | | X | | | | | | | | | | | | | | | |
| Islets, pancreatic | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Adenoma | | | | | | | | | | | | | X | | | | | | | | | | | | |
| Parathyroid gland | + | + | + | + | + | + | + | M | + | + | + | M | + | + | + | + | + | + | + | + | + | + | M | + | + |
| Adenoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Pituitary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Pars distalis, adenoma | X | | | | X | X | X | X | X | | X | X | X | X | | X | X | X | | X | X | X | X | X | |
| Pars distalis, adenoma, multiple | | | | | | | | | | | | | | | | | | | X | | | | | | |
| Thyroid gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| C-cell, adenoma | | | | X | | | | | | | X | | | | | | | X | | | | | X | | |
| **General Body System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| None | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Genital System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Epididymis | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Penis | | | | | + | | | | | | | | | | | | | | | | | | | | |
| Preputial gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Adenoma | | | | | | | | | | | | | | | | | | X | | | | | | | |
| Prostate | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Seminal vesicle | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Testes | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Bilateral, interstitial cell, adenoma | | | | | | | | | | | X | | | | | | | X | X | | | | | | |
| Interstitial cell, adenoma | | | | X | | | | | | X | | | | | X | X | | | | X | | | X | | X |

**TABLE A2**
**Individual Animal Tumor Pathology of Male Rats in the 2-Year Dermal Study of Triethanolamine: 125 mg/kg**
(continued)

| | | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Number of Days on Study** | 684 | 688 | 690 | 691 | 718 | 722 | 729 | 729 | 729 | 729 | 729 | 729 | 730 | 730 | 730 | 730 | 730 | 730 | 731 | 731 | 731 | 731 | 731 | 731 | 731 | |
| **Carcass ID Number** | 205 | 235 | 238 | 192 | 237 | 234 | 181 | 188 | 196 | 212 | 213 | 228 | 185 | 191 | 218 | 221 | 223 | 239 | 184 | 189 | 195 | 197 | 200 | 208 | 217 | Total Tissues/ Tumors |
| **Alimentary System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Esophagus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Intestine large, colon | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Intestine large, rectum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Intestine large, cecum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Intestine small, duodenum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Intestine small, jejunum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Fibrous histiocytoma, metastatic, spleen | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Mast cell tumor malignant | | | | | | | | | | | | | | | | | | | | | | | X | | | 1 |
| Intestine small, ileum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Fibrous histiocytoma, metastatic, spleen | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Liver | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Hepatocellular adenoma | | | | | | | | | | | | | | | | | | | | | | | | | X | 1 |
| Mesentery | | + | | | | | | | | | | | | | | | + | | | | | | | | | 5 |
| Pancreas | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Salivary glands | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Stomach, forestomach | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Stomach, glandular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Cardiovascular System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Blood vessel | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Heart | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Endocrine System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Adrenal cortex | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Adrenal medulla | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Pheochromocytoma benign | | | | X | | | | | | | | | | | | | | | X | | | | | | | 3 |
| Islets, pancreatic | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Adenoma | | | | | | | | | X | | | X | | | X | | | | | | | X | | | | 5 |
| Parathyroid gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 47 |
| Adenoma | | | | | | | | | | | | | | | | | | | | | X | | | | | 1 |
| Pituitary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Pars distalis, adenoma | X | | X | X | X | X | X | | X | X | | X | X | X | | | X | X | X | X | X | X | X | | X | 37 |
| Pars distalis, adenoma, multiple | | | | | | | | X | | | | | | | X | X | | | | | | | | | | 4 |
| Thyroid gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| C-cell, adenoma | | | | | | | | | | | X | | | | | | | | | | X | | | | | 6 |
| **General Body System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| None | | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Genital System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Epididymis | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Penis | | | | + | | | | | | | | | | | | | | | | | | | | | | 2 |
| Preputial gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Adenoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Prostate | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Seminal vesicle | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Testes | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Bilateral, interstitial cell, adenoma | | | | X | | | X | | | | | | | | | | X | | | | | X | X | | X | 9 |
| Interstitial cell, adenoma | | X | X | | | | | | | | | X | X | | | X | | | X | X | X | | | X | | 16 |

**TABLE A2**
**Individual Animal Tumor Pathology of Male Rats in the 2-Year Dermal Study of Triethanolamine: 125 mg/kg**
(continued)

| Number of Days on Study | 404 | 424 | 444 | 459 | 502 | 502 | 535 | 543 | 546 | 558 | 558 | 562 | 563 | 572 | 572 | 579 | 617 | 642 | 642 | 645 | 649 | 664 | 665 | 667 | 670 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 225 | 206 | 224 | 198 | 182 | 210 | 236 | 227 | 219 | 187 | 199 | 226 | 203 | 232 | 233 | 230 | 202 | 190 | 200 | 240 | 215 | 183 | 229 | 186 | 209 |
| **Hematopoietic System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone marrow | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Lymph node | | + | | | | | | | | | | | | | + | | | | | + | | | | | |
| Lymph node, mandibular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Lymph node, mesenteric | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | M | + | + |
| Spleen | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Fibrous histiocytoma | | | X | | | | | | | | | | | | | | | | | | | | | | |
| Thymus | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Integumentary System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Mammary gland | + | + | + | + | + | + | M | M | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Skin | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Abdominal, ventral, keratoacanthoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Head, basosquamous tumor benign | | | | | | | | | | | | | | | | | | | | | | | | | |
| Inguinal, subcutaneous tissue, sarcoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Pinna, sarcoma | | | | | X | | | | | | | | | | | | | | | | | | | | |
| Site of application-mass, keratoacanthoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Subcutaneous tissue, fibrous histiocytoma, metastatic, spleen | | | X | | | | | | | | | | | | | | | | | | | | | | |
| **Musculoskeletal System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Skeletal muscle | | | | | | | | | | | + | | | | | | | | | | | | | | |
| **Nervous System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Brain | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Astrocytoma NOS | | | | | | | | | | | | | | | | | X | | | | | | | | |
| **Respiratory System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lung | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Nose | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Trachea | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Special Senses System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Ear | | | | | | | | | | | | | | | | | | | | | | | | | |
| Eye | | | | | | | | | | | | | | | | | | | | | | | | | |
| Zymbal's gland | | | | | | | | | | | | | | + | | | | | | | | | | | |
| Carcinoma | | | | | | | | | | | | | | X | | | | | | | | | | | |
| **Urinary System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Kidney | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Renal tubule, adenoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Urinary bladder | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Systemic Lesions** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Multiple organs | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Leukemia mononuclear | | X | | | | | | | | | | | | | X | | | | X | X | | | | X | |
| Mesothelioma NOS | | | | | | | | | | | X | | | | | | | | | | | | | | |

**Table A2**
**Individual Animal Tumor Pathology of Male Rats in the 2-Year Dermal Study of Triethanolamine: 125 mg/kg**
(continued)

| | | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Number of Days on Study** | 6<br>8<br>4 | 6<br>8<br>8 | 6<br>9<br>0 | 6<br>9<br>1 | 7<br>1<br>8 | 7<br>2<br>2 | 7<br>2<br>9 | 7<br>2<br>9 | 7<br>2<br>9 | 7<br>2<br>9 | 7<br>2<br>9 | 7<br>2<br>9 | 7<br>3<br>0 | 7<br>3<br>0 | 7<br>3<br>0 | 7<br>3<br>0 | 7<br>3<br>0 | 7<br>3<br>0 | 7<br>3<br>1 | 7<br>3<br>1 | 7<br>3<br>1 | 7<br>3<br>1 | 7<br>3<br>1 | 7<br>3<br>1 | 7<br>3<br>1 | |
| **Carcass ID Number** | 2<br>0<br>5 | 2<br>3<br>5 | 2<br>3<br>8 | 1<br>9<br>2 | 2<br>3<br>7 | 2<br>3<br>4 | 1<br>8<br>1 | 1<br>8<br>8 | 1<br>9<br>6 | 2<br>1<br>2 | 2<br>1<br>3 | 2<br>2<br>8 | 1<br>8<br>5 | 1<br>9<br>1 | 2<br>1<br>8 | 2<br>2<br>1 | 2<br>2<br>3 | 2<br>3<br>9 | 1<br>8<br>4 | 1<br>8<br>9 | 1<br>9<br>5 | 1<br>9<br>7 | 2<br>0<br>0 | 2<br>0<br>8 | 2<br>1<br>7 | Total Tissues/ Tumors |
| **Hematopoietic System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone marrow | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Lymph node | | + | | | | | + | | | + | | | | | | | + | + | + | | | | | | | 9 |
| Lymph node, mandibular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Lymph node, mesenteric | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Spleen | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Fibrous histiocytoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Thymus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| **Integumentary System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Mammary gland | + | M | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | 45 |
| Skin | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Abdominal, ventral, keratoacanthoma | | | | | | | | | | | | | | | | X | | | | | | | | | | 1 |
| Head, basosquamous tumor benign | | | | | | | | | X | | | | | | | | | | | | | | | | | 1 |
| Inguinal, subcutaneous tissue, sarcoma | | | | | | | | X | | | | | | | | | | | | | | | | | | 1 |
| Pinna, sarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Site of application-mass, keratoacanthoma | | | | | | | | | | X | | | | | | | | | | | | | | | | 1 |
| Subcutaneous tissue, fibrous histiocytoma, metastatic, spleen | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| **Musculoskeletal System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Skeletal muscle | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| **Nervous System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Brain | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Astrocytoma NOS | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| **Respiratory System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lung | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Nose | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Trachea | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Special Senses System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Ear | | | | + | | | | | | | | | | | | | | | | | | | | | | 1 |
| Eye | | | | | + | | | | | | | | | | | | | | | | | | | | + | 2 |
| Zymbal's gland | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| **Urinary System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Kidney | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Renal tubule, adenoma | | | | | | | | | X | X | | | | | | | | | | | | | | | | 2 |
| Urinary bladder | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | M | + | 49 |
| **Systemic Lesions** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Multiple organs | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Leukemia mononuclear | | X | | X | X | X | X | X | | X | X | X | | X | | X | X | X | X | X | X | | | X | | 22 |
| Mesothelioma NOS | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |

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

| | 0 mg/kg | 32 mg/kg | 63 mg/kg | 125 mg/kg |
|---|---|---|---|---|
| **Adrenal Medulla: Benign Pheochromocytoma** | | | | |
| Overall rate[a] | 3/50 (6%) | 8/50 (16%) | 4/49 (8%) | 3/50 (6%) |
| Adjusted rate[b] | 11.8% | 44.9% | 16.8% | 11.8% |
| Terminal rate[c] | 1/21 (5%) | 4/11 (36%) | 2/18 (11%) | 1/19 (5%) |
| First incidence (days) | 702 | 573 | 586 | 558 |
| Life table test[d] | P=0.357N | P=0.025 | P=0.473 | P=0.592 |
| Logistic regression test[d] | P=0.354N | P=0.069 | P=0.489 | P=0.641 |
| Cochran-Armitage test[d] | P=0.340N | | | |
| Fisher exact test[d] | | P=0.100 | P=0.489 | P=0.661N |
| **Adrenal Medulla: Benign or Complex Pheochromocytoma** | | | | |
| Overall rate | 3/50 (6%) | 8/50 (16%) | 5/49 (10%) | 3/50 (6%) |
| Adjusted rate | 11.8% | 44.9% | 18.9% | 11.8% |
| Terminal rate | 1/21 (5%) | 4/11 (36%) | 2/18 (11%) | 1/19 (5%) |
| First incidence (days) | 702 | 573 | 584 | 558 |
| Life table test | P=0.379N | P=0.025 | P=0.335 | P=0.592 |
| Logistic regression test | P=0.371N | P=0.069 | P=0.343 | P=0.641 |
| Cochran-Armitage test | P=0.359N | | | |
| Fisher exact test | | P=0.100 | P=0.346 | P=0.661N |
| **Kidney (Renal Tubule): Adenoma (Single Sections)** | | | | |
| Overall rate | 0/50 (0%) | 1/50 (2%) | 4/49 (8%) | 2/50 (4%) |
| Adjusted rate | 0.0% | 5.6% | 15.2% | 10.5% |
| Terminal rate | 0/21 (0%) | 0/11 (0%) | 1/18 (6%) | 2/19 (11%) |
| First incidence (days) | —[e] | 718 | 649 | 729 (T) |
| Life table test | P=0.179 | P=0.460 | P=0.060 | P=0.215 |
| Logistic regression test | P=0.155 | P=0.454 | P=0.060 | P=0.215 |
| Cochran-Armitage test | P=0.165 | | | |
| Fisher exact test | | P=0.500 | P=0.056 | P=0.247 |
| **Kidney (Renal Tubule): Adenoma (Single and Step Sections)** | | | | |
| Overall rate | 1/50 (2%) | 2/50 (4%) | 6/49 (12%) | 4/50 (8%) |
| Adjusted rate | 4.3% | 9.8% | 25.2% | 21.1% |
| Terminal rate | 0/21 (0%) | 0/11 (0%) | 3/18 (17%) | 4/19 (21%) |
| First incidence (days) | 710 | 690 | 649 | 729 (T) |
| Life table test | P=0.127 | P=0.432 | P=0.054 | P=0.150 |
| Logistic regression test | P=0.099 | P=0.441 | P=0.054 | P=0.140 |
| Cochran-Armitage test | P=0.113 | | | |
| Fisher exact test | | P=0.500 | P=0.053 | P=0.181 |
| **Liver: Hepatocellular Adenoma** | | | | |
| Overall rate | 3/50 (6%) | 0/50 (0%) | 0/49 (0%) | 1/50 (2%) |
| Adjusted rate | 8.9% | 0.0% | 0.0% | 5.3% |
| Terminal rate | 0/21 (0%) | 0/11 (0%) | 0/18 (0%) | 1/19 (5%) |
| First incidence (days) | 550 | — | — | 729 (T) |
| Life table test | P=0.256N | P=0.160N | P=0.129N | P=0.343N |
| Logistic regression test | P=0.249N | P=0.119N | P=0.125N | P=0.307N |
| Cochran-Armitage test | P=0.248N | | | |
| Fisher exact test | | P=0.121N | P=0.125N | P=0.309N |

**TABLE A3**
**Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Dermal Study of Triethanolamine** (continued)

| | 0 mg/kg | 32 mg/kg | 63 mg/kg | 125 mg/kg |
|---|---|---|---|---|
| **Liver: Hepatocellular Adenoma or Carcinoma** | | | | |
| Overall rate | 3/50 (6%) | 0/50 (0%) | 1/49 (2%) | 1/50 (2%) |
| Adjusted rate | 8.9% | 0.0% | 4.5% | 5.3% |
| Terminal rate | 0/21 (0%) | 0/11 (0%) | 0/18 (0%) | 1/19 (5%) |
| First incidence (days) | 550 | — | 722 | 729 (T) |
| Life table test | P=0.304N | P=0.160N | P=0.316N | P=0.343N |
| Logistic regression test | P=0.301N | P=0.119N | P=0.312N | P=0.307N |
| Cochran-Armitage test | P=0.297N | | | |
| Fisher exact test | | P=0.121N | P=0.316N | P=0.309N |
| **Pancreatic Islets: Adenoma** | | | | |
| Overall rate | 1/50 (2%) | 3/50 (6%) | 3/49 (6%) | 5/50 (10%) |
| Adjusted rate | 4.8% | 17.1% | 14.5% | 23.1% |
| Terminal rate | 1/21 (5%) | 1/11 (9%) | 2/18 (11%) | 4/19 (21%) |
| First incidence (days) | 729 (T) | 667 | 710 | 563 |
| Life table test | P=0.088 | P=0.167 | P=0.275 | P=0.080 |
| Logistic regression test | P=0.070 | P=0.243 | P=0.300 | P=0.084 |
| Cochran-Armitage test | P=0.079 | | | |
| Fisher exact test | | P=0.309 | P=0.301 | P=0.102 |
| **Pituitary Gland (Pars Distalis): Adenoma** | | | | |
| Overall rate | 35/50 (70%) | 38/50 (76%) | 32/48 (67%) | 41/50 (82%) |
| Adjusted rate | 87.0% | 88.5% | 82.5% | 95.1% |
| Terminal rate | 16/21 (76%) | 7/11 (64%) | 11/17 (65%) | 17/19 (89%) |
| First incidence (days) | 536 | 416 | 379 | 404 |
| Life table test | P=0.251 | P=0.043 | P=0.557N | P=0.110 |
| Logistic regression test | P=0.132 | P=0.305 | P=0.460N | P=0.081 |
| Cochran-Armitage test | P=0.142 | | | |
| Fisher exact test | | P=0.326 | P=0.445N | P=0.121 |
| **Skin: Squamous Cell Papilloma** | | | | |
| Overall rate | 3/50 (6%) | 0/50 (0%) | 1/49 (2%) | 0/50 (0%) |
| Adjusted rate | 9.7% | 0.0% | 5.6% | 0.0% |
| Terminal rate | 1/21 (5%) | 0/11 (0%) | 1/18 (6%) | 0/19 (0%) |
| First incidence (days) | 550 | — | 729 (T) | — |
| Life table test | P=0.091N | P=0.180N | P=0.343N | P=0.134N |
| Logistic regression test | P=0.088N | P=0.120N | P=0.312N | P=0.120N |
| Cochran-Armitage test | P=0.087N | | | |
| Fisher exact test | | P=0.121N | P=0.316N | P=0.121N |
| **Skin: Keratoacanthoma** | | | | |
| Overall rate | 5/50 (10%) | 0/50 (0%) | 2/49 (4%) | 2/50 (4%) |
| Adjusted rate | 21.7% | 0.0% | 11.1% | 10.5% |
| Terminal rate | 4/21 (19%) | 0/11 (0%) | 2/18 (11%) | 2/19 (11%) |
| First incidence (days) | 670 | — | 729 (T) | 729 (T) |
| Life table test | P=0.252N | P=0.100N | P=0.273N | P=0.257N |
| Logistic regression test | P=0.273N | P=0.052N | P=0.213N | P=0.255N |
| Cochran-Armitage test | P=0.264N | | | |
| Fisher exact test | | P=0.028N | P=0.226N | P=0.218N |

**TABLE A3**
**Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Dermal Study of Triethanolamine** (continued)

| | 0 mg/kg | 32 mg/kg | 63 mg/kg | 125 mg/kg |
|---|---|---|---|---|
| **Skin (Subcutaneous Tissue): Fibroma, Fibrosarcoma, Neurofibrosarcoma, or Sarcoma** | | | | |
| Overall rate | 3/50 (6%) | 2/50 (4%) | 3/49 (6%) | 1/50 (2%) |
| Adjusted rate | 11.4% | 6.6% | 10.2% | 5.3% |
| Terminal rate | 1/21 (5%) | 0/11 (0%) | 1/18 (6%) | 1/19 (5%) |
| First incidence (days) | 586 | 613 | 431 | 729 (T) |
| Life table test | P=0.271N | P=0.641N | P=0.611 | P=0.353N |
| Logistic regression test | P=0.264N | P=0.508N | P=0.652 | P=0.327N |
| Cochran-Armitage test | P=0.264N | | | |
| Fisher exact test | | P=0.500N | P=0.651 | P=0.309N |
| **Testes: Adenoma** | | | | |
| Overall rate | 31/50 (62%) | 33/50 (66%) | 33/49 (67%) | 25/50 (50%) |
| Adjusted rate | 85.3% | 100.0% | 86.0% | 76.1% |
| Terminal rate | 16/21 (76%) | 11/11 (100%) | 13/18 (72%) | 12/19 (63%) |
| First incidence (days) | 538 | 558 | 353 | 459 |
| Life table test | P=0.157N | P=0.020 | P=0.294 | P=0.351N |
| Logistic regression test | P=0.108N | P=0.203 | P=0.338 | P=0.205N |
| Cochran-Armitage test | P=0.095N | | | |
| Fisher exact test | | P=0.418 | P=0.365 | P=0.157N |
| **Thyroid Gland (C-cell): Adenoma** | | | | |
| Overall rate | 6/50 (12%) | 4/50 (8%) | 7/49 (14%) | 6/50 (12%) |
| Adjusted rate | 25.8% | 17.3% | 23.4% | 20.1% |
| Terminal rate | 5/21 (24%) | 1/11 (9%) | 2/18 (11%) | 2/19 (11%) |
| First incidence (days) | 591 | 573 | 584 | 459 |
| Life table test | P=0.464 | P=0.626 | P=0.431 | P=0.566 |
| Logistic regression test | P=0.450 | P=0.413N | P=0.483 | P=0.607 |
| Cochran-Armitage test | P=0.454 | | | |
| Fisher exact test | | P=0.370N | P=0.484 | P=0.620N |
| **Thyroid Gland (C-cell): Adenoma or Carcinoma** | | | | |
| Overall rate | 6/50 (12%) | 5/50 (10%) | 8/49 (16%) | 6/50 (12%) |
| Adjusted rate | 25.8% | 19.3% | 26.9% | 20.1% |
| Terminal rate | 5/21 (24%) | 1/11 (9%) | 2/18 (11%) | 2/19 (11%) |
| First incidence (days) | 591 | 558 | 584 | 459 |
| Life table test | P=0.493 | P=0.495 | P=0.328 | P=0.566 |
| Logistic regression test | P=0.480 | P=0.527N | P=0.368 | P=0.607 |
| Cochran-Armitage test | P=0.484 | | | |
| Fisher exact test | | P=0.500N | P=0.371 | P=0.620N |
| **All Organs: Mononuclear Cell Leukemia** | | | | |
| Overall rate | 24/50 (48%) | 16/50 (32%) | 21/49 (43%) | 22/50 (44%) |
| Adjusted rate | 72.3% | 57.6% | 64.3% | 77.5% |
| Terminal rate | 13/21 (62%) | 2/11 (18%) | 8/18 (44%) | 13/19 (68%) |
| First incidence (days) | 452 | 558 | 500 | 424 |
| Life table test | P=0.512 | P=0.493N | P=0.493N | P=0.559 |
| Logistic regression test | P=0.466 | P=0.102N | P=0.378N | P=0.506N |
| Cochran-Armitage test | P=0.506 | | | |
| Fisher exact test | | P=0.076N | P=0.378N | P=0.421N |

**TABLE A3**
**Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Dermal Study of Triethanolamine** (continued)

| | 0 mg/kg | 32 mg/kg | 63 mg/kg | 125 mg/kg |
|---|---|---|---|---|
| **All Organs: Benign Neoplasms** | | | | |
| Overall rate | 45/50 (90%) | 49/50 (98%) | 48/49 (98%) | 48/50 (96%) |
| Adjusted rate | 100.0% | 100.0% | 100.0% | 100.0% |
| Terminal rate | 21/21 (100%) | 11/11 (100%) | 18/18 (100%) | 19/19 (100%) |
| First incidence (days) | 535 | 416 | 353 | 404 |
| Life table test | P=0.400 | P=0.011 | P=0.227 | P=0.192 |
| Logistic regression test | P=0.124 | P=0.033 | P=0.032 | P=0.067 |
| Cochran-Armitage test | P=0.195 | | | |
| Fisher exact test | | P=0.102 | P=0.107 | P=0.218 |
| **All Organs: Malignant Neoplasms** | | | | |
| Overall rate | 26/50 (52%) | 24/50 (48%) | 27/49 (55%) | 26/50 (52%) |
| Adjusted rate | 76.8% | 68.9% | 72.4% | 82.5% |
| Terminal rate | 14/21 (67%) | 2/11 (18%) | 9/18 (50%) | 14/19 (74%) |
| First incidence (days) | 452 | 467 | 379 | 424 |
| Life table test | P=0.473 | P=0.218 | P=0.365 | P=0.398 |
| Logistic regression test | P=0.449 | P=0.475N | P=0.458 | P=0.516 |
| Cochran-Armitage test | P=0.466 | | | |
| Fisher exact test | | P=0.421N | P=0.457 | P=0.579N |
| **All Organs: Benign or Malignant Neoplasms** | | | | |
| Overall rate | 48/50 (96%) | 49/50 (98%) | 48/49 (98%) | 50/50 (100%) |
| Adjusted rate | 100.0% | 100.0% | 100.0% | 100.0% |
| Terminal rate | 21/21 (100%) | 11/11 (100%) | 18/18 (100%) | 19/19 (100%) |
| First incidence (days) | 452 | 416 | 353 | 404 |
| Life table test | P=0.418 | P=0.031 | P=0.366 | P=0.238 |
| Logistic regression test | P=0.117 | P=0.442 | P=0.403 | P=0.293 |
| Cochran-Armitage test | P=0.154 | | | |
| Fisher exact test | | P=0.500 | P=0.508 | P=0.247 |

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

**TABLE A4**
**Historical Incidence of Renal Tubule Adenomas in Control Male F344/N Rats[a]**

| Study | Incidence in Controls |
|---|---|
| **Historical Incidence in Dermal Studies (with Acetone Vehicle) at Battelle Columbus Laboratories** | |
| 4-Vinyl-1-cyclohexene diepoxide | 0/50 |
| Triethanolamine | 0/50 |
| **Overall Historical Incidence in Feed Studies** | |
| Total | 9/1,200 (0.8%) |
| Standard deviation | 1.5% |
| Range | 0%-6% |

[a] Data as of 17 June 1994

**Table A5**
**Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Dermal Study of Triethanolamine[a]**

| | 0 mg/kg | 32 mg/kg | 63 mg/kg | 125 mg/kg |
|---|---|---|---|---|
| **Disposition Summary** | | | | |
| Animals initially in study | 60 | 60 | 60 | 60 |
| ***15-Month interim evaluation*** | 10 | 10 | 10 | 10 |
| Early deaths | | | | |
| Accidental deaths | 2 | | | |
| Moribund | 18 | 27 | 25 | 23 |
| Natural deaths | 9 | 12 | 6 | 8 |
| Survivors | | | | |
| Terminal sacrifice | 21 | 11 | 18 | 19 |
| Missexed | | | 1 | |
| Animals examined microscopically | 60 | 60 | 59 | 60 |
| ***15-Month Interim Evaluation*** | | | | |
| **Alimentary System** | | | | |
| Intestine large, colon | (10) | (10) | (10) | (10) |
| Parasite metazoan | | 1 (10%) | | |
| Intestine large, rectum | (10) | (10) | (10) | (10) |
| Parasite metazoan | | 2 (20%) | 3 (30%) | |
| Liver | (10) | (10) | (10) | (10) |
| Basophilic focus | | | | 1 (10%) |
| Clear cell focus | | 1 (10%) | | |
| Eosinophilic focus | | | 1 (10%) | |
| Hepatodiaphragmatic nodule | 1 (10%) | | 2 (20%) | 1 (10%) |
| Inflammation, chronic | 5 (50%) | 7 (70%) | 9 (90%) | 8 (80%) |
| Bile duct, hyperplasia | 8 (80%) | 10 (100%) | 9 (90%) | 5 (50%) |
| Hepatocyte, degeneration, cystic | | 1 (10%) | | |
| Mesentery | | (1) | (1) | |
| Fat, inflammation, necrotizing | | 1 (100%) | 1 (100%) | |
| Pancreas | (10) | (10) | (10) | (10) |
| Inflammation, subacute | | | | 1 (10%) |
| Acinus, atrophy | 2 (20%) | 2 (20%) | 5 (50%) | 3 (30%) |
| Artery, inflammation, chronic active | | 1 (10%) | | 1 (10%) |
| Stomach, glandular | (10) | (10) | (10) | (10) |
| Hyperplasia, glandular | | | 1 (10%) | |
| **Cardiovascular System** | | | | |
| Heart | (10) | (10) | (10) | (10) |
| Cardiomyopathy, chronic | 5 (50%) | 10 (100%) | 7 (70%) | 9 (90%) |
| **Endocrine System** | | | | |
| Adrenal cortex | (10) | (10) | (10) | (10) |
| Hypertrophy | 1 (10%) | | 1 (10%) | |
| Adrenal medulla | (10) | (10) | (10) | (10) |
| Hyperplasia | | 1 (10%) | | |
| Parathyroid gland | (6) | (10) | (9) | (9) |
| Hyperplasia | 1 (17%) | | | |
| Pituitary gland | (10) | (10) | (10) | (10) |
| Pars distalis, cyst | | | 1 (10%) | 1 (10%) |
| Pars distalis, hyperplasia | 3 (30%) | 3 (30%) | 2 (20%) | 8 (80%) |

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

**TABLE A5**
**Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Dermal Study of Triethanolamine**
(continued)

| | 0 mg/kg | 32 mg/kg | 63 mg/kg | 125 mg/kg |
|---|---|---|---|---|
| ***15-Month Interim Evaluation*** (continued) | | | | |
| **Endocrine System** (continued) | | | | |
| Thyroid gland | (10) | (10) | (10) | (10) |
| Cyst | | | | 1 (10%) |
| C-cell, hyperplasia | 1 (10%) | 1 (10%) | 1 (10%) | 2 (20%) |
| **Genital System** | | | | |
| Epididymis | (10) | (10) | (10) | (10) |
| Mineralization | 1 (10%) | | | |
| Preputial gland | (10) | (10) | (10) | (10) |
| Hyperplasia | | 2 (20%) | | |
| Inflammation, chronic active | 10 (100%) | 9 (90%) | 10 (100%) | 10 (100%) |
| Duct, dilatation | | | 1 (10%) | |
| Prostate | (10) | (10) | (10) | (10) |
| Inflammation, chronic active | 7 (70%) | 8 (80%) | 8 (80%) | 9 (90%) |
| Testes | (10) | (10) | (10) | (10) |
| Interstitial cell, hyperplasia | 6 (60%) | 5 (50%) | 7 (70%) | 9 (90%) |
| Seminiferous tubule, atrophy | | | | 1 (10%) |
| **Integumentary System** | | | | |
| Mammary gland | (10) | (10) | (9) | (9) |
| Cyst | 1 (10%) | | | |
| Hyperplasia, cystic | 2 (20%) | 2 (20%) | 1 (11%) | |
| Skin | (10) | (10) | (10) | (10) |
| Site of application-no mass, acanthosis | | | | 2 (20%) |
| **Musculoskeletal System** | | | | |
| Bone | (10) | (10) | (10) | (10) |
| Femur, cyst | | | | 1 (10%) |
| **Nervous System** | | | | |
| Brain | (10) | (10) | (10) | (10) |
| Compression | | 1 (10%) | | |
| Hemorrhage | 1 (10%) | | | |
| Hydrocephalus | | 1 (10%) | | |
| **Respiratory System** | | | | |
| Lung | (10) | (10) | (10) | (10) |
| Inflammation, chronic active | 1 (10%) | 1 (10%) | 2 (20%) | 3 (30%) |
| Alveolus, infiltration cellular, mononuclear cell | | 3 (30%) | 2 (20%) | 4 (40%) |
| Nose | (10) | (10) | (10) | (10) |
| Inflammation, chronic | 1 (10%) | | | |
| Nasolacrimal duct, inflammation, suppurative | | | 1 (10%) | |

**Table A5**
**Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Dermal Study of Triethanolamine**
(continued)

| | 0 mg/kg | 32 mg/kg | 63 mg/kg | 125 mg/kg |
|---|---|---|---|---|
| ***15-Month Interim Evaluation*** (continued) | | | | |
| **Special Senses System** | | | | |
| Eye | (1) | | | |
| Lens, cataract | 1 (100%) | | | |
| Retina, atrophy | 1 (100%) | | | |
| **Urinary System** | | | | |
| Kidney | (10) | (10) | (10) | (10) |
| Necrosis, coagulative | | 1 (10%) | | |
| Nephropathy, chronic | 10 (100%) | 9 (90%) | 10 (100%) | 10 (100%) |
| ***Systems Examined with No Lesions Observed*** | | | | |
| **General Body System** | | | | |
| **Hematopoietic System** | | | | |
| ***2-Year Study*** | | | | |
| **Alimentary System** | | | | |
| Intestine large, colon | (50) | (50) | (49) | (50) |
| Inflammation, necrotizing | 1 (2%) | | | |
| Parasite metazoan | 4 (8%) | 4 (8%) | 2 (4%) | 3 (6%) |
| Intestine large, rectum | (50) | (50) | (49) | (50) |
| Parasite metazoan | 6 (12%) | 4 (8%) | 8 (16%) | 8 (16%) |
| Intestine large, cecum | (50) | (50) | (49) | (50) |
| Inflammation, necrotizing | | 1 (2%) | | |
| Inflammation, suppurative | 2 (4%) | | | |
| Parasite metazoan | | 1 (2%) | | |
| Intestine small, duodenum | (50) | (50) | (49) | (50) |
| Inflammation, necrotizing | 2 (4%) | | | |
| Intestine small, ileum | (50) | (50) | (49) | (50) |
| Parasite metazoan | | 1 (2%) | | |
| Liver | (50) | (50) | (49) | (50) |
| Angiectasis | 1 (2%) | | 2 (4%) | |
| Basophilic focus | 7 (14%) | 7 (14%) | 4 (8%) | 9 (18%) |
| Clear cell focus | 5 (10%) | 3 (6%) | 4 (8%) | 1 (2%) |
| Congestion | | | | 1 (2%) |
| Eosinophilic focus | 2 (4%) | 4 (8%) | 2 (4%) | 2 (4%) |
| Hepatodiaphragmatic nodule | 3 (6%) | 5 (10%) | 5 (10%) | 2 (4%) |
| Hyperplasia, nodular | | 1 (2%) | | |
| Inflammation, chronic | 7 (14%) | 17 (34%) | 10 (20%) | 7 (14%) |
| Leukocytosis | | | 1 (2%) | |
| Mixed cell focus | 1 (2%) | 3 (6%) | | 2 (4%) |
| Necrosis, coagulative | 1 (2%) | 2 (4%) | 2 (4%) | 2 (4%) |
| Bile duct, hyperplasia | 48 (96%) | 39 (78%) | 44 (90%) | 47 (94%) |
| Hepatocyte, degeneration, cystic | 8 (16%) | 5 (10%) | 6 (12%) | 8 (16%) |
| Hepatocyte, vacuolization cytoplasmic | 6 (12%) | 7 (14%) | 5 (10%) | 6 (12%) |
| Mesentery | (9) | (9) | (10) | (5) |
| Fat, inflammation, necrotizing | 6 (67%) | 6 (67%) | 5 (50%) | 4 (80%) |

**Table A5**
**Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Dermal Study of Triethanolamine**
(continued)

| | 0 mg/kg | 32 mg/kg | 63 mg/kg | 125 mg/kg |
|---|---|---|---|---|
| ***2-Year Study*** (continued) | | | | |
| **Alimentary System** (continued) | | | | |
| Pancreas | (50) | (50) | (49) | (50) |
| Acinus, atrophy | 21 (42%) | 19 (38%) | 14 (29%) | 14 (28%) |
| Acinus, hyperplasia, nodular | | 1 (2%) | | 3 (6%) |
| Artery, inflammation, chronic active | 1 (2%) | | | 1 (2%) |
| Artery, thrombosis | 1 (2%) | | | |
| Perivascular, inflammation, chronic active | | 1 (2%) | | |
| Stomach, forestomach | (50) | (50) | (49) | (50) |
| Foreign body, multiple | 1 (2%) | | | |
| Granuloma | 1 (2%) | | | |
| Inflammation, chronic active | | 1 (2%) | 1 (2%) | |
| Inflammation, necrotizing | 4 (8%) | 3 (6%) | 8 (16%) | 6 (12%) |
| Mineralization | | 1 (2%) | | |
| Epithelium, hyperplasia | 6 (12%) | 6 (12%) | 9 (18%) | 5 (10%) |
| Stomach, glandular | (50) | (50) | (49) | (50) |
| Cyst epithelial inclusion | 1 (2%) | | | |
| Erosion | 5 (10%) | 3 (6%) | 1 (2%) | |
| Inflammation, necrotizing | 2 (4%) | 2 (4%) | 3 (6%) | |
| Mineralization | | 1 (2%) | | |
| Necrosis, coagulative | | 1 (2%) | 1 (2%) | |
| Tongue | (1) | | | |
| Cyst | 1 (100%) | | | |
| Tooth | | (1) | | |
| Inflammation, chronic active | | 1 (100%) | | |
| **Cardiovascular System** | | | | |
| Blood vessel | (50) | (50) | (49) | (49) |
| Mineralization | 1 (2%) | 1 (2%) | | |
| Mesenteric artery, polyarteritis, chronic | 1 (2%) | | | |
| Mesenteric artery, thrombosis | | | | 1 (2%) |
| Heart | (50) | (50) | (49) | (50) |
| Cardiomyopathy, chronic | 46 (92%) | 42 (84%) | 45 (92%) | 46 (92%) |
| Inflammation, chronic active | 1 (2%) | | | |
| Inflammation, suppurative | | 1 (2%) | | |
| Mineralization | | 1 (2%) | | |
| Atrium, thrombosis | 2 (4%) | 1 (2%) | 1 (2%) | 1 (2%) |
| Endocardium, atrium, proliferation | | | 1 (2%) | |
| Valve, bacterium | | 1 (2%) | | |
| Valve, inflammation, chronic active | | 2 (4%) | | |
| **Endocrine System** | | | | |
| Adrenal cortex | (50) | (50) | (49) | (50) |
| Accessory adrenal cortical nodule | | 1 (2%) | | |
| Degeneration, fatty | 21 (42%) | 17 (34%) | 20 (41%) | 22 (44%) |
| Hyperplasia | 15 (30%) | 17 (34%) | 19 (39%) | 24 (48%) |
| Hypertrophy | 6 (12%) | 5 (10%) | 5 (10%) | 5 (10%) |
| Karyomegaly | | | | 1 (2%) |
| Necrosis, coagulative | | | | 1 (2%) |
| Adrenal medulla | (50) | (50) | (49) | (50) |
| Hyperplasia | 28 (56%) | 21 (42%) | 22 (45%) | 21 (42%) |
| Islets, pancreatic | (50) | (50) | (49) | (50) |
| Hyperplasia | 2 (4%) | 3 (6%) | | 1 (2%) |

**Table A5**
**Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Dermal Study of Triethanolamine**
(continued)

| | 0 mg/kg | 32 mg/kg | 63 mg/kg | 125 mg/kg |
|---|---|---|---|---|
| ***2-Year Study*** (continued) | | | | |
| **Endocrine System** (continued) | | | | |
| Parathyroid gland | (49) | (47) | (44) | (47) |
| Cyst | | 1 (2%) | 1 (2%) | 1 (2%) |
| Hyperplasia | 2 (4%) | 3 (6%) | 3 (7%) | 1 (2%) |
| Pituitary gland | (50) | (50) | (48) | (50) |
| Craniopharyngeal duct, pars distalis, cyst | | | 1 (2%) | |
| Pars distalis, angiectasis | 30 (60%) | 36 (72%) | 29 (60%) | 39 (78%) |
| Pars distalis, cyst | 4 (8%) | 2 (4%) | 2 (4%) | 3 (6%) |
| Pars distalis, hyperplasia | 6 (12%) | 13 (26%) | 13 (27%) | 10 (20%) |
| Pars distalis, infarct | 1 (2%) | | 1 (2%) | 1 (2%) |
| Pars distalis, pigmentation, hemosiderin | 23 (46%) | 24 (48%) | 32 (67%) | 35 (70%) |
| Pars intermedia, hyperplasia | | | 1 (2%) | |
| Thyroid gland | (50) | (50) | (49) | (50) |
| Hyperplasia | | | 1 (2%) | |
| C-cell, hyperplasia | 7 (14%) | 6 (12%) | 7 (14%) | 7 (14%) |
| Follicle, cyst | 1 (2%) | 1 (2%) | | 1 (2%) |
| Follicular cell, hyperplasia | 1 (2%) | | | |
| **General Body System** | | | | |
| Tissue NOS | (1) | | | |
| Ectasia | 1 (100%) | | | |
| **Genital System** | | | | |
| Epididymis | (50) | (50) | (49) | (50) |
| Atrophy | 26 (52%) | 25 (50%) | 27 (55%) | 20 (40%) |
| Fibrosis | | | | 1 (2%) |
| Granuloma sperm | | | 1 (2%) | |
| Inflammation, chronic active | | 1 (2%) | | |
| Mineralization | | 1 (2%) | | |
| Fat, necrosis | | | 1 (2%) | |
| Preputial gland | (50) | (50) | (48) | (50) |
| Hyperplasia | | 1 (2%) | | |
| Inflammation, chronic active | 44 (88%) | 44 (88%) | 41 (85%) | 48 (96%) |
| Duct, dilatation | 5 (10%) | 4 (8%) | 4 (8%) | 2 (4%) |
| Prostate | (50) | (49) | (49) | (50) |
| Hyperplasia, cystic | | | | 1 (2%) |
| Inflammation, chronic active | 45 (90%) | 44 (90%) | 42 (86%) | 47 (94%) |
| Inflammation, hemorrhagic | 1 (2%) | | 1 (2%) | |
| Epithelium, hyperplasia | 1 (2%) | | | |
| Seminal vesicle | (50) | (50) | (49) | (50) |
| Atrophy | 24 (48%) | 22 (44%) | 23 (47%) | 13 (26%) |
| Mineralization | | 1 (2%) | | |
| Testes | (50) | (50) | (49) | (50) |
| Polyarteritis | 9 (18%) | 4 (8%) | 9 (18%) | 6 (12%) |
| Interstitial cell, hyperplasia | 15 (30%) | 17 (34%) | 12 (24%) | 16 (32%) |
| Seminiferous tubule, atrophy | 10 (20%) | 8 (16%) | 14 (29%) | 8 (16%) |

**TABLE A5**
**Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Dermal Study of Triethanolamine**
(continued)

| | 0 mg/kg | 32 mg/kg | 63 mg/kg | 125 mg/kg |
|---|---|---|---|---|
| ***2-Year Study*** (continued) | | | | |
| **Hematopoietic System** | | | | |
| Bone marrow | (50) | (50) | (49) | (50) |
| Hyperplasia | 1 (2%) | 3 (6%) | 5 (10%) | 4 (8%) |
| Myelofibrosis | | 1 (2%) | 1 (2%) | |
| Lymph node | (14) | (10) | (16) | (9) |
| Inguinal, sinus, ectasia | | 1 (10%) | | |
| Mediastinal, sinus, hemorrhage | | | 1 (6%) | |
| Lymph node, mandibular | (50) | (50) | (49) | (50) |
| Hyperplasia, lymphoid | 1 (2%) | | | |
| Necrosis, coagulative | | 1 (2%) | | |
| Lymph node, mesenteric | (50) | (50) | (49) | (49) |
| Sinus, ectasia | 1 (2%) | | | 1 (2%) |
| Spleen | (50) | (50) | (49) | (50) |
| Congestion | 1 (2%) | | 1 (2%) | |
| Developmental malformation | | | 1 (2%) | |
| Fibrosis | 10 (20%) | 3 (6%) | 5 (10%) | 7 (14%) |
| Hematopoietic cell proliferation | | 1 (2%) | 2 (4%) | 1 (2%) |
| Necrosis, coagulative | 3 (6%) | 1 (2%) | 2 (4%) | 2 (4%) |
| Thrombosis | | | 1 (2%) | |
| Red pulp, atrophy | | 1 (2%) | | |
| Thymus | (46) | (49) | (48) | (49) |
| Cyst | 1 (2%) | | | |
| Developmental malformation | | | | 1 (2%) |
| **Integumentary System** | | | | |
| Mammary gland | (48) | (43) | (45) | (45) |
| Hyperplasia, cystic | 44 (92%) | 35 (81%) | 36 (80%) | 42 (93%) |
| Inflammation, chronic | 1 (2%) | | | |
| Inflammation, chronic active | 2 (4%) | 2 (5%) | | 1 (2%) |
| Inflammation, proliferative | 1 (2%) | | | 1 (2%) |
| Skin | (50) | (50) | (49) | (50) |
| Dermis, site of application-no mass, fibrosis | | 1 (2%) | 1 (2%) | 1 (2%) |
| Dermis, site of application-mass, fibrosis | 1 (2%) | | | |
| Epidermis, site of application-no mass, erosion | | | | 1 (2%) |
| Foot, acanthosis | 1 (2%) | | | |
| Foot, hyperkeratosis | 1 (2%) | | | |
| Foot, inflammation, chronic active | 1 (2%) | | | |
| Foot, ulcer | | 1 (2%) | | |
| Inguinal, acanthosis | 2 (4%) | 1 (2%) | 1 (2%) | |
| Inguinal, inflammation, chronic active | | 2 (4%) | 1 (2%) | |
| Inguinal, ulcer | | 1 (2%) | | |
| Neck, ventral, inflammation, chronic active | | | | 1 (2%) |
| Prepuce, inflammation, suppurative | | | | 1 (2%) |
| Site of application-no mass, acanthosis | 1 (2%) | 1 (2%) | 1 (2%) | 9 (18%) |
| Site of application-no mass, inflammation, chronic active | | 2 (4%) | | 8 (16%) |
| Site of application-no mass, ulcer | | | | 4 (8%) |
| Site of application-no mass, ulcer, multiple | | | | 1 (2%) |
| Tail, acanthosis | | | | 1 (2%) |
| Tail, hyperkeratosis | | | | 1 (2%) |
| Tail, inflammation, chronic active | | 1 (2%) | | 1 (2%) |
| Tail, ulcer | | 1 (2%) | | |

**Table A5**
**Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Dermal Study of Triethanolamine** (continued)

| | 0 mg/kg | 32 mg/kg | 63 mg/kg | 125 mg/kg |
|---|---|---|---|---|
| ***2-Year Study*** (continued) | | | | |
| **Musculoskeletal System** | | | | |
| Bone | (50) | (50) | (49) | (50) |
| Fibrous osteodystrophy | | 1 (2%) | | 1 (2%) |
| Maxilla, abscess | 1 (2%) | | 1 (2%) | 1 (2%) |
| Maxilla, fibrosis | 2 (4%) | | 1 (2%) | 1 (2%) |
| **Nervous System** | | | | |
| Brain | (50) | (50) | (48) | (50) |
| Compression | 15 (30%) | 18 (36%) | 10 (21%) | 21 (42%) |
| Gliosis | 1 (2%) | | | |
| Hemorrhage | | 4 (8%) | 1 (2%) | |
| Hydrocephalus | 14 (28%) | 18 (36%) | 9 (19%) | 18 (36%) |
| Peripheral nerve | (2) | | (2) | |
| Sciatic, myelin, degeneration | | | 1 (50%) | |
| Spinal cord | (2) | | (2) | |
| Hemorrhage | | | 1 (50%) | |
| White matter, degeneration | | | 1 (50%) | |
| **Respiratory System** | | | | |
| Lung | (50) | (50) | (49) | (50) |
| Inflammation, chronic active | 7 (14%) | 4 (8%) | 4 (8%) | 2 (4%) |
| Inflammation, suppurative | 1 (2%) | | | |
| Metaplasia, osseous | 1 (2%) | | | |
| Mineralization | | 1 (2%) | | |
| Alveolar epithelium, hyperplasia | | 2 (4%) | 3 (6%) | 1 (2%) |
| Alveolus, infiltration cellular, mononuclear cell | 17 (34%) | 20 (40%) | 18 (37%) | 9 (18%) |
| Fat, mediastinum, atrophy | | 1 (2%) | | |
| Mediastinum, fibrosis | | | | 1 (2%) |
| Perivascular, edema | 1 (2%) | | | |
| Nose | (50) | (50) | (49) | (50) |
| Fungus | 1 (2%) | | | 1 (2%) |
| Inflammation, chronic active | 5 (10%) | 4 (8%) | 3 (6%) | 9 (18%) |
| Nasolacrimal duct, inflammation, suppurative | 12 (24%) | 11 (22%) | 7 (14%) | 8 (16%) |
| Respiratory epithelium, hyperplasia | 2 (4%) | | | 1 (2%) |
| **Special Senses System** | | | | |
| Ear | (1) | (2) | (2) | (1) |
| Cyst epithelial inclusion | | 1 (50%) | | |
| Eye | (2) | | (3) | (2) |
| Lens, cataract | | | 3 (100%) | 2 (100%) |
| Retina, atrophy | | | 3 (100%) | 2 (100%) |
| Zymbal's gland | | (2) | (2) | (1) |
| Abscess | | | 1 (50%) | |

**Table A5**
**Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Dermal Study of Triethanolamine**
(continued)

| | 0 mg/kg | 32 mg/kg | 63 mg/kg | 125 mg/kg |
|---|---|---|---|---|
| ***2-Year Study*** (continued) | | | | |
| **Urinary System** | | | | |
| Kidney | (50) | (50) | (49) | (50) |
| Hydronephrosis | 1 (2%) | 1 (2%) | | |
| Hyperplasia | 1 (2%) | | 1 (2%) | |
| Inflammation, suppurative | | 1 (2%) | | |
| Mineralization | | 1 (2%) | | |
| Necrosis, coagulative | 1 (2%) | | | |
| Nephropathy, chronic | 48 (96%) | 49 (98%) | 49 (100%) | 50 (100%) |
| Pigmentation, hemosiderin | | | 1 (2%) | |
| Cortex, cyst | 2 (4%) | | 1 (2%) | |
| Renal tubule, hyperplasia | | | | 1 (2%) |
| Urinary bladder | (50) | (50) | (48) | (49) |
| Dilatation | 1 (2%) | | | |
| Inflammation, hemorrhagic | 2 (4%) | | | 1 (2%) |

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


TABLE B1 Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Dermal Study of Triethanolamine . . . . . . . . . . . . . . . . . . . . . . . . . . . . . 118

TABLE B2 Individual Animal Tumor Pathology of Female Rats in the 2-Year Dermal Study of Triethanolamine . . . . . . . . . . . . . . . . . . . . . . . . . . . . . 122

TABLE B3 Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Dermal Study of Triethanolamine . . . . . . . . . . . . . . . . . . . . . . . . . . . . . 138

TABLE B4 Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Dermal Study of Triethanolamine . . . . . . . . . . . . . . . . . . . . . . . . . . . . . 141

**Table B1**
**Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Dermal Study of Triethanolamine**[a]

| | 0 mg/kg | 63 mg/kg | 125 mg/kg | 250 mg/kg |
|---|---|---|---|---|
| **Disposition Summary** | | | | |
| Animals initially in study | 60 | 60 | 60 | 60 |
| ***15-Month interim evaluation*** | 10 | 10 | 10 | 10 |
| Early deaths | | | | |
| Moribund | 11 | 4 | 12 | 17 |
| Natural deaths | 14 | 17 | 13 | 15 |
| Survivors | | | | |
| Died last week of study | | | | 1 |
| Terminal sacrifice | 25 | 29 | 25 | 17 |
| Animals examined microscopically | 60 | 60 | 60 | 60 |
| ***15-Month Interim Evaluation*** | | | | |
| **Endocrine System** | | | | |
| Adrenal medulla | (10) | (10) | (10) | (10) |
| Pheochromocytoma benign | | | | 1 (10%) |
| Islets, pancreatic | (10) | (10) | (10) | (10) |
| Adenoma | | | | 1 (10%) |
| Pituitary gland | (10) | (10) | (10) | (10) |
| Pars distalis, adenoma | | 1 (10%) | 2 (20%) | 4 (40%) |
| Thyroid gland | (10) | (10) | (10) | (10) |
| Follicular cell, adenoma | | | 1 (10%) | 1 (10%) |
| **Genital System** | | | | |
| Uterus | (10) | (10) | (10) | (10) |
| Polyp stromal | 2 (20%) | 1 (10%) | | 2 (20%) |
| **Special Senses System** | | | | |
| Zymbal's gland | (1) | | | |
| Carcinoma | 1 (100%) | | | |

***Systems Examined with No Neoplasms Observed***
**Alimentary System**
**Cardiovascular System**
**General Body System**
**Hematopoietic System**
**Integumentary System**
**Musculoskeletal System**
**Nervous System**
**Respiratory System**
**Urinary System**

**TABLE B1**
**Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Dermal Study of Triethanolamine** (continued)

| | 0 mg/kg | 63 mg/kg | 125 mg/kg | 250 mg/kg |
|---|---|---|---|---|
| ***2-Year Study*** | | | | |
| **Alimentary System** | | | | |
| Esophagus | (50) | (50) | (50) | (50) |
| Periesophageal tissue, lipoma | | | 1 (2%) | |
| Liver | (50) | (50) | (50) | (50) |
| Hepatocellular adenoma | | | | 1 (2%) |
| Mesentery | (3) | (2) | (2) | (2) |
| Rhabdomyosarcoma, metastatic, skeletal muscle | | | | 1 (50%) |
| Pancreas | (50) | (50) | (50) | (50) |
| Stomach, forestomach | (50) | (50) | (50) | (50) |
| Squamous cell papilloma | | 1 (2%) | | |
| **Cardiovascular System** | | | | |
| Heart | (50) | (50) | (50) | (50) |
| Schwannoma benign | | 1 (2%) | | |
| Schwannoma malignant | | 1 (2%) | | |
| **Endocrine System** | | | | |
| Adrenal cortex | (50) | (50) | (50) | (50) |
| Adenoma | | 1 (2%) | 1 (2%) | |
| Adrenal medulla | (50) | (50) | (50) | (49) |
| Pheochromocytoma benign | | 1 (2%) | | |
| Bilateral, pheochromocytoma benign | | 1 (2%) | | |
| Islets, pancreatic | (50) | (50) | (50) | (50) |
| Adenoma | | 2 (4%) | | 1 (2%) |
| Carcinoma | | | 1 (2%) | |
| Parathyroid gland | (41) | (48) | (47) | (43) |
| Adenoma | 1 (2%) | | | |
| Pituitary gland | (50) | (50) | (50) | (50) |
| Pars distalis, adenoma | 32 (64%) | 25 (50%) | 29 (58%) | 23 (46%) |
| Pars distalis, adenoma, multiple | 1 (2%) | 1 (2%) | 1 (2%) | |
| Thyroid gland | (50) | (50) | (50) | (49) |
| C-cell, adenoma | 1 (2%) | 2 (4%) | 2 (4%) | 5 (10%) |
| C-cell, carcinoma | | | | 1 (2%) |
| Follicular cell, adenoma | 2 (4%) | 1 (2%) | 1 (2%) | 1 (2%) |
| Follicular cell, carcinoma | 1 (2%) | 1 (2%) | | |
| **General Body System** | | | | |
| None | | | | |
| **Genital System** | | | | |
| Clitoral gland | (48) | (49) | (50) | (50) |
| Adenoma | 2 (4%) | 6 (12%) | 2 (4%) | 2 (4%) |
| Carcinoma | 1 (2%) | | | |
| Bilateral, carcinoma | 1 (2%) | | | |
| Ovary | (50) | (50) | (50) | (50) |
| Granulosa cell tumor malignant | 1 (2%) | | | |
| Uterus | (50) | (50) | (50) | (50) |
| Leiomyoma | 1 (2%) | | | |
| Polyp stromal | 2 (4%) | 1 (2%) | 8 (16%) | 5 (10%) |

**Table B1**
**Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Dermal Study of Triethanolamine** (continued)

| | 0 mg/kg | 63 mg/kg | 125 mg/kg | 250 mg/kg |
|---|---|---|---|---|
| ***2-Year Study*** (continued) | | | | |
| **Hematopoietic System** | | | | |
| Bone marrow | (50) | (50) | (50) | (50) |
| Lymph node | (6) | (5) | (6) | (3) |
| Mediastinal, rhabdomyosarcoma, metastatic, skeletal muscle | | | | 1 (33%) |
| Mediastinal, schwannoma malignant, metastatic, heart | | 1 (20%) | | |
| Lymph node, mandibular | (49) | (50) | (50) | (50) |
| Lymph node, mesenteric | (50) | (50) | (49) | (50) |
| Spleen | (50) | (50) | (50) | (50) |
| Thymus | (49) | (47) | (47) | (48) |
| Rhabdomyosarcoma, metastatic, skeletal muscle | | | | 1 (2%) |
| Thymoma benign | | | 1 (2%) | |
| Thymoma malignant | | | | 1 (2%) |
| Mediastinum, schwannoma malignant, metastatic, heart | | 1 (2%) | | |
| **Integumentary System** | | | | |
| Mammary gland | (50) | (50) | (50) | (50) |
| Adenoma | | 1 (2%) | 1 (2%) | |
| Carcinoma | | 1 (2%) | | |
| Fibroadenoma | 12 (24%) | 13 (26%) | 7 (14%) | 6 (12%) |
| Fibroadenoma, multiple | 1 (2%) | | 3 (6%) | 2 (4%) |
| Skin | (50) | (50) | (50) | (50) |
| Face, squamous cell papilloma | 1 (2%) | | | |
| Inguinal, keratoacanthoma | | 1 (2%) | | |
| Subcutaneous tissue, neurofibrosarcoma | 1 (2%) | | | |
| **Musculoskeletal System** | | | | |
| Skeletal muscle | (1) | | | (2) |
| Hemangiosarcoma | 1 (100%) | | | |
| Rhabdomyosarcoma | | | | 1 (50%) |
| **Nervous System** | | | | |
| Brain | (50) | (50) | (50) | (50) |
| Medulloblastoma NOS | | | | 1 (2%) |
| **Respiratory System** | | | | |
| Lung | (50) | (50) | (50) | (50) |
| Mediastinum, rhabdomyosarcoma, metastatic, skeletal muscle | | | | 1 (2%) |
| Nose | (50) | (50) | (50) | (50) |

**TABLE B1**
**Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Dermal Study of Triethanolamine** (continued)

| | 0 mg/kg | 63 mg/kg | 125 mg/kg | 250 mg/kg |
|---|---|---|---|---|
| ***2-Year Study*** (continued) | | | | |
| **Special Senses System** | | | | |
| Ear | | (1) | (2) | (1) |
| Middle ear, carcinoma, metastatic, Zymbal's gland | | | | 1 (100%) |
| Pinna, fibrosarcoma | | | 1 (50%) | |
| Zymbal's gland | | (1) | | (1) |
| Carcinoma | | 1 (100%) | | 1 (100%) |
| **Urinary System** | | | | |
| Kidney | (50) | (50) | (50) | (50) |
| Renal tubule, adenoma | 1 (2%) | 1 (2%) | | |
| Urinary bladder | (49) | (50) | (50) | (50) |
| Leiomyoma | | | 1 (2%) | |
| Transitional epithelium, papilloma | | | 1 (2%) | |
| **Systemic Lesions** | | | | |
| Multiple organs[b] | (50) | (50) | (50) | (50) |
| Leukemia mononuclear | 13 (26%) | 14 (28%) | 13 (26%) | 16 (32%) |
| **Neoplasm Summary** | | | | |
| Total animals with primary neoplasms[c] | | | | |
| 15-Month interim evaluation | 3 | 2 | 3 | 7 |
| 2-Year study | 47 | 42 | 44 | 37 |
| Total primary neoplasms | | | | |
| 15-Month interim evaluation | 3 | 2 | 3 | 9 |
| 2-Year study | 76 | 77 | 74 | 67 |
| Total animals with benign neoplasms | | | | |
| 15-Month interim evaluation | 2 | 2 | 3 | 7 |
| 2-Year study | 43 | 37 | 39 | 30 |
| Total benign neoplasms | | | | |
| 15-Month interim evaluation | 2 | 2 | 3 | 9 |
| 2-Year study | 57 | 59 | 59 | 46 |
| Total animals with malignant neoplasms | | | | |
| 15-Month interim evaluation | 1 | | | |
| 2-Year study | 16 | 17 | 13 | 18 |
| Total malignant neoplasms | | | | |
| 15-Month interim evaluation | 1 | | | |
| 2-Year study | 19 | 18 | 15 | 20 |
| Total animals with metastatic neoplasms | | | | |
| 2-Year study | | 1 | | 2 |
| Total metastatic neoplasms | | | | |
| 2-Year study | | 2 | | 5 |
| Total animals with uncertain neoplasms-benign or malignant | | | | |
| 2-Year study | | | | 1 |
| Total uncertain neoplasms | | | | |
| 2-Year study | | | | 1 |

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

**Table B2**
**Individual Animal Tumor Pathology of Female Rats in the 2-Year Dermal Study of Triethanolamine: 0 mg/kg**

| Number of Days on Study | 338 | 390 | 466 | 542 | 555 | 567 | 582 | 593 | 634 | 636 | 638 | 639 | 663 | 671 | 674 | 674 | 691 | 690 | 710 | 710 | 713 | 718 | 719 | 719 | 728 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 258 | 285 | 251 | 256 | 300 | 246 | 280 | 276 | 290 | 242 | 294 | 284 | 241 | 293 | 253 | 260 | 278 | 247 | 265 | 295 | 286 | 272 | 264 | 297 | 279 |
| **Alimentary System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Esophagus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine large, colon | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine large, rectum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine large, cecum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine small, duodenum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine small, jejunum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine small, ileum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Liver | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Mesentery | | | | | | | | | | + | | | | | | | | | | + | | | | | |
| Pancreas | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Salivary glands | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Stomach, forestomach | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Stomach, glandular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Cardiovascular System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Blood vessel | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Heart | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Endocrine System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Adrenal cortex | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Adrenal medulla | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Islets, pancreatic | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Parathyroid gland | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | M | M | + | + | + |
| Adenoma | | | | | | | | | | | | | | | X | | | | | | | | | | |
| Pituitary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Pars distalis, adenoma | | X | X | X | X | X | X | X | X | | | X | | X | | X | | | | X | X | | X | | X |
| Pars distalis, adenoma, multiple | | | | | | | | | | | | | | | | | | | | | | | | | |
| Thyroid gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| C-cell, adenoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Follicular cell, adenoma | | | | | | | X | | | | | | | | | | | | | | | | | | |
| Follicular cell, carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| **General Body System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| None | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Genital System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Clitoral gland | + | + | + | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + | M | + | + | + | + | + | + |
| Adenoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Carcinoma | | | | | | | | X | | | | | | | | | | | | | | | | | |
| Bilateral, carcinoma | | | | | | | | | | | | | | | | | | | | | | | | X | |
| Ovary | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Granulosa cell tumor malignant | | | | | | | | | | | | | | | | | | | | | | | | | |
| Uterus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Leiomyoma | | | | | X | | | | | | | | | | | | | | | | | | | | |
| Polyp stromal | | | | | X | | | | | | | | | | | | | | | | | | | | |

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

**TABLE B2**
**Individual Animal Tumor Pathology of Female Rats in the 2-Year Dermal Study of Triethanolamine: 0 mg/kg**
(continued)

| Number of Days on Study | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 730 | 730 | 730 | 730 | 730 | 730 | 730 | 730 | 730 | 731 | 731 | 731 | 731 | 731 | 731 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 243 | 249 | 254 | 261 | 262 | 263 | 270 | 282 | 296 | 299 | 245 | 248 | 257 | 267 | 271 | 274 | 281 | 291 | 298 | 244 | 252 | 268 | 287 | 288 | 289 | Total Tissues/ Tumors |
| **Alimentary System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Esophagus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Intestine large, colon | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Intestine large, rectum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Intestine large, cecum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Intestine small, duodenum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Intestine small, jejunum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Intestine small, ileum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Liver | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Mesentery | | | | | | | | | | | | | | | | | | | | | | | | | + | 3 |
| Pancreas | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Salivary glands | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Stomach, forestomach | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Stomach, glandular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Cardiovascular System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Blood vessel | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Heart | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Endocrine System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Adrenal cortex | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Adrenal medulla | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Islets, pancreatic | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Parathyroid gland | + | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + | M | M | M | + | + | + | M | M | + | 41 |
| Adenoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Pituitary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Pars distalis, adenoma | | X | X | | X | | X | X | | X | | | X | X | X | X | X | | X | X | X | X | X | | X | 32 |
| Pars distalis, adenoma, multiple | | | | | | | | | | | | | | | | | | X | | | | | | | | 1 |
| Thyroid gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| C-cell, adenoma | | | | | | | | | | | | | | X | | | | | | | | | | | | 1 |
| Follicular cell, adenoma | | | | | | | | | | | | | | | | | | | | | | | X | | | 2 |
| Follicular cell, carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | X | 1 |
| **General Body System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| None | | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Genital System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Clitoral gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 48 |
| Adenoma | X | | | | | | | | | | | | | | | | | | | X | | | | | | 2 |
| Carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Bilateral, carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Ovary | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Granulosa cell tumor malignant | | | | | | | | | | | | | | | | | X | | | | | | | | | 1 |
| Uterus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Leiomyoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Polyp stromal | | | | | | | | | | | | | | | X | | | | | | | | | | | 2 |

**TABLE B2**
**Individual Animal Tumor Pathology of Female Rats in the 2-Year Dermal Study of Triethanolamine: 0 mg/kg**
(continued)

| Number of Days on Study | 338 | 390 | 466 | 542 | 555 | 567 | 582 | 593 | 634 | 636 | 638 | 639 | 663 | 671 | 674 | 674 | 691 | 690 | 710 | 710 | 713 | 718 | 719 | 719 | 728 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 258 | 285 | 251 | 256 | 300 | 246 | 280 | 276 | 290 | 242 | 294 | 284 | 241 | 293 | 253 | 260 | 278 | 247 | 265 | 295 | 286 | 272 | 264 | 297 | 279 |
| **Hematopoietic System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone marrow | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Lymph node | | | | | | | | | | + | | | | | | | + | | | | | | | | |
| Lymph node, mandibular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + |
| Lymph node, mesenteric | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Spleen | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Thymus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Integumentary System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Mammary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Fibroadenoma | | | | | | | | | | X | | | | | X | | | | X | | | X | | X | X |
| Fibroadenoma, multiple | | | | | | | | | | | | | | | | | | | | | | | | | |
| Skin | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Face, squamous cell papilloma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Subcutaneous tissue, neurofibrosarcoma | | | | | | | | | | | | | | | | | | | | | | X | | | |
| **Musculoskeletal System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Skeletal muscle | | | | | | | | | | | | | | | | | | | | | | | + | | |
| Hemangiosarcoma | | | | | | | | | | | | | | | | | | | | | | | X | | |
| **Nervous System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Brain | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Peripheral nerve | | | | | | + | | | | | | | | | | | | | | | | | | | |
| Spinal cord | | | | | | + | | | | | | | | | | | | | | | | | | | |
| **Respiratory System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lung | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Nose | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Trachea | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Special Senses System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Eye | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Urinary System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Kidney | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Renal tubule, adenoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Urinary bladder | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Systemic Lesions** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Multiple organs | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Leukemia mononuclear | | | | | | | | | | X | X | | X | | | | X | | | | | X | X | | |

**TABLE B2**
**Individual Animal Tumor Pathology of Female Rats in the 2-Year Dermal Study of Triethanolamine: 0 mg/kg**
(continued)

| Number of Days on Study | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 730 | 730 | 730 | 730 | 730 | 730 | 730 | 730 | 730 | 731 | 731 | 731 | 731 | 731 | 731 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 243 | 249 | 254 | 261 | 262 | 263 | 270 | 282 | 296 | 299 | 245 | 248 | 257 | 267 | 271 | 274 | 281 | 291 | 298 | 244 | 252 | 268 | 287 | 288 | 289 | Total Tissues/ Tumors |
| **Hematopoietic System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone marrow | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Lymph node | | | | | | | + | | | | | | + | | + | | | | | + | | | | | | 6 |
| Lymph node, mandibular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Lymph node, mesenteric | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Spleen | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Thymus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + | 49 |
| **Integumentary System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Mammary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Fibroadenoma | | X | | | | | X | X | | X | X | | | | | | | | | | | | X | | | 12 |
| Fibroadenoma, multiple | | | | | | | | | | | | X | | | | | | | | | | | | | | 1 |
| Skin | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Face, squamous cell papilloma | | | | | | | | | | | | | | | | | | | | | | | | X | | 1 |
| Subcutaneous tissue, neurofibrosarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| **Musculoskeletal System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Skeletal muscle | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Hemangiosarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| **Nervous System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Brain | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Peripheral nerve | | | | | | + | | | | | | | | | | | | | | | | | | | | 2 |
| Spinal cord | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| **Respiratory System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lung | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Nose | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Trachea | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Special Senses System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Eye | | | | | | | | | | | | | | + | | | | | | | | | | | | 1 |
| **Urinary System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Kidney | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Renal tubule, adenoma | | | | | | | | | X | | | | | | | | | | | | | | | | | 1 |
| Urinary bladder | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + | 49 |
| **Systemic Lesions** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Multiple organs | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Leukemia mononuclear | | | | | | X | X | | | | | | X | | X | | X | X | | X | | | | | | 13 |

**TABLE B2**
**Individual Animal Tumor Pathology of Female Rats in the 2-Year Dermal Study of Triethanolamine: 63 mg/kg**

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

**Table B2**
**Individual Animal Tumor Pathology of Female Rats in the 2-Year Dermal Study of Triethanolamine: 63 mg/kg**
(continued)

| **Number of Days on Study** | 729 | 729 | 729 | 729 | 729 | 730 | 730 | 730 | 730 | 730 | 730 | 730 | 730 | 731 | 731 | 731 | 731 | 731 | 731 | 731 | 731 | 731 | 731 | 731 | 731 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 343 | 347 | 354 | 355 | 359 | 307 | 312 | 314 | 315 | 317 | 329 | 331 | 345 | 301 | 302 | 304 | 308 | 332 | 336 | 338 | 339 | 342 | 353 | 356 | 360 | Total Tissues/ Tumors |
| **Alimentary System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Esophagus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Intestine large, colon | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Intestine large, rectum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Intestine large, cecum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Intestine small, duodenum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Intestine small, jejunum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Intestine small, ileum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Liver | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Mesentery | | | | | | | | + | | | | | + | | | | | | | | | | | | | 2 |
| Pancreas | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Salivary glands | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Stomach, forestomach | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Squamous cell papilloma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Stomach, glandular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Cardiovascular System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Blood vessel | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Heart | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Schwannoma benign | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Schwannoma malignant | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| **Endocrine System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Adrenal cortex | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Adenoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Adrenal medulla | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Pheochromocytoma benign | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Bilateral, pheochromocytoma benign | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Islets, pancreatic | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Adenoma | | | | | | | | | | | | | | | | | | | | | | | | X | | 2 |
| Parathyroid gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 48 |
| Pituitary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Pars distalis, adenoma | | | X | X | X | X | | X | | | | X | X | X | | X | X | | X | X | | | | | | 25 |
| Pars distalis, adenoma, multiple | | | | | | | | | X | | | | | | | | | | | | | | | | | 1 |
| Thyroid gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| C-cell, adenoma | | | | X | | | | X | | | | | | | | | | | | | | | | | | 2 |
| Follicular cell, adenoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Follicular cell, carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| **General Body System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| None | | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Genital System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Clitoral gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Adenoma | X | | | X | | | | | | | | | | | | | | X | | | | | | | | 6 |
| Ovary | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Uterus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Polyp stromal | | | | | | | | | | | | | | X | | | | | | | | | | | | 1 |

**Table B2**
**Individual Animal Tumor Pathology of Female Rats in the 2-Year Dermal Study of Triethanolamine: 63 mg/kg**
(continued)

| Number of Days on Study | 400 | 434 | 443 | 504 | 536 | 562 | 576 | 579 | 583 | 595 | 600 | 649 | 662 | 664 | 673 | 678 | 691 | 699 | 708 | 715 | 727 | 729 | 729 | 729 | 729 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 351 | 305 | 310 | 306 | 324 | 346 | 352 | 323 | 357 | 319 | 330 | 335 | 344 | 325 | 333 | 341 | 334 | 349 | 309 | 321 | 340 | 303 | 313 | 322 | 328 |
| **Hematopoietic System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone marrow | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Lymph node | | | | | | | | | | | + | | | | | + | + | | | | | | | | |
| Mediastinal, schwannoma malignant, metastatic, heart | | | | | | | | | | | | | | | | X | | | | | | | | | |
| Lymph node, mandibular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Lymph node, mesenteric | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Spleen | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Thymus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + |
| Mediastinum, schwannoma malignant, metastatic, heart | | | | | | | | | | | | | | | | X | | | | | | | | | |
| **Integumentary System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Mammary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Adenoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Fibroadenoma | | | | | | | | | | | | | | | | | | | | | | X | | X | X |
| Skin | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Inguinal, keratoacanthoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Musculoskeletal System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Nervous System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Brain | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Respiratory System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lung | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Nose | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Trachea | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Special Senses System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Ear | | | | | | | | | | | | | + | | | | | | | | | | | | |
| Eye | | | | | | | | | + | | | | | | | | | | | | | | | | |
| Harderian gland | | | | | | | | | + | | | | | | | | | | | | | | | | |
| Zymbal's gland | | | | | | | + | | | | | | | | | | | | | | | | | | |
| Carcinoma | | | | | | | X | | | | | | | | | | | | | | | | | | |
| **Urinary System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Kidney | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Renal tubule, adenoma | | | | | | | | | | | | | | | | X | | | | | | | | | |
| Urinary bladder | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Systemic Lesions** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Multiple organs | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Leukemia mononuclear | | | X | | | | | | | | X | | | | | X | X | X | | | | X | | X | |

**TABLE B2**
**Individual Animal Tumor Pathology of Female Rats in the 2-Year Dermal Study of Triethanolamine: 63 mg/kg**
(continued)

| | | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Number of Days on Study** | 7<br>2<br>9 | 7<br>2<br>9 | 7<br>2<br>9 | 7<br>2<br>9 | 7<br>2<br>9 | 7<br>3<br>0 | 7<br>3<br>0 | 7<br>3<br>0 | 7<br>3<br>0 | 7<br>3<br>0 | 7<br>3<br>0 | 7<br>3<br>0 | 7<br>3<br>0 | 7<br>3<br>1 | 7<br>3<br>1 | 7<br>3<br>1 | 7<br>3<br>1 | 7<br>3<br>1 | 7<br>3<br>1 | 7<br>3<br>1 | 7<br>3<br>1 | 7<br>3<br>1 | 7<br>3<br>1 | 7<br>3<br>1 | 7<br>3<br>1 | |
| **Carcass ID Number** | 3<br>4<br>3 | 3<br>4<br>7 | 3<br>5<br>4 | 3<br>5<br>5 | 3<br>5<br>9 | 3<br>0<br>7 | 3<br>1<br>2 | 3<br>1<br>4 | 3<br>1<br>5 | 3<br>1<br>7 | 3<br>2<br>9 | 3<br>3<br>1 | 3<br>4<br>5 | 3<br>0<br>1 | 3<br>0<br>2 | 3<br>0<br>4 | 3<br>0<br>8 | 3<br>3<br>2 | 3<br>3<br>6 | 3<br>3<br>8 | 3<br>3<br>9 | 3<br>4<br>2 | 3<br>5<br>3 | 3<br>5<br>6 | 3<br>6<br>0 | Total Tissues/ Tumors |
| **Hematopoietic System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone marrow | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Lymph node | | | | | + | | | | | | | | | | | | | | | | | | + | | | 5 |
| Mediastinal, schwannoma malignant, metastatic, heart | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Lymph node, mandibular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Lymph node, mesenteric | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Spleen | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Thymus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | M | + | + | M | 47 |
| Mediastinum, schwannoma malignant, metastatic, heart | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| **Integumentary System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Mammary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Adenoma | | | | | | | | | | | | | | | | X | | | | | | | | | | 1 |
| Carcinoma | | | | | | | | | | | | | | | | | | | | | | X | | | | 1 |
| Fibroadenoma | | | X | X | X | | X | | | | X | X | | | | X | | | | | X | X | X | | | 13 |
| Skin | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Inguinal, keratoacanthoma | | | | | | | | | | | | | | | | | | | | | | X | | | | 1 |
| **Musculoskeletal System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Nervous System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Brain | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Respiratory System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lung | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Nose | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Trachea | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Special Senses System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Ear | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Eye | | | | | | | | | | | + | | | | | | | | | | | | | | | 2 |
| Harderian gland | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Zymbal's gland | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| **Urinary System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Kidney | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Renal tubule, adenoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Urinary bladder | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Systemic Lesions** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Multiple organs | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Leukemia mononuclear | | | | | X | | | X | | | | | | | X | | | X | X | | X | | X | | | 14 |

**Table B2**
**Individual Animal Tumor Pathology of Female Rats in the 2-Year Dermal Study of Triethanolamine: 125 mg/kg**

| | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 2 | 3 | 4 | 4 | 5 | 5 | 5 | 5 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 |
| **Number of Days on Study** | 2 | 9 | 7 | 8 | 4 | 4 | 7 | 9 | 0 | 1 | 3 | 3 | 3 | 4 | 7 | 7 | 9 | 0 | 1 | 1 | 1 | 1 | 2 | 2 | 2 |
| | 2 | 9 | 7 | 4 | 4 | 4 | 4 | 3 | 0 | 9 | 1 | 9 | 9 | 8 | 0 | 3 | 1 | 0 | 0 | 4 | 8 | 9 | 4 | 5 | 8 |
| | 3 | 3 | 4 | 4 | 3 | 3 | 4 | 4 | 3 | 3 | 4 | 3 | 4 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 4 | 4 | 3 | 4 |
| **Carcass ID Number** | 8 | 8 | 0 | 0 | 6 | 9 | 2 | 0 | 7 | 8 | 1 | 7 | 1 | 7 | 9 | 7 | 9 | 7 | 9 | 6 | 9 | 0 | 0 | 6 | 1 |
| | 9 | 0 | 2 | 4 | 1 | 3 | 0 | 0 | 7 | 1 | 0 | 0 | 6 | 2 | 0 | 9 | 1 | 4 | 8 | 3 | 4 | 3 | 8 | 2 | 2 |
| **Alimentary System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Esophagus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Periesophageal tissue, lipoma | | | | | | | X | | | | | | | | | | | | | | | | | | |
| Intestine large, colon | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine large, rectum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine large, cecum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine small, duodenum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine small, jejunum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine small, ileum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Liver | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Mesentery | | | | | | | | | | | | + | | | | | | | | | | | | | + |
| Pancreas | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Salivary glands | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Stomach, forestomach | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Stomach, glandular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Cardiovascular System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Blood vessel | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Heart | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Endocrine System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Adrenal cortex | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Adenoma | | | | | | | | | | | | | | | | | X | | | | | | | | |
| Adrenal medulla | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Islets, pancreatic | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Parathyroid gland | + | + | + | + | M | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Pituitary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Pars distalis, adenoma | | | | | X | | X | X | X | X | | | | | | X | X | | X | X | X | X | X | X | X |
| Pars distalis, adenoma, multiple | | | | | | | | | | | | | | X | | | | | | | | | | | |
| Thyroid gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| C-cell, adenoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Follicular cell, adenoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| **General Body System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Tissue NOS | | | | | | | | | | | | | | | | | + | | | | | | | | |
| **Genital System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Clitoral gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Adenoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Ovary | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Uterus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Polyp stromal | | | | | | | | | | | | | | | | | | X | | | | | | | |

**TABLE B2**
**Individual Animal Tumor Pathology of Female Rats in the 2-Year Dermal Study of Triethanolamine: 125 mg/kg**
(continued)

| | | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | |
| **Number of Days on Study** | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | |
| | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 1 | |
| | 3 | 3 | 3 | 3 | 3 | 4 | 4 | 4 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 4 | 4 | 4 | 4 | 4 | 3 | 3 | 3 | 3 | 4 | Total |
| **Carcass ID Number** | 6 | 6 | 7 | 8 | 9 | 0 | 1 | 1 | 6 | 6 | 7 | 8 | 8 | 9 | 9 | 0 | 0 | 0 | 1 | 1 | 7 | 8 | 9 | 9 | 1 | Tissues/ |
| | 6 | 8 | 5 | 3 | 7 | 6 | 5 | 7 | 4 | 5 | 6 | 4 | 5 | 2 | 6 | 1 | 5 | 7 | 1 | 9 | 8 | 2 | 5 | 4 | 4 | Tumors |
| **Alimentary System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Esophagus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Periesophageal tissue, lipoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Intestine large, colon | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Intestine large, rectum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Intestine large, cecum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Intestine small, duodenum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Intestine small, jejunum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Intestine small, ileum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Liver | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Mesentery | | | | | | | | | | | | | | | | | | | | | | | | | | 2 |
| Pancreas | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Salivary glands | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Stomach, forestomach | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Stomach, glandular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Cardiovascular System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Blood vessel | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Heart | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Endocrine System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Adrenal cortex | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Adenoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Adrenal medulla | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Islets, pancreatic | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Carcinoma | | | | | | | | | | | | X | | | | | | | | | | | | | | 1 |
| Parathyroid gland | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 47 |
| Pituitary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Pars distalis, adenoma | X | X | | | | X | | X | X | X | | X | | X | | | X | X | X | X | X | X | | | X | 29 |
| Pars distalis, adenoma, multiple | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Thyroid gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| C-cell, adenoma | | | | | | | | | | | X | | | | | | | | | | | X | | | | 2 |
| Follicular cell, adenoma | | | X | | | | | | | | | | | | | | | | | | | | | | | 1 |
| **General Body System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Tissue NOS | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| **Genital System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Clitoral gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Adenoma | | | | X | | | | | | | X | | | | | | | | | | | | | | | 2 |
| Ovary | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Uterus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Polyp stromal | | | X | | X | | X | | X | | X | | | | | X | | | | | X | | | | | 8 |

**TABLE B2**
**Individual Animal Tumor Pathology of Female Rats in the 2-Year Dermal Study of Triethanolamine: 125 mg/kg**
(continued)

| | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Number of Days on Study** | 222 | 399 | 477 | 484 | 544 | 544 | 574 | 593 | 600 | 619 | 631 | 639 | 639 | 648 | 670 | 673 | 691 | 700 | 710 | 714 | 718 | 719 | 724 | 725 | 728 |
| **Carcass ID Number** | 389 | 380 | 402 | 404 | 361 | 393 | 420 | 400 | 377 | 381 | 410 | 370 | 416 | 372 | 390 | 379 | 391 | 374 | 398 | 363 | 394 | 403 | 408 | 362 | 412 |
| **Hematopoietic System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Blood | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone marrow | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Lymph node | | | + | | | + | | | | | + | + | | | | | | | | | | + | | + | |
| Lymph node, mandibular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Lymph node, mesenteric | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Spleen | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Thymus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | M | + | + | M | + | + | + | + | + |
| Thymoma benign | | | | | | | | | X | | | | | | | | | | | | | | | | |
| **Integumentary System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Mammary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Adenoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Fibroadenoma | | | | | | | | | | X | | | | | X | X | | X | X | | | | | | |
| Fibroadenoma, multiple | | | | | | | | | | | | | | X | | | | | | | | X | | | |
| Skin | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Musculoskeletal System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Nervous System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Brain | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Respiratory System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lung | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Nose | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Trachea | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Special Senses System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Ear | | | | | | | | | | + | | | | | | | | | | | | | | | |
| Pinna, fibrosarcoma | | | | | | | | | | X | | | | | | | | | | | | | | | |
| Eye | | | | | | | | | | | | | + | | | | | | | + | | + | | | |
| **Urinary System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Kidney | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Urinary bladder | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Leiomyoma | | | | | | | | | | | | | | | | X | | | | | | | | | |
| Transitional epithelium, papilloma | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Systemic Lesions** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Multiple organs | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Leukemia mononuclear | | | | X | | X | | | | X | X | X | | | | | | | | | X | X | | X | |

**TABLE B2**
**Individual Animal Tumor Pathology of Female Rats in the 2-Year Dermal Study of Triethanolamine: 125 mg/kg**
(continued)

| | | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | |
| **Number of Days on Study** | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | |
| | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 1 | |
| | 3 | 3 | 3 | 3 | 3 | 4 | 4 | 4 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 4 | 4 | 4 | 4 | 4 | 3 | 3 | 3 | 3 | 4 | Total |
| **Carcass ID Number** | 6 | 6 | 7 | 8 | 9 | 0 | 1 | 1 | 6 | 6 | 7 | 8 | 8 | 9 | 9 | 0 | 0 | 0 | 1 | 1 | 7 | 8 | 9 | 9 | 1 | Tissues/ |
| | 6 | 8 | 5 | 3 | 7 | 6 | 5 | 7 | 4 | 5 | 6 | 4 | 5 | 2 | 6 | 1 | 5 | 7 | 1 | 9 | 8 | 2 | 5 | 9 | 4 | Tumors |
| **Hematopoietic System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Blood | | | | | | | | | | | | | | | | | | | | | | | | | + | 1 |
| Bone marrow | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Lymph node | | | | | | | | | | | | | | | | | | | | | | | | | | 6 |
| Lymph node, mandibular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Lymph node, mesenteric | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Spleen | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Thymus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | 47 |
| Thymoma benign | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| **Integumentary System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Mammary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Adenoma | | | | | | | | | | | | | | | | | | | | | | | X | | | 1 |
| Fibroadenoma | | | | | | | | | | | | X | | | | | | | | | | X | | | | 7 |
| Fibroadenoma, multiple | | | | | | X | | | | | | | | | | | | | | | | | | | | 3 |
| Skin | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Musculoskeletal System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Nervous System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Brain | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Respiratory System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lung | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Nose | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Trachea | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Special Senses System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Ear | | | | | | | | | | | | | | | + | | | | | | | | | | | 2 |
| Pinna, fibrosarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Eye | | + | | | | | | | | | | | | + | | | | | | | | + | | | | 6 |
| **Urinary System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Kidney | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Urinary bladder | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Leiomyoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Transitional epithelium, papilloma | | | | | | | X | | | | | | | | | | | | | | | | | | | 1 |
| **Systemic Lesions** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Multiple organs | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Leukemia mononuclear | | X | | | | X | | | | | | X | X | | | | | | | X | | | | | | 13 |

**TABLE B2**
**Individual Animal Tumor Pathology of Female Rats in the 2-Year Dermal Study of Triethanolamine: 250 mg/kg**

| **Number of Days on Study** | 125 | 250 | 353 | 353 | 358 | 389 | 394 | 420 | 429 | 439 | 459 | 463 | 522 | 524 | 556 | 588 | 588 | 610 | 617 | 624 | 631 | 633 | 644 | 649 | 657 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 458 | 449 | 437 | 445 | 471 | 444 | 451 | 476 | 464 | 440 | 452 | 439 | 467 | 443 | 472 | 448 | 463 | 423 | 455 | 477 | 450 | 438 | 454 | 478 | 422 |
| **Alimentary System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Esophagus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine large, colon | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine large, rectum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine large, cecum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine small, duodenum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine small, jejunum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine small, ileum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Liver | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Hepatocellular adenoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Mesentery | | | | | | | | | | | | | | + | | | | | | | | | | | |
| Rhabdomyosarcoma, metastatic, skeletal muscle | | | | | | | | | | | | | | X | | | | | | | | | | | |
| Pancreas | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Salivary glands | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Stomach, forestomach | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Stomach, glandular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Cardiovascular System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Blood vessel | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Heart | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Endocrine System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Adrenal cortex | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Adrenal medulla | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Islets, pancreatic | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Adenoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Parathyroid gland | + | M | + | + | + | + | + | M | + | + | + | + | M | + | + | + | + | + | + | M | + | + | + | + | + |
| Pituitary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Pars distalis, adenoma | | | | | | | | | X | | | | | | X | | X | | | X | | | | | X |
| Thyroid gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| C-cell, adenoma | | | | | | | | | X | | | | | | X | | | | | | | | | | |
| C-cell, carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Follicular cell, adenoma | | | | | | | | | | | | | | X | | | | | | | | | | | |
| **General Body System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| None | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Genital System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Clitoral gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Adenoma | | | | | | X | | | | | | | | | | | | | | | | | | | |
| Ovary | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Uterus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Polyp stromal | | | X | | | | | | | | | | X | X | | | | | | | | | | | |

**Table B2**
**Individual Animal Tumor Pathology of Female Rats in the 2-Year Dermal Study of Triethanolamine: 250 mg/kg**
(continued)

| | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Number of Days on Study** | 667 | 670 | 670 | 690 | 700 | 713 | 718 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 730 | 730 | 730 | 730 | 731 | 731 | 731 | 731 | 731 | 731 | 731 | |
| **Carcass ID Number** | 421 | 427 | 470 | 442 | 430 | 447 | 461 | 433 | 435 | 436 | 473 | 474 | 479 | 480 | 434 | 460 | 462 | 465 | 424 | 441 | 456 | 457 | 466 | 468 | 475 | Total Tissues/ Tumors |
| **Alimentary System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Esophagus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Intestine large, colon | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Intestine large, rectum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Intestine large, cecum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Intestine small, duodenum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Intestine small, jejunum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Intestine small, ileum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Liver | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Hepatocellular adenoma | | | | | X | | | | | | | | | | | | | | | | | | | | | 1 |
| Mesentery | | | | | | | | | | + | | | | | | | | | | | | | | | | 2 |
| Rhabdomyosarcoma, metastatic, skeletal muscle | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Pancreas | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Salivary glands | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Stomach, forestomach | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Stomach, glandular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Cardiovascular System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Blood vessel | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Heart | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Endocrine System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Adrenal cortex | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Adrenal medulla | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Islets, pancreatic | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Adenoma | | | | X | | | | | | | | | | | | | | | | | | | | | | 1 |
| Parathyroid gland | + | + | M | + | + | + | + | M | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 43 |
| Pituitary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Pars distalis, adenoma | X | X | X | X | X | | X | | X | X | | X | | X | X | X | X | X | | X | X | X | | | X | 23 |
| Thyroid gland | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| C-cell, adenoma | | | | | | | | | | | | | | | | X | | | | | | X | | X | | 5 |
| C-cell, carcinoma | | | | | | | | | | | | | X | | | | | | | | | | | | | 1 |
| Follicular cell, adenoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| **General Body System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| None | | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Genital System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Clitoral gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Adenoma | | | | | | | | | | | | | | | | | X | | | | | | | | | 2 |
| Ovary | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Uterus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Polyp stromal | | | | | | | | | | | | X | | | | | | | | | | | X | | | 5 |

**TABLE B2**
**Individual Animal Tumor Pathology of Female Rats in the 2-Year Dermal Study of Triethanolamine: 250 mg/kg**
(continued)

| | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Number of Days on Study** | 125 | 250 | 353 | 353 | 358 | 389 | 394 | 420 | 429 | 439 | 459 | 463 | 522 | 524 | 556 | 588 | 588 | 610 | 617 | 624 | 631 | 633 | 644 | 649 | 657 |
| **Carcass ID Number** | 458 | 449 | 437 | 445 | 471 | 444 | 451 | 476 | 464 | 440 | 452 | 439 | 467 | 443 | 472 | 448 | 463 | 423 | 455 | 477 | 450 | 438 | 454 | 478 | 422 |
| **Hematopoietic System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Blood | | | | + | | | | | | | | | | | | | | | | | | | | | |
| Bone marrow | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Lymph node | | | | | | | | | | | | | | + | | | | | | | | | | | |
| Mediastinal, rhabdomyosarcoma, metastatic, skeletal muscle | | | | | | | | | | | | | | X | | | | | | | | | | | |
| Lymph node, mandibular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Lymph node, mesenteric | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Spleen | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Thymus | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Rhabdomyosarcoma, metastatic, skeletal muscle | | | | | | | | | | | | | | X | | | | | | | | | | | |
| Thymoma malignant | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Integumentary System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Mammary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Fibroadenoma | | | | | | | | | | | | | | | X | | X | | | | | | | | |
| Fibroadenoma, multiple | | | | | | | | | | | X | | | | | | | | | | | | | | |
| Skin | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Musculoskeletal System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Skeletal muscle | | | | | | | | | | | | | | + | | | | | | | | | | | |
| Rhabdomyosarcoma | | | | | | | | | | | | | | X | | | | | | | | | | | |
| **Nervous System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Brain | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Medulloblastoma NOS | | | | | | | | | | | | | | | | | | | X | | | | | | |
| Peripheral nerve | | | | | | | | | | | | | | | | + | | | | | | | | | |
| Spinal cord | | | | | | | | | | | | | | | | + | | | | | | | | | |
| **Respiratory System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lung | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Mediastinum, rhabdomyosarcoma, metastatic, skeletal muscle | | | | | | | | | | | | | | X | | | | | | | | | | | |
| Nose | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Trachea | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Special Senses System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Ear | | | | | | | | | | | | | | | + | | | | | | | | | | |
| Middle ear, carcinoma, metastatic, Zymbal's gland | | | | | | | | | | | | | | | X | | | | | | | | | | |
| Eye | | | | | | | | | | | | | | | | | | | | | | | | | |
| Zymbal's gland | | | | | | | | | | | | | | | + | | | | | | | | | | |
| Carcinoma | | | | | | | | | | | | | | | X | | | | | | | | | | |
| **Urinary System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Kidney | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Urinary bladder | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Systemic Lesions** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Multiple organs | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Leukemia mononuclear | | | | | | | | | | X | | | X | | | X | | X | | | X | | | | |

**Table B2**
**Individual Animal Tumor Pathology of Female Rats in the 2-Year Dermal Study of Triethanolamine: 250 mg/kg**
(continued)

| | | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Number of Days on Study** | 667 | 670 | 670 | 690 | 700 | 713 | 718 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 730 | 730 | 730 | 730 | 731 | 731 | 731 | 731 | 731 | 731 | 731 | |
| **Carcass ID Number** | 421 | 427 | 470 | 442 | 430 | 447 | 461 | 433 | 435 | 436 | 473 | 474 | 479 | 480 | 434 | 460 | 462 | 465 | 424 | 441 | 456 | 457 | 466 | 468 | 475 | Total Tissues/ Tumors |
| **Hematopoietic System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Blood | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Bone marrow | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Lymph node | + | | | | | | + | | | | | | | | | | | | | | | | | | | 3 |
| Mediastinal, rhabdomyosarcoma, metastatic, skeletal muscle | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Lymph node, mandibular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Lymph node, mesenteric | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Spleen | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Thymus | + | + | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | 48 |
| Rhabdomyosarcoma, metastatic, skeletal muscle | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Thymoma malignant | | | | | | | X | | | | | | | | | | | | | | | | | | | 1 |
| **Integumentary System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Mammary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Fibroadenoma | | | | | | | X | | | | | X | | X | | | | | | | | | | X | | 6 |
| Fibroadenoma, multiple | | | | | | | | | | | | | | | | | | | | | | | X | | | 2 |
| Skin | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Musculoskeletal System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Skeletal muscle | | | | | | | | | | | | | | | | | | | | | | | + | | | 2 |
| Rhabdomyosarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| **Nervous System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Brain | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Medulloblastoma NOS | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Peripheral nerve | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Spinal cord | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| **Respiratory System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lung | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Mediastinum, rhabdomyosarcoma, metastatic, skeletal muscle | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Nose | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Trachea | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Special Senses System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Ear | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Middle ear, carcinoma, metastatic, Zymbal's gland | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Eye | | | | | | | | | | | | | | | | | | | | | | | | | + | 1 |
| Zymbal's gland | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| **Urinary System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Kidney | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Urinary bladder | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Systemic Lesions** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Multiple organs | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Leukemia mononuclear | X | X | X | X | | | X | X | | | | X | X | | | | X | | | | | X | X | | | 16 |

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

| | 0 mg/kg | 63 mg/kg | 125 mg/kg | 250 mg/kg |
|---|---|---|---|---|
| **Clitoral Gland: Adenoma** | | | | |
| Overall rate[a] | 2/48 (4%) | 6/49 (12%) | 2/50 (4%) | 2/50 (4%) |
| Adjusted rate[b] | 8.0% | 17.3% | 8.0% | 7.7% |
| Terminal rate[c] | 2/25 (8%) | 3/29 (10%) | 2/25 (8%) | 1/18 (6%) |
| First incidence (days) | 729 (T) | 579 | 729 (T) | 389 |
| Life table test[d] | P=0.512N | P=0.170 | P=0.697 | P=0.595 |
| Logistic regression test[d] | P=0.383N | P=0.139 | P=0.697 | P=0.693N |
| Cochran-Armitage test[d] | P=0.325N | | | |
| Fisher exact test[d] | | P=0.141 | P=0.676N | P=0.676N |
| **Clitoral Gland: Adenoma or Carcinoma** | | | | |
| Overall rate | 4/48 (8%) | 6/49 (12%) | 2/50 (4%) | 2/50 (4%) |
| Adjusted rate | 13.3% | 17.3% | 8.0% | 7.7% |
| Terminal rate | 2/25 (8%) | 3/29 (10%) | 2/25 (8%) | 1/18 (6%) |
| First incidence (days) | 593 | 579 | 729 (T) | 389 |
| Life table test | P=0.276N | P=0.421 | P=0.336N | P=0.480N |
| Logistic regression test | P=0.166N | P=0.381 | P=0.323N | P=0.328N |
| Cochran-Armitage test | P=0.138N | | | |
| Fisher exact test | | P=0.383 | P=0.319N | P=0.319N |
| **Mammary Gland: Fibroadenoma** | | | | |
| Overall rate | 13/50 (26%) | 13/50 (26%) | 10/50 (20%) | 8/50 (16%) |
| Adjusted rate | 40.8% | 44.8% | 28.4% | 32.1% |
| Terminal rate | 7/25 (28%) | 13/29 (45%) | 3/25 (12%) | 4/18 (22%) |
| First incidence (days) | 636 | 729 (T) | 619 | 459 |
| Life table test | P=0.383N | P=0.451N | P=0.335N | P=0.460N |
| Logistic regression test | P=0.275N | P=0.584N | P=0.327N | P=0.345N |
| Cochran-Armitage test | P=0.102N | | | |
| Fisher exact test | | P=0.590N | P=0.318N | P=0.163N |
| **Mammary Gland: Fibroadenoma, Adenoma, or Carcinoma** | | | | |
| Overall rate | 13/50 (26%) | 13/50 (26%) | 11/50 (22%) | 8/50 (16%) |
| Adjusted rate | 40.8% | 44.8% | 31.7% | 32.1% |
| Terminal rate | 7/25 (28%) | 13/29 (45%) | 4/25 (16%) | 4/18 (22%) |
| First incidence (days) | 636 | 729 (T) | 619 | 459 |
| Life table test | P=0.404N | P=0.451N | P=0.418N | P=0.460N |
| Logistic regression test | P=0.296N | P=0.584N | P=0.420N | P=0.345N |
| Cochran-Armitage test | P=0.109N | | | |
| Fisher exact test | | P=0.590N | P=0.408N | P=0.163N |
| **Pituitary Gland (Pars Distalis): Adenoma** | | | | |
| Overall rate | 33/50 (66%) | 26/50 (52%) | 30/50 (60%) | 23/50 (46%) |
| Adjusted rate | 81.3% | 66.1% | 74.5% | 78.3% |
| Terminal rate | 18/25 (72%) | 16/29 (55%) | 15/25 (60%) | 12/18 (67%) |
| First incidence (days) | 390 | 504 | 544 | 429 |
| Life table test | P=0.433 | P=0.082N | P=0.380N | P=0.516N |
| Logistic regression test | P=0.259N | P=0.112N | P=0.354N | P=0.175N |
| Cochran-Armitage test | P=0.051N | | | |
| Fisher exact test | | P=0.111N | P=0.339N | P=0.035N |

**Table B3**
**Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Dermal Study of Triethanolamine** (continued)

| | 0 mg/kg | 63 mg/kg | 125 mg/kg | 250 mg/kg |
|---|---|---|---|---|
| **Thyroid Gland (C-cell): Adenoma** | | | | |
| Overall rate | 1/50 (2%) | 2/50 (4%) | 2/50 (4%) | 5/49 (10%) |
| Adjusted rate | 4.0% | 6.9% | 8.0% | 20.9% |
| Terminal rate | 1/25 (4%) | 2/29 (7%) | 2/25 (8%) | 3/18 (17%) |
| First incidence (days) | 729 (T) | 729 (T) | 729 (T) | 429 |
| Life table test | P=0.015 | P=0.552 | P=0.500 | P=0.053 |
| Logistic regression test | P=0.027 | P=0.552 | P=0.500 | P=0.081 |
| Cochran-Armitage test | P=0.047 | | | |
| Fisher exact test | | P=0.500 | P=0.500 | P=0.098 |
| **Thyroid Gland (C-cell): Adenoma or Carcinoma** | | | | |
| Overall rate | 1/50 (2%) | 2/50 (4%) | 2/50 (4%) | 6/49 (12%) |
| Adjusted rate | 4.0% | 6.9% | 8.0% | 26.2% |
| Terminal rate | 1/25 (4%) | 2/29 (7%) | 2/25 (8%) | 4/18 (22%) |
| First incidence (days) | 729 (T) | 729 (T) | 729 (T) | 429 |
| Life table test | P=0.004 | P=0.552 | P=0.500 | P=0.024 |
| Logistic regression test | P=0.009 | P=0.552 | P=0.500 | P=0.037 |
| Cochran-Armitage test | P=0.019 | | | |
| Fisher exact test | | P=0.500 | P=0.500 | P=0.053 |
| **Thyroid Gland (Follicular Cell): Adenoma or Carcinoma** | | | | |
| Overall rate | 3/50 (6%) | 2/50 (4%) | 1/50 (2%) | 1/49 (2%) |
| Adjusted rate | 10.1% | 5.5% | 4.0% | 2.7% |
| Terminal rate | 2/25 (8%) | 0/29 (0%) | 1/25 (4%) | 0/18 (0%) |
| First incidence (days) | 582 | 562 | 729 (T) | 524 |
| Life table test | P=0.285N | P=0.465N | P=0.308N | P=0.411N |
| Logistic regression test | P=0.192N | P=0.499N | P=0.308N | P=0.305N |
| Cochran-Armitage test | P=0.204N | | | |
| Fisher exact test | | P=0.500N | P=0.309N | P=0.316N |
| **Uterus: Stromal Polyp** | | | | |
| Overall rate | 2/50 (4%) | 1/50 (2%) | 8/50 (16%) | 5/50 (10%) |
| Adjusted rate | 6.1% | 3.4% | 30.2% | 17.5% |
| Terminal rate | 1/25 (4%) | 1/29 (3%) | 7/25 (28%) | 2/18 (11%) |
| First incidence (days) | 555 | 729 (T) | 700 | 353 |
| Life table test | P=0.023 | P=0.468N | P=0.046 | P=0.137 |
| Logistic regression test | P=0.061 | P=0.500N | P=0.045 | P=0.300 |
| Cochran-Armitage test | P=0.079 | | | |
| Fisher exact test | | P=0.500N | P=0.046 | P=0.218 |
| **All Organs: Mononuclear Cell Leukemia** | | | | |
| Overall rate | 13/50 (26%) | 14/50 (28%) | 13/50 (26%) | 16/50 (32%) |
| Adjusted rate | 39.7% | 39.8% | 36.2% | 54.1% |
| Terminal rate | 7/25 (28%) | 9/29 (31%) | 5/25 (20%) | 6/18 (33%) |
| First incidence (days) | 636 | 443 | 484 | 439 |
| Life table test | P=0.055 | P=0.569N | P=0.581 | P=0.079 |
| Logistic regression test | P=0.155 | P=0.494 | P=0.582 | P=0.142 |
| Cochran-Armitage test | P=0.297 | | | |
| Fisher exact test | | P=0.500 | P=0.590N | P=0.330 |

**Table B3**
**Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Dermal Study of Triethanolamine** (continued)

| | 0 mg/kg | 63 mg/kg | 125 mg/kg | 250 mg/kg |
|---|---|---|---|---|
| **All Organs: Benign Neoplasms** | | | | |
| Overall rate | 43/50 (86%) | 38/50 (76%) | 39/50 (78%) | 33/50 (66%) |
| Adjusted rate | 95.4% | 90.3% | 92.8% | 91.2% |
| Terminal rate | 23/25 (92%) | 25/29 (86%) | 22/25 (88%) | 15/18 (83%) |
| First incidence (days) | 390 | 400 | 544 | 353 |
| Life table test | P=0.268 | P=0.109N | P=0.323N | P=0.417 |
| Logistic regression test | P=0.230N | P=0.151N | P=0.233N | P=0.130N |
| Cochran-Armitage test | P=0.017N | | | |
| Fisher exact test | | P=0.154N | P=0.218N | 0.017N |
| **All Organs: Malignant Neoplasms** | | | | |
| Overall rate | 17/50 (34%) | 17/50 (34%) | 13/50 (26%) | 18/50 (36%) |
| Adjusted rate | 47.6% | 46.0% | 36.2% | 56.6% |
| Terminal rate | 8/25 (32%) | 10/29 (34%) | 5/25 (20%) | 6/18 (33%) |
| First incidence (days) | 466 | 443 | 484 | 439 |
| Life table test | P=0.122 | P=0.470N | P=0.280N | P=0.142 |
| Logistic regression test | P=0.342 | P=0.581 | P=0.259N | P=0.352 |
| Cochran-Armitage test | P=0.490 | | | |
| Fisher exact test | | P=0.583N | P=0.257N | P=0.500 |
| **All Organs: Benign or Malignant Neoplasms** | | | | |
| Overall rate | 47/50 (94%) | 43/50 (86%) | 44/50 (88%) | 39/50 (78%) |
| Adjusted rate | 97.9% | 93.4% | 95.6% | 95.0% |
| Terminal rate | 24/25 (96%) | 26/29 (90%) | 23/25 (92%) | 16/18 (89%) |
| First incidence (days) | 390 | 400 | 484 | 353 |
| Life table test | P=0.133 | P=0.155N | P=0.391N | P=0.238 |
| Logistic regression test | P=0.263N | P=0.153N | P=0.267N | P=0.193N |
| Cochran-Armitage test | P=0.020N | | | |
| Fisher exact test | | P=0.159N | P=0.243N | P=0.020N |

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for clitoral gland, pituitary gland, thyroid gland, and uterus; for other tissues, denominator is number of animals necropsied.
[b] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the controls and that dosed group. The life table test regards neoplasms in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. For all tests, a negative trend or a lower incidence in a dose group is indicated by **N**.

**TABLE B4**
**Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Dermal Study of Triethanolamine[a]**

| | 0 mg/kg | 63 mg/kg | 125 mg/kg | 250 mg/kg |
|---|---|---|---|---|
| **Disposition Summary** | | | | |
| Animals initially in study | 60 | 60 | 60 | 60 |
| ***15-Month interim evaluation*** | 10 | 10 | 10 | 10 |
| Early deaths | | | | |
| Moribund | 11 | 4 | 12 | 17 |
| Natural deaths | 14 | 17 | 13 | 15 |
| Survivors | | | | |
| Died last week of study | | | | 1 |
| Terminal sacrifice | 25 | 29 | 25 | 17 |
| Animals examined microscopically | 60 | 60 | 60 | 60 |
| ***15-Month Interim Evaluation*** | | | | |
| **Alimentary System** | | | | |
| Intestine large, colon | (10) | (10) | (10) | (10) |
| Parasite metazoan | 1 (10%) | | 1 (10%) | |
| Intestine large, rectum | (10) | (10) | (10) | (10) |
| Parasite metazoan | 1 (10%) | 1 (10%) | | 3 (30%) |
| Liver | (10) | (10) | (10) | (10) |
| Basophilic focus | | 1 (10%) | 2 (20%) | |
| Hepatodiaphragmatic nodule | 3 (30%) | | 2 (20%) | 2 (20%) |
| Inflammation, chronic | 7 (70%) | 8 (80%) | 6 (60%) | 6 (60%) |
| Necrosis, coagulative | | | | 1 (10%) |
| Bile duct, hyperplasia | 5 (50%) | 4 (40%) | 3 (30%) | 2 (20%) |
| Pancreas | (10) | (10) | (10) | (10) |
| Acinus, atrophy | | 1 (10%) | | 1 (10%) |
| Duct, ectasia | 1 (10%) | | | |
| **Cardiovascular System** | | | | |
| Heart | (10) | (10) | (10) | (10) |
| Cardiomyopathy, chronic | 9 (90%) | 9 (90%) | 9 (90%) | 10 (100%) |
| **Endocrine System** | | | | |
| Adrenal cortex | (10) | (10) | (10) | (10) |
| Degeneration, fatty | | 1 (10%) | | |
| Pituitary gland | (10) | (10) | (10) | (10) |
| Pars distalis, cyst | 6 (60%) | 8 (80%) | 8 (80%) | 3 (30%) |
| Pars distalis, hyperplasia | 3 (30%) | 6 (60%) | 2 (20%) | 3 (30%) |
| Pars intermedia, cyst | 1 (10%) | 1 (10%) | | |
| Thyroid gland | (10) | (10) | (10) | (10) |
| C-cell, hyperplasia | | 1 (10%) | | 1 (10%) |
| **Genital System** | | | | |
| Clitoral gland | (10) | (10) | (10) | (10) |
| Hyperplasia | 1 (10%) | | | |
| Inflammation, chronic active | | 3 (30%) | 2 (20%) | 2 (20%) |
| Ovary | (10) | (10) | (10) | (10) |
| Cyst | 1 (10%) | | | |

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

**Table B4**
**Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Dermal Study of Triethanolamine**
(continued)

| | 0 mg/kg | 63 mg/kg | 125 mg/kg | 250 mg/kg |
|---|---|---|---|---|
| ***15-Month Interim Evaluation*** (continued) | | | | |
| **Hematopoietic System** | | | | |
| Bone marrow | (10) | (10) | (10) | (10) |
| Hyperplasia | | 1 (10%) | 1 (10%) | 1 (10%) |
| **Integumentary System** | | | | |
| Mammary gland | (10) | (10) | (10) | (10) |
| Hyperplasia, cystic | 5 (50%) | 5 (50%) | 8 (80%) | 7 (70%) |
| Skin | (10) | (10) | (10) | (10) |
| Site of application-no mass, acanthosis | | 1 (10%) | 7 (70%) | 6 (60%) |
| Site of application-no mass, inflammation, chronic active | | 1 (10%) | 7 (70%) | 6 (60%) |
| Site of application-no mass, ulcer | | | 3 (30%) | 1 (10%) |
| Site of application-no mass, ulcer, multiple | | 1 (10%) | 4 (40%) | 5 (50%) |
| **Respiratory System** | | | | |
| Lung | (10) | (10) | (10) | (10) |
| Inflammation, chronic active | 2 (20%) | 2 (20%) | 1 (10%) | 4 (40%) |
| Alveolus, infiltration cellular, mononuclear cell | 5 (50%) | 8 (80%) | 7 (70%) | 8 (80%) |
| Nose | (10) | (10) | (10) | (10) |
| Nasolacrimal duct, inflammation, suppurative | | 1 (10%) | | |
| **Special Senses System** | | | | |
| Eye | (1) | (2) | | |
| Lens, cataract | 1 (100%) | 2 (100%) | | |
| Retina, atrophy | 1 (100%) | 2 (100%) | | |
| **Urinary System** | | | | |
| Kidney | (10) | (10) | (10) | (10) |
| Nephropathy, chronic | 9 (90%) | 8 (80%) | 8 (80%) | 4 (40%) |
| Cortex, cyst | | | 1 (10%) | |
| ***Systems Examined with No Lesions Observed*** | | | | |
| **General Body System** | | | | |
| **Musculoskeletal System** | | | | |
| **Nervous System** | | | | |

**TABLE B4**
**Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Dermal Study of Triethanolamine**
(continued)

| | 0 mg/kg | 63 mg/kg | 125 mg/kg | 250 mg/kg |
|---|---|---|---|---|
| ***2-Year Study*** | | | | |
| **Alimentary System** | | | | |
| Esophagus | (50) | (50) | (50) | (50) |
| Perforation | 2 (4%) | | | |
| Intestine large, colon | (50) | (50) | (50) | (50) |
| Parasite metazoan | 1 (2%) | 4 (8%) | 2 (4%) | 2 (4%) |
| Intestine large, rectum | (50) | (50) | (50) | (50) |
| Parasite metazoan | 2 (4%) | 7 (14%) | 6 (12%) | 5 (10%) |
| Intestine large, cecum | (50) | (50) | (50) | (50) |
| Inflammation, suppurative | | | | 1 (2%) |
| Parasite metazoan | 1 (2%) | | | |
| Intestine small, jejunum | (50) | (50) | (50) | (50) |
| Necrosis, coagulative | | | 1 (2%) | |
| Liver | (50) | (50) | (50) | (50) |
| Angiectasis | 1 (2%) | 3 (6%) | 3 (6%) | |
| Basophilic focus | 21 (42%) | 27 (54%) | 29 (58%) | 11 (22%) |
| Clear cell focus | 1 (2%) | 2 (4%) | | |
| Eosinophilic focus | 2 (4%) | 1 (2%) | 5 (10%) | 5 (10%) |
| Hepatodiaphragmatic nodule | 8 (16%) | 11 (22%) | 10 (20%) | 2 (4%) |
| Inflammation, chronic | 14 (28%) | 14 (28%) | 23 (46%) | 17 (34%) |
| Inflammation, necrotizing | 1 (2%) | 1 (2%) | | |
| Mixed cell focus | | 2 (4%) | 1 (2%) | 1 (2%) |
| Necrosis, coagulative | 2 (4%) | 1 (2%) | | 1 (2%) |
| Bile duct, hyperplasia | 11 (22%) | 11 (22%) | 15 (30%) | 11 (22%) |
| Hepatocyte, vacuolization cytoplasmic | 3 (6%) | 2 (4%) | 5 (10%) | 4 (8%) |
| Kupffer cell, hypertrophy | | 1 (2%) | | |
| Mesentery | (3) | (2) | (2) | (2) |
| Fat, inflammation, necrotizing | 2 (67%) | 2 (100%) | | |
| Perivascular, inflammation, chronic active | | | 1 (50%) | 1 (50%) |
| Pancreas | (50) | (50) | (50) | (50) |
| Acinus, atrophy | 5 (10%) | 8 (16%) | 17 (34%) | 5 (10%) |
| Artery, inflammation, chronic active | 1 (2%) | | 1 (2%) | |
| Perivascular, inflammation, chronic active | | | 1 (2%) | |
| Salivary glands | (50) | (50) | (50) | (50) |
| Duct, ectasia | | | 1 (2%) | |
| Stomach, forestomach | (50) | (50) | (50) | (50) |
| Inflammation, necrotizing | 2 (4%) | 4 (8%) | 2 (4%) | 3 (6%) |
| Epithelium, hyperplasia | 3 (6%) | 2 (4%) | 1 (2%) | 3 (6%) |
| Stomach, glandular | (50) | (50) | (50) | (50) |
| Erosion | 1 (2%) | 3 (6%) | 1 (2%) | 1 (2%) |
| Inflammation, necrotizing | 1 (2%) | | | |
| **Cardiovascular System** | | | | |
| Blood vessel | (50) | (50) | (50) | (50) |
| Aorta, polyarteritis, chronic | | | 1 (2%) | |
| Mesenteric artery, polyarteritis, chronic | | | 1 (2%) | |
| Heart | (50) | (50) | (50) | (50) |
| Cardiomyopathy, chronic | 32 (64%) | 24 (48%) | 32 (64%) | 26 (52%) |
| Inflammation, chronic active | 1 (2%) | | | |
| Atrium, thrombosis | 2 (4%) | 3 (6%) | | 4 (8%) |

**Table B4**
**Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Dermal Study of Triethanolamine**
(continued)

| | 0 mg/kg | 63 mg/kg | 125 mg/kg | 250 mg/kg |
|---|---|---|---|---|
| ***2-Year Study*** (continued) | | | | |
| **Endocrine System** | | | | |
| Adrenal cortex | (50) | (50) | (50) | (50) |
| Degeneration, fatty | 15 (30%) | 15 (30%) | 19 (38%) | 11 (22%) |
| Hyperplasia | 15 (30%) | 21 (42%) | 17 (34%) | 6 (12%) |
| Hypertrophy | 2 (4%) | | 2 (4%) | 1 (2%) |
| Karyomegaly | | | 1 (2%) | |
| Necrosis, coagulative | 1 (2%) | | 1 (2%) | |
| Adrenal medulla | (50) | (50) | (50) | (49) |
| Hyperplasia | 9 (18%) | 8 (16%) | 4 (8%) | 4 (8%) |
| Islets, pancreatic | (50) | (50) | (50) | (50) |
| Hyperplasia | | | | 1 (2%) |
| Parathyroid gland | (41) | (48) | (47) | (43) |
| Cyst | | | 1 (2%) | |
| Hyperplasia | | | | 1 (2%) |
| Pituitary gland | (50) | (50) | (50) | (50) |
| Craniopharyngeal duct, pars distalis, cyst | 1 (2%) | 1 (2%) | | |
| Pars distalis, angiectasis | 37 (74%) | 35 (70%) | 36 (72%) | 29 (58%) |
| Pars distalis, cyst | 24 (48%) | 14 (28%) | 25 (50%) | 17 (34%) |
| Pars distalis, hyperplasia | 15 (30%) | 18 (36%) | 18 (36%) | 12 (24%) |
| Pars distalis, pigmentation, hemosiderin | 33 (66%) | 29 (58%) | 27 (54%) | 22 (44%) |
| Thyroid gland | (50) | (50) | (50) | (49) |
| C-cell, hyperplasia | 8 (16%) | 4 (8%) | 10 (20%) | 2 (4%) |
| Follicle, cyst | | | 1 (2%) | |
| Follicular cell, hyperplasia | | 1 (2%) | | |
| **General Body System** | | | | |
| None | | | | |
| **Genital System** | | | | |
| Clitoral gland | (48) | (49) | (50) | (50) |
| Hyperplasia | 2 (4%) | 8 (16%) | 4 (8%) | 1 (2%) |
| Inflammation, chronic active | 11 (23%) | 16 (33%) | 18 (36%) | 8 (16%) |
| Duct, dilatation | 2 (4%) | 1 (2%) | 4 (8%) | 3 (6%) |
| Ovary | (50) | (50) | (50) | (50) |
| Atrophy | 1 (2%) | | | |
| Cyst | 2 (4%) | 4 (8%) | 4 (8%) | 2 (4%) |
| Hematocyst | 1 (2%) | | | |
| Uterus | (50) | (50) | (50) | (50) |
| Hyperplasia, cystic, glandular | 1 (2%) | | | |
| Horn, dilatation | | | | 3 (6%) |
| Lumen, hemorrhage | 1 (2%) | | | 1 (2%) |

**Table B4**
**Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Dermal Study of Triethanolamine** (continued)

| | 0 mg/kg | 63 mg/kg | 125 mg/kg | 250 mg/kg |
|---|---|---|---|---|
| ***2-Year Study*** (continued) | | | | |
| **Hematopoietic System** | | | | |
| Bone marrow | (50) | (50) | (50) | (50) |
| Hyperplasia | 2 (4%) | 2 (4%) | 1 (2%) | 4 (8%) |
| Myelofibrosis | | 1 (2%) | | |
| Lymph node | (6) | (5) | (6) | (3) |
| Mediastinal, pigmentation, hemosiderin | | | 1 (17%) | |
| Mediastinal, sinus, infiltration cellular, mononuclear cell | | | 1 (17%) | |
| Lymph node, mandibular | (49) | (50) | (50) | (50) |
| Inflammation, necrotizing | | 1 (2%) | | |
| Inflammation, suppurative | 1 (2%) | | | |
| Sinus, ectasia | | | 1 (2%) | |
| Lymph node, mesenteric | (50) | (50) | (49) | (50) |
| Inflammation, chronic active | 1 (2%) | | | |
| Spleen | (50) | (50) | (50) | (50) |
| Fibrosis | 2 (4%) | | | 2 (4%) |
| Hematopoietic cell proliferation | 2 (4%) | 1 (2%) | | 1 (2%) |
| Infiltration cellular, lipocyte | | 1 (2%) | | |
| Red pulp, atrophy | 1 (2%) | | 1 (2%) | |
| Thymus | (49) | (47) | (47) | (48) |
| Fibrosis | | | | 1 (2%) |
| Granuloma | | | 1 (2%) | |
| **Integumentary System** | | | | |
| Mammary gland | (50) | (50) | (50) | (50) |
| Hyperplasia, cystic | 42 (84%) | 39 (78%) | 42 (84%) | 37 (74%) |
| Inflammation, chronic active | 1 (2%) | | | |
| Skin | (50) | (50) | (50) | (50) |
| Epidermis, site of application-no mass, erosion | 1 (2%) | 6 (12%) | 16 (32%) | 14 (28%) |
| Face, abscess | 1 (2%) | | | |
| Head, acanthosis | | | | 2 (4%) |
| Head, inflammation, chronic active | 1 (2%) | | | 2 (4%) |
| Head, ulcer | | | | 1 (2%) |
| Inguinal, acanthosis | 1 (2%) | 1 (2%) | | |
| Inguinal, inflammation, chronic active | 2 (4%) | 1 (2%) | 2 (4%) | 1 (2%) |
| Site of application-no mass, acanthosis | 2 (4%) | 10 (20%) | 30 (60%) | 32 (64%) |
| Site of application-no mass, inflammation, chronic active | 2 (4%) | 10 (20%) | 30 (60%) | 32 (64%) |
| Site of application-no mass, ulcer | | | 4 (8%) | 8 (16%) |
| Site of application-no mass, ulcer, multiple | 2 (4%) | 7 (14%) | 18 (36%) | 19 (38%) |
| Tail, acanthosis | | | | 1 (2%) |
| Tail, hyperkeratosis | | | | 1 (2%) |
| Tail, inflammation, chronic active | | | | 1 (2%) |
| **Musculoskeletal System** | | | | |
| Bone | (50) | (50) | (50) | (50) |
| Osteopetrosis | | 3 (6%) | 1 (2%) | |
| Maxilla, abscess | | 1 (2%) | | |
| Skeletal muscle | (1) | | | (2) |
| Fibrosis | | | | 1 (50%) |

**TABLE B4**
**Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Dermal Study of Triethanolamine**
(continued)

| | 0 mg/kg | 63 mg/kg | 125 mg/kg | 250 mg/kg |
|---|---|---|---|---|
| ***2-Year Study*** (continued) | | | | |
| **Nervous System** | | | | |
| Brain | (50) | (50) | (50) | (50) |
| Compression | 18 (36%) | 15 (30%) | 15 (30%) | 12 (24%) |
| Hemorrhage | 3 (6%) | | | 1 (2%) |
| Hydrocephalus | 10 (20%) | 9 (18%) | 10 (20%) | 13 (26%) |
| Necrosis | 1 (2%) | | | |
| Peripheral nerve | (2) | | | (1) |
| Sciatic, myelin, degeneration | | | | 1 (100%) |
| **Respiratory System** | | | | |
| Lung | (50) | (50) | (50) | (50) |
| Inflammation, chronic active | 14 (28%) | 16 (32%) | 16 (32%) | 18 (36%) |
| Inflammation, necrotizing | | 1 (2%) | | |
| Metaplasia, osseous | | 1 (2%) | | |
| Pigmentation, hemosiderin | | | | 1 (2%) |
| Alveolar epithelium, hyperplasia | 4 (8%) | | 1 (2%) | 1 (2%) |
| Alveolus, infiltration cellular, mononuclear cell | 29 (58%) | 35 (70%) | 30 (60%) | 26 (52%) |
| Artery, mediastinum, polyarteritis, chronic | | | 1 (2%) | |
| Perivascular, edema | | 1 (2%) | | |
| Nose | (50) | (50) | (50) | (50) |
| Inflammation, chronic active | 9 (18%) | 5 (10%) | 8 (16%) | 1 (2%) |
| Nasolacrimal duct, inflammation, suppurative | 11 (22%) | 8 (16%) | 9 (18%) | 8 (16%) |
| **Special Senses System** | | | | |
| Eye | (1) | (2) | (6) | (1) |
| Lens, cataract | 1 (100%) | 1 (50%) | 5 (83%) | 1 (100%) |
| Retina, atrophy | 1 (100%) | 1 (50%) | 6 (100%) | 1 (100%) |
| **Urinary System** | | | | |
| Kidney | (50) | (50) | (50) | (50) |
| Nephropathy, chronic | 45 (90%) | 44 (88%) | 41 (82%) | 42 (84%) |
| Cortex, cyst | | | 1 (2%) | |
| Renal tubule, hyperplasia | | | | 1 (2%) |

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


TABLE C1 Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Dermal Study of Triethanolamine . . . . . 148

TABLE C2 Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study of Triethanolamine . . . . . 152

TABLE C3 Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Dermal Study of Triethanolamine . . . . . 168

TABLE C4 Historical Incidence of Liver Neoplasms in Control Male $B6C3F_1$ Mice . . . . . 172

TABLE C5 Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Dermal Study of Triethanolamine . . . . . 173

**TABLE C1**
**Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Dermal Study of Triethanolamine[a]**

| | 0 mg/kg | 200 mg/kg | 630 mg/kg | 2,000 mg/kg |
|---|---|---|---|---|
| **Disposition Summary** | | | | |
| Animals initially in study | 60 | 60 | 60 | 60 |
| *15-Month interim evaluation* | 10 | 10 | 10 | 10 |
| Early deaths | | | | |
| Moribund | 2 | 5 | 3 | 6 |
| Natural deaths | 2 | 5 | 8 | 3 |
| Survivors | | | | |
| Died last week of study | | 1 | | |
| Terminal sacrifice | 46 | 39 | 39 | 41 |
| Animals examined microscopically | 60 | 60 | 60 | 60 |
| ***15-Month Interim Evaluation*** | | | | |
| **Alimentary System** | | | | |
| Liver | (10) | (10) | (10) | (10) |
| Hepatocellular carcinoma | 1 (10%) | 2 (20%) | | 1 (10%) |
| Hepatocellular adenoma | | 2 (20%) | 1 (10%) | 4 (40%) |
| Hepatocellular adenoma, multiple | 1 (10%) | | | |
| ***Systems Examined with No Neoplasms Observed*** | | | | |
| **Cardiovascular System** | | | | |
| **Endocrine System** | | | | |
| **General Body System** | | | | |
| **Genital System** | | | | |
| **Hematopoietic System** | | | | |
| **Integumentary System** | | | | |
| **Musculoskeletal System** | | | | |
| **Nervous System** | | | | |
| **Respiratory System** | | | | |
| **Special Senses System** | | | | |
| **Urinary System** | | | | |
| ***2-Year Study*** | | | | |
| **Alimentary System** | | | | |
| Intestine small, duodenum | (50) | (50) | (50) | (50) |
| Polyp adenomatous | 1 (2%) | | | |
| Intestine small, jejunum | (50) | (50) | (50) | (50) |
| Carcinoma | | | | 1 (2%) |
| Liver | (50) | (50) | (50) | (50) |
| Carcinoma, metastatic, pancreas | | 1 (2%) | | |
| Hemangioma | | 1 (2%) | | 1 (2%) |
| Hemangiosarcoma | | 3 (6%) | 1 (2%) | 1 (2%) |
| Hemangiosarcoma, multiple | 2 (4%) | | | |
| Hepatoblastoma | | | | 3 (6%) |
| Hepatocellular carcinoma | 9 (18%) | 12 (24%) | 8 (16%) | 9 (18%) |
| Hepatocellular carcinoma, multiple | 6 (12%) | 8 (16%) | 7 (14%) | 5 (10%) |
| Hepatocellular adenoma | 10 (20%) | 9 (18%) | 12 (24%) | 8 (16%) |
| Hepatocellular adenoma, multiple | 17 (34%) | 18 (36%) | 17 (34%) | 29 (58%) |
| Histiocytic sarcoma | | | | 1 (2%) |

**Table C1**
**Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Dermal Study of Triethanolamine** (continued)

| | 0 mg/kg | 200 mg/kg | 630 mg/kg | 2,000 mg/kg |
|---|---|---|---|---|
| ***2-Year Study*** (continued) | | | | |
| **Alimentary System** (continued) | | | | |
| Mesentery | | (3) | | (1) |
| Carcinoma, metastatic, pancreas | | 1 (33%) | | |
| Hepatoblastoma, metastatic, liver | | | | 1 (100%) |
| Pancreas | (50) | (50) | (50) | (50) |
| Carcinoma | | 1 (2%) | | |
| Stomach, forestomach | (50) | (49) | (50) | (50) |
| Squamous cell carcinoma | | | | 1 (2%) |
| Stomach, glandular | (50) | (50) | (50) | (50) |
| Carcinoid tumor NOS | | 1 (2%) | | |
| **Cardiovascular System** | | | | |
| None | | | | |
| **Endocrine System** | | | | |
| Adrenal cortex | (50) | (50) | (50) | (50) |
| Capsule, spindle cell, adenoma | 1 (2%) | 1 (2%) | | |
| Adrenal medulla | (50) | (50) | (50) | (50) |
| Pheochromocytoma benign | 1 (2%) | | 1 (2%) | 1 (2%) |
| Islets, pancreatic | (50) | (50) | (50) | (50) |
| Adenoma | 1 (2%) | | 1 (2%) | |
| Thyroid gland | (50) | (50) | (50) | (50) |
| Bilateral, follicular cell, adenoma | | | | 1 (2%) |
| Follicular cell, adenoma | 2 (4%) | | | |
| **General Body System** | | | | |
| Tissue NOS | (1) | | | |
| Hemangioma | 1 (100%) | | | |
| **Genital System** | | | | |
| Epididymis | (50) | (50) | (50) | (50) |
| Sarcoma | | | 1 (2%) | |
| Prostate | (50) | (50) | (50) | (50) |
| Hemangiosarcoma | | | | 1 (2%) |
| Seminal vesicle | (50) | (50) | (50) | (50) |
| Carcinoma, metastatic, pancreas | | 1 (2%) | | |
| Testes | (50) | (50) | (50) | (50) |
| Bilateral, interstitial cell, adenoma | | 1 (2%) | | |
| Interstitial cell, adenoma | | 1 (2%) | | |
| **Hematopoietic System** | | | | |
| Lymph node | (2) | (2) | (3) | (1) |
| Lumbar, histiocytic sarcoma | | | 1 (33%) | |
| Mediastinal, carcinoma, metastatic, pancreas | | 1 (50%) | | |
| Mediastinal, hepatocellular carcinoma, metastatic, liver | | 1 (50%) | | |
| Pancreatic, hepatoblastoma, metastatic, liver | | | | 1 (100%) |

**Table C1**
**Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Dermal Study of Triethanolamine** (continued)

| | 0 mg/kg | 200 mg/kg | 630 mg/kg | 2,000 mg/kg |
|---|---|---|---|---|
| ***2-Year Study*** (continued) | | | | |
| **Hematopoietic System** (continued) | | | | |
| Lymph node, mandibular | (47) | (47) | (48) | (48) |
| Lymph node, mesenteric | (46) | (47) | (47) | (48) |
| Hepatoblastoma, metastatic, liver | | | | 1 (2%) |
| Histiocytic sarcoma | | | | 1 (2%) |
| Spleen | (50) | (50) | (50) | (50) |
| Hemangiosarcoma | 1 (2%) | | | 1 (2%) |
| Histiocytic sarcoma | | | | 1 (2%) |
| Thymus | (44) | (36) | (47) | (43) |
| **Integumentary System** | | | | |
| Skin | (50) | (50) | (50) | (50) |
| Neck, basal cell carcinoma | 1 (2%) | | | |
| Neck, subcutaneous tissue, hemangiosarcoma | | 1 (2%) | | |
| Neck, subcutaneous tissue, fat, hemangioma | | | | 1 (2%) |
| Subcutaneous tissue, sarcoma | | | | 1 (2%) |
| **Musculoskeletal System** | | | | |
| Skeletal muscle | (1) | (1) | (1) | |
| Carcinoma, metastatic, pancreas | | 1 (100%) | | |
| Hemangiosarcoma | 1 (100%) | | | |
| **Nervous System** | | | | |
| None | | | | |
| **Respiratory System** | | | | |
| Lung | (50) | (50) | (50) | (50) |
| Alveolar/bronchiolar adenoma | 14 (28%) | 11 (22%) | 14 (28%) | 8 (16%) |
| Alveolar/bronchiolar adenoma, multiple | 1 (2%) | 4 (8%) | | 2 (4%) |
| Alveolar/bronchiolar carcinoma | 2 (4%) | 5 (10%) | 1 (2%) | 1 (2%) |
| Carcinoma, metastatic, pancreas | | 1 (2%) | | |
| Hepatocellular carcinoma, metastatic, liver | 4 (8%) | 6 (12%) | 3 (6%) | 2 (4%) |
| **Special Senses System** | | | | |
| Harderian gland | (4) | (5) | (6) | (1) |
| Adenoma | 4 (100%) | 5 (100%) | 5 (83%) | 1 (100%) |
| **Urinary System** | | | | |
| Kidney | (50) | (50) | (50) | (50) |
| Histiocytic sarcoma | | | | 1 (2%) |
| Renal tubule, adenoma | 1 (2%) | | | 2 (4%) |

**Table C1**
**Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Dermal Study of Triethanolamine** (continued)

| | 0 mg/kg | 200 mg/kg | 630 mg/kg | 2,000 mg/kg |
|---|---|---|---|---|
| ***2-Year Study*** (continued) | | | | |
| **Systemic Lesions** | | | | |
| Multiple organs[b] | (50) | (50) | (50) | (50) |
| Histiocytic sarcoma | | | 1 (2%) | 1 (2%) |
| Leukemia lymphocytic | | | 1 (2%) | |
| Lymphoma malignant lymphocytic | | | 3 (6%) | |
| Lymphoma malignant mixed | 4 (8%) | 1 (2%) | 5 (10%) | 1 (2%) |
| Lymphoma malignant undifferentiated cell | | | 1 (2%) | |
| **Neoplasm Summary** | | | | |
| Total animals with primary neoplasms[c] | | | | |
| 15-Month interim evaluation | 2 | 4 | 1 | 5 |
| 2-Year study | 39 | 45 | 42 | 48 |
| Total primary neoplasms | | | | |
| 15-Month interim evaluation | 2 | 4 | 1 | 5 |
| 2-Year study | 80 | 83 | 79 | 80 |
| Total animals with benign neoplasms | | | | |
| 15-Month interim evaluation | 1 | 2 | 1 | 4 |
| 2-Year study | 35 | 38 | 35 | 41 |
| Total benign neoplasms | | | | |
| 15-Month interim evaluation | 1 | 2 | 1 | 4 |
| 2-Year study | 54 | 51 | 50 | 54 |
| Total animals with malignant neoplasms | | | | |
| 15-Month interim evaluation | 1 | 2 | | 1 |
| 2-Year study | 19 | 28 | 25 | 23 |
| Total malignant neoplasms | | | | |
| 15-Month interim evaluation | 1 | 2 | | 1 |
| 2-Year study | 26 | 31 | 29 | 26 |
| Total animals with metastatic neoplasms | | | | |
| 2-Year study | 4 | 7 | 3 | 3 |
| Total metastatic neoplasms | | | | |
| 2-Year study | 4 | 13 | 3 | 5 |
| Total animals with uncertain neoplasms-benign or malignant | | | | |
| 2-Year study | | 1 | | |
| Total uncertain neoplasms | | | | |
| 2-Year study | | 1 | | |

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

**TABLE C2**
**Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study of Triethanolamine: 0 mg/kg**

| | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Number of Days on Study** | 367 | 616 | 678 | 712 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 730 | 730 | 730 | 730 | 730 | 730 | 730 | 730 | 730 |
| **Carcass ID Number** | 023 | 005 | 003 | 054 | 002 | 007 | 016 | 017 | 025 | 032 | 035 | 047 | 050 | 051 | 056 | 057 | 001 | 021 | 022 | 039 | 040 | 042 | 045 | 055 | 058 |
| **Alimentary System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Esophagus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Gallbladder | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine large, colon | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine large, rectum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine large, cecum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine small, duodenum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Polyp adenomatous | | | | | | | | | | | X | | | | | | | | | | | | | | |
| Intestine small, jejunum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine small, ileum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Liver | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Hemangiosarcoma, multiple | | | | | | | | | X | | | | | | | | | | | | | | | | |
| Hepatocellular carcinoma | | | X | X | | | | | | X | | | | | | | | X | | | | | | | |
| Hepatocellular carcinoma, multiple | | | | | X | | | | X | | | | | | | | | | | | | | | | |
| Hepatocellular adenoma | X | | X | | | | | | X | | | | X | | | | | | | X | | | X | | |
| Hepatocellular adenoma, multiple | | X | | X | X | X | | | | X | X | | | | X | X | | | | | X | | | | |
| Pancreas | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Salivary glands | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Stomach, forestomach | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Stomach, glandular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Cardiovascular System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Blood vessel | + | + | + | + | + | + | + | + | + | + | + | + | M | + | + | + | + | M | + | + | + | + | M | + | + |
| Heart | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Endocrine System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Adrenal cortex | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Capsule, spindle cell, adenoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Adrenal medulla | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Pheochromocytoma benign | | | | | | | | | | | | | | | | | | | | X | | | | | |
| Islets, pancreatic | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Adenoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Parathyroid gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | M | + | + | M | + | + | + | + |
| Pituitary gland | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Thyroid gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Follicular cell, adenoma | | | | | | | | | X | | | | | X | | | | | | | | | | | |
| **General Body System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Tissue NOS | | | | | | | | | | | | | | | | | | | | | | | | | |
| Hemangioma | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Genital System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Epididymis | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Preputial gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Prostate | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Seminal vesicle | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Testes | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |

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

**TABLE C2**
**Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study of Triethanolamine: 0 mg/kg**
(continued)

| **Number of Days on Study** | 731 | 731 | 731 | 731 | 731 | 731 | 731 | 731 | 731 | 731 | 731 | 731 | 731 | 731 | 731 | 732 | 732 | 732 | 732 | 732 | 732 | 732 | 732 | 732 | 732 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 004 | 006 | 013 | 014 | 019 | 026 | 036 | 037 | 041 | 043 | 046 | 048 | 049 | 053 | 060 | 008 | 009 | 011 | 012 | 024 | 028 | 029 | 031 | 033 | 059 | Total Tissues/ Tumors |
| **Alimentary System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Esophagus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Gallbladder | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Intestine large, colon | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Intestine large, rectum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Intestine large, cecum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Intestine small, duodenum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Polyp adenomatous | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Intestine small, jejunum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Intestine small, ileum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Liver | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Hemangiosarcoma, multiple | | | | | | | | | | | | | | | | | | | X | | | | | | | 2 |
| Hepatocellular carcinoma | | | | | | X | | | | | | | X | | X | | | X | | | | | | X | | 9 |
| Hepatocellular carcinoma, multiple | | | | | | | X | | | | | X | | | | | | | X | | | | X | | | 6 |
| Hepatocellular adenoma | | | | | | X | X | | | | | | | | X | | X | | | | | | | | | 10 |
| Hepatocellular adenoma, multiple | X | X | | | | | | | | | | | X | X | | | | | X | X | X | | X | | | 17 |
| Pancreas | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Salivary glands | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Stomach, forestomach | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Stomach, glandular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Cardiovascular System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Blood vessel | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 47 |
| Heart | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Endocrine System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Adrenal cortex | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Capsule, spindle cell, adenoma | | | | | | | | | | | | | | | | | | | | | X | | | | | 1 |
| Adrenal medulla | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Pheochromocytoma benign | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Islets, pancreatic | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Adenoma | | | | | | | | | | | | | | | | | | | | X | | | | | | 1 |
| Parathyroid gland | + | + | + | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | 47 |
| Pituitary gland | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 48 |
| Thyroid gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Follicular cell, adenoma | | | | | | | | | | | | | | | | | | | | | | | | | | 2 |
| **General Body System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Tissue NOS | + | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Hemangioma | X | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| **Genital System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Epididymis | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Preputial gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Prostate | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Seminal vesicle | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Testes | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |

**TABLE C2**
**Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study of Triethanolamine: 0 mg/kg**
(continued)

| Number of Days on Study | 367 | 616 | 678 | 712 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 730 | 730 | 730 | 730 | 730 | 730 | 730 | 730 | 730 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 023 | 005 | 003 | 054 | 002 | 007 | 016 | 017 | 025 | 032 | 035 | 047 | 050 | 051 | 056 | 057 | 001 | 021 | 022 | 039 | 040 | 042 | 045 | 055 | 058 |
| **Hematopoietic System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone marrow | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Lymph node | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lymph node, mandibular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | M | + | + |
| Lymph node, mesenteric | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | M | + | + | M | + | + | + | + |
| Spleen | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Hemangiosarcoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Thymus | + | + | M | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Integumentary System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Mammary gland | M | M | M | M | M | M | M | M | M | M | M | M | M | M | M | M | M | M | M | M | M | M | M | M | M |
| Skin | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Neck, basal cell carcinoma | | | | | | | | | | | | | | | | | | X | | | | | | | |
| **Musculoskeletal System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Skeletal muscle | | | | | | | | | | | | | | | | | | | | | | | | | |
| Hemangiosarcoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Nervous System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Brain | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Respiratory System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lung | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Alveolar/bronchiolar adenoma | | | | | | X | | | | X | X | | X | | X | | | | | X | | X | | | |
| Alveolar/bronchiolar adenoma, multiple | | | | | | | | | | | | | | | | | | | X | | | | | | |
| Alveolar/bronchiolar carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Hepatocellular carcinoma, metastatic, liver | | | | | | | | | | | | | | | | | | | | | | | | | |
| Nose | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Trachea | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Special Senses System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Harderian gland | | | | | | | | | | | | | | | | + | | | | | | + | | | + |
| Adenoma | | | | | | | | | | | | | | | | X | | | | | | X | | | X |
| **Urinary System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Kidney | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Renal tubule, adenoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Urinary bladder | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Systemic Lesions** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Multiple organs | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Lymphoma malignant mixed | | | | | | X | | | | | | | | | | | | | | | | | | | |

**TABLE C2**
**Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study of Triethanolamine: 0 mg/kg**
(continued)

| Number of Days on Study | 731 | 731 | 731 | 731 | 731 | 731 | 731 | 731 | 731 | 731 | 731 | 731 | 731 | 731 | 731 | 732 | 732 | 732 | 732 | 732 | 732 | 732 | 732 | 732 | 732 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 004 | 006 | 013 | 014 | 019 | 026 | 036 | 037 | 041 | 043 | 046 | 048 | 049 | 053 | 060 | 008 | 009 | 011 | 012 | 024 | 028 | 029 | 031 | 033 | 059 | Total Tissues/ Tumors |
| **Hematopoietic System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone marrow | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Lymph node | | | | | | | + | | | | | | | | | | + | | | | | | | | | 2 |
| Lymph node, mandibular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | | + | + | + | + | + | + | + | M | 47 |
| Lymph node, mesenteric | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 46 |
| Spleen | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Hemangiosarcoma | | | | | | | | | | | | | | | | | | | X | | | | | | | 1 |
| Thymus | M | + | + | + | + | + | + | + | + | + | + | + | + | M | + | + | + | + | M | + | + | + | M | + | + | 44 |
| **Integumentary System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Mammary gland | M | M | M | M | M | M | M | M | M | M | M | M | M | M | M | M | M | M | M | M | M | M | M | M | M | |
| Skin | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Neck, basal cell carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| **Musculoskeletal System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Skeletal muscle | | | | | | | | | | | | | | | | | | | + | | | | | | | 1 |
| Hemangiosarcoma | | | | | | | | | | | | | | | | | | | X | | | | | | | 1 |
| **Nervous System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Brain | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Respiratory System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lung | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Alveolar/bronchiolar adenoma | X | | | | | X | | | | X | | | | | X | | | | | X | | X | | X | | 14 |
| Alveolar/bronchiolar adenoma, multiple | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Alveolar/bronchiolar carcinoma | | | | | | | | | | X | | | | | | | | | X | | | | | | | 2 |
| Hepatocellular carcinoma, metastatic, liver | | | | | | X | X | | | | | X | | | | | | | | | | | | X | | 4 |
| Nose | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Trachea | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Special Senses System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Harderian gland | + | | | | | | | | | | | | | | | | | | | | | | | | | 4 |
| Adenoma | X | | | | | | | | | | | | | | | | | | | | | | | | | 4 |
| **Urinary System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Kidney | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Renal tubule, adenoma | | | | | | | | X | | | | | | | | | | | | | | | | | | 1 |
| Urinary bladder | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Systemic Lesions** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Multiple organs | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Lymphoma malignant mixed | | | | | | | X | | | | | | | | | | X | | | | | | | | X | 4 |

**TABLE C2**
**Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study of Triethanolamine: 200 mg/kg**

| **Number of Days on Study** | 5 | 5 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1 | 3 | 2 | 6 | 6 | 6 | 8 | 8 | 8 | 1 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 3 | 3 | 3 | 3 | 3 |
| | 5 | 7 | 1 | 5 | 6 | 7 | 2 | 3 | 8 | 6 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 0 | 0 | 0 | 0 | 0 |
| **Carcass ID Number** | 0 | 0 | 0 | 1 | 0 | 0 | 1 | 1 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 1 | 0 | 0 | 0 | 1 | 1 |
| | 6 | 9 | 7 | 1 | 7 | 7 | 0 | 1 | 1 | 1 | 7 | 7 | 8 | 9 | 9 | 0 | 0 | 0 | 1 | 1 | 7 | 7 | 9 | 0 | 0 |
| | 9 | 3 | 6 | 1 | 4 | 1 | 7 | 4 | 6 | 5 | 0 | 2 | 0 | 0 | 6 | 0 | 1 | 8 | 0 | 7 | 8 | 9 | 7 | 3 | 5 |
| **Alimentary System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Esophagus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Gallbladder | + | + | + | + | + | + | + | M | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine large, colon | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine large, rectum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine large, cecum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine small, duodenum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine small, jejunum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine small, ileum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Liver | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Carcinoma, metastatic, pancreas | | | | | | X | | | | | | | | | | | | | | | | | | | |
| Hemangioma | | | | | | X | | | | | | | | | | | | | | | | | | | |
| Hemangiosarcoma | | | | | | | | | | | | | | | | | X | | X | | | | | | |
| Hepatocellular carcinoma | | X | | X | X | | | X | | | | | | | X | X | X | | | | | | | | |
| Hepatocellular carcinoma, multiple | | | X | | | | X | | | | | X | | | | | | | | | | | | X | |
| Hepatocellular adenoma | | | | | | | X | | | | | | X | | | | | | | | | X | X | | |
| Hepatocellular adenoma, multiple | | | | X | | | | | | X | X | | | X | X | X | X | | | X | | | | X | |
| Mesentery | | | | | | + | | | | | | | | | | | | | | | | | | | + |
| Carcinoma, metastatic, pancreas | | | | | | X | | | | | | | | | | | | | | | | | | | |
| Pancreas | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Carcinoma | | | | | | X | | | | | | | | | | | | | | | | | | | |
| Salivary glands | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Stomach, forestomach | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Stomach, glandular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Carcinoid tumor NOS | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Cardiovascular System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Blood vessel | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Heart | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Endocrine System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Adrenal cortex | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Capsule, spindle cell, adenoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Adrenal medulla | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Islets, pancreatic | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Parathyroid gland | + | + | M | + | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | M |
| Pituitary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + |
| Thyroid gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **General Body System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| None | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Genital System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Epididymis | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Preputial gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Prostate | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Seminal vesicle | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Carcinoma, metastatic, pancreas | | | | | | X | | | | | | | | | | | | | | | | | | | |
| Testes | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Bilateral, interstitial cell, adenoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Interstitial cell, adenoma | | | | | | | | | | | | | | | | | | | | | | | | | |

**Table C2**
**Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study of Triethanolamine: 200 mg/kg**
(continued)

| Number of Days on Study | 7<br>3<br>0 | 7<br>3<br>0 | 7<br>3<br>0 | 7<br>3<br>1 | 7<br>3<br>1 | 7<br>3<br>1 | 7<br>3<br>1 | 7<br>3<br>1 | 7<br>3<br>1 | 7<br>3<br>1 | 7<br>3<br>1 | 7<br>3<br>1 | 7<br>3<br>1 | 7<br>3<br>1 | 7<br>3<br>1 | 7<br>3<br>1 | 7<br>3<br>1 | 7<br>3<br>1 | 7<br>3<br>2 | 7<br>3<br>2 | 7<br>3<br>2 | 7<br>3<br>2 | 7<br>3<br>2 | 7<br>3<br>2 | 7<br>3<br>2 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 1<br>0<br>6 | 1<br>1<br>2 | 1<br>1<br>3 | 0<br>6<br>3 | 0<br>6<br>5 | 0<br>6<br>7 | 0<br>8<br>2 | 0<br>8<br>4 | 0<br>8<br>5 | 0<br>8<br>6 | 0<br>8<br>7 | 0<br>8<br>8 | 0<br>8<br>9 | 0<br>9<br>1 | 0<br>9<br>5 | 0<br>9<br>8 | 1<br>0<br>4 | 1<br>2<br>0 | 0<br>6<br>1 | 0<br>6<br>2 | 0<br>6<br>4 | 0<br>6<br>8 | 0<br>9<br>9 | 1<br>0<br>9 | 1<br>1<br>8 | Total<br>Tissues/<br>Tumors |
| **Alimentary System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Esophagus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Gallbladder | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 48 |
| Intestine large, colon | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Intestine large, rectum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Intestine large, cecum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Intestine small, duodenum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Intestine small, jejunum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Intestine small, ileum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Liver | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Carcinoma, metastatic, pancreas | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Hemangioma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Hemangiosarcoma | | | | | | | | | | | X | | | | | | | | | | | | | | | 3 |
| Hepatocellular carcinoma | | | | X | | | | | | | | | X | | | | | X | | X | | | X | | | 12 |
| Hepatocellular carcinoma, multiple | X | | | | X | | | | | | | X | | | X | | | | | | | | | | | 8 |
| Hepatocellular adenoma | | | | | | | | | X | X | | | | | | | | X | | X | X | | | | | 9 |
| Hepatocellular adenoma, multiple | X | | | X | | | | | | | X | | X | | X | X | X | | | | | | X | | X | 18 |
| Mesentery | | | | | | | | | | | | | | + | | | | | | | | | | | | 3 |
| Carcinoma, metastatic, pancreas | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Pancreas | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Salivary glands | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Stomach, forestomach | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | | + | + | + | 49 |
| Stomach, glandular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Carcinoid tumor NOS | | | X | | | | | | | | | | | | | | | | | | | | | | | 1 |
| **Cardiovascular System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Blood vessel | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Heart | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Endocrine System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Adrenal cortex | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Capsule, spindle cell, adenoma | | | | | | | | | | | | | | | | | | | | | | X | | | | 1 |
| Adrenal medulla | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Islets, pancreatic | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Parathyroid gland | + | + | M | + | + | + | + | + | + | + | + | M | + | + | M | + | + | + | + | + | + | + | + | + | + | 44 |
| Pituitary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Thyroid gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **General Body System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| None | | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Genital System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Epididymis | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Preputial gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Prostate | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Seminal vesicle | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Carcinoma, metastatic, pancreas | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Testes | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Bilateral, interstitial cell, adenoma | | | | | | | | | | | | | | | | | | X | | | | | | | | 1 |
| Interstitial cell, adenoma | | | | | | | | | | | | | | | | | | | | | | X | | | | 1 |

**TABLE C2**
**Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study of Triethanolamine: 200 mg/kg**
(continued)

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

**TABLE C2**
**Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study of Triethanolamine: 200 mg/kg**
(continued)

| Number of Days on Study | 730 | 730 | 730 | 731 | 731 | 731 | 731 | 731 | 731 | 731 | 731 | 731 | 731 | 731 | 731 | 731 | 731 | 731 | 732 | 732 | 732 | 732 | 732 | 732 | 732 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 106 | 112 | 113 | 063 | 065 | 067 | 082 | 084 | 085 | 086 | 087 | 088 | 089 | 091 | 095 | 098 | 104 | 120 | 061 | 062 | 064 | 068 | 099 | 109 | 118 | Total Tissues/ Tumors |
| **Hematopoietic System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone marrow | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Lymph node | | | | | | | | | | | | | | | | | | | | | | | | | | 2 |
| Mediastinal, carcinoma, metastatic, pancreas | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Mediastinal, hepatocellular carcinoma, metastatic, liver | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Lymph node, mandibular | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 47 |
| Lymph node, mesenteric | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | M | + | + | 47 |
| Spleen | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Thymus | M | + | + | + | + | + | + | + | + | M | + | M | M | M | + | + | + | + | + | M | + | + | M | + | M | 36 |
| **Integumentary System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Mammary gland | M | M | M | M | M | M | M | M | M | M | M | M | M | M | M | M | M | M | M | M | M | M | M | M | M | |
| Skin | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Neck, subcutaneous tissue, hemangiosarcoma | | | | | | | | X | | | | | | | | | | | | | | | | | | 1 |
| **Musculoskeletal System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Skeletal muscle | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Carcinoma, metastatic, pancreas | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| **Nervous System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Brain | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Peripheral nerve | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Spinal cord | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| **Respiratory System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lung | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Alveolar/bronchiolar adenoma | X | X | | | X | X | | | | | | X | | X | X | | X | | | | | X | | | | 11 |
| Alveolar/bronchiolar adenoma, multiple | | | X | X | | | | | | | | | | | | | | | | | X | | | | | 4 |
| Alveolar/bronchiolar carcinoma | | | | | | | X | | | | | | | | | X | | | | | X | | | | | 5 |
| Carcinoma, metastatic, pancreas | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Hepatocellular carcinoma, metastatic, liver | | | | | X | | | | | | | X | X | | | | | | | X | | | | | | 6 |
| Nose | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Trachea | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Special Senses System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Ear | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Eye | | | | | | | + | | | | | | | | | | | | | | | | + | | + | 3 |
| Harderian gland | | | | | | | | | | | | | + | | + | | | | | | | | + | | + | 5 |
| Adenoma | | | | | | | | | | | | | X | | X | | | | | | | | X | | X | 5 |
| **Urinary System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Kidney | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Urinary bladder | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Systemic Lesions** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Multiple organs | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Lymphoma malignant mixed | | | | | | | | | | | | | | | | X | | | | | | | | | | 1 |

**Table C2**
**Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study of Triethanolamine: 630 mg/kg**

| Number of Days on Study | 373 | 493 | 507 | 540 | 607 | 645 | 652 | 670 | 674 | 694 | 697 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 730 | 730 | 730 | 730 | 730 | 730 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 152 | 133 | 162 | 122 | 129 | 173 | 158 | 127 | 171 | 151 | 164 | 121 | 135 | 138 | 140 | 156 | 159 | 170 | 175 | 126 | 142 | 143 | 150 | 153 | 157 |
| **Alimentary System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Esophagus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Gallbladder | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + |
| Intestine large, colon | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine large, rectum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine large, cecum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine small, duodenum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine small, jejunum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine small, ileum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Liver | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Hemangiosarcoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Hepatocellular carcinoma | | | X | | | | | X | X | | X | | | | | | | | | | | | | | |
| Hepatocellular carcinoma, multiple | | | | | X | | | | | X | | X | X | | | | | | | X | | | | | |
| Hepatocellular adenoma | | | | | X | | | | | | | | | X | X | | | | X | | X | | X | | |
| Hepatocellular adenoma, multiple | | | | | | | | X | | X | X | X | X | | | | | X | | X | | X | | | |
| Pancreas | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Salivary glands | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Stomach, forestomach | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Stomach, glandular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Cardiovascular System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Blood vessel | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Heart | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Endocrine System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Adrenal cortex | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Adrenal medulla | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Pheochromocytoma benign | | | | | | | | | | | | | | | | | | | | | | | | | |
| Islets, pancreatic | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Adenoma | | | | | | | | | | | | | | | | | | | | | | X | | | |
| Parathyroid gland | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Pituitary gland | + | + | M | + | + | + | M | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | M | + | + |
| Thyroid gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **General Body System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| None | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Genital System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Epididymis | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Sarcoma | | | | | | | | | | | | | | | | | | | | | X | | | | |
| Preputial gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Prostate | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Seminal vesicle | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Testes | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Hematopoietic System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone marrow | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Lymph node | | | | | | | | | | | | | | | | | | + | | + | | | | | |
| Lumbar, histiocytic sarcoma | | | | | | | | | | | | | | | | | | X | | | | | | | |
| Lymph node, mandibular | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | M | + | + |
| Lymph node, mesenteric | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Spleen | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Thymus | + | + | + | + | M | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + |

**Table C2**
**Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study of Triethanolamine: 630 mg/kg**
(continued)

| Number of Days on Study | 730 | 730 | 730 | 731 | 731 | 731 | 731 | 731 | 731 | 731 | 731 | 731 | 731 | 731 | 732 | 732 | 732 | 732 | 732 | 732 | 732 | 732 | 732 | 732 | 732 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 166 | 174 | 176 | 124 | 132 | 144 | 148 | 149 | 154 | 155 | 160 | 163 | 169 | 180 | 123 | 125 | 131 | 136 | 141 | 147 | 161 | 165 | 167 | 177 | 179 | Total Tissues/ Tumors |
| **Alimentary System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Esophagus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Gallbladder | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Intestine large, colon | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Intestine large, rectum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Intestine large, cecum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Intestine small, duodenum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Intestine small, jejunum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Intestine small, ileum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Liver | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Hemangiosarcoma | | | | | | | | X | | | | | | | | | | | | | | | | | | 1 |
| Hepatocellular carcinoma | | | | | | | | | | X | X | | | | | | | | | | | | | X | X | 8 |
| Hepatocellular carcinoma, multiple | X | | | | | | | | | | | | | | | | | | | | X | | | | | 7 |
| Hepatocellular adenoma | | | | X | | | | | | | | | | | | | | X | X | X | X | | | X | | 12 |
| Hepatocellular adenoma, multiple | X | | | | X | | X | | X | X | | X | X | | X | | X | | | | | | | | | 17 |
| Pancreas | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Salivary glands | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Stomach, forestomach | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Stomach, glandular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Cardiovascular System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Blood vessel | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Heart | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Endocrine System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Adrenal cortex | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Adrenal medulla | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Pheochromocytoma benign | | | | | X | | | | | | | | | | | | | | | | | | | | | 1 |
| Islets, pancreatic | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Adenoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Parathyroid gland | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 48 |
| Pituitary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 46 |
| Thyroid gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **General Body System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| None | | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Genital System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Epididymis | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Sarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Preputial gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Prostate | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Seminal vesicle | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Testes | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Hematopoietic System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone marrow | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | M | + | 48 |
| Lymph node | | | | | | | | | | | | | | | | + | | | | | | | | | | 3 |
| Lumbar, histiocytic sarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Lymph node, mandibular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 48 |
| Lymph node, mesenteric | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | M | + | + | + | 47 |
| Spleen | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Thymus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | M | + | + | + | + | 47 |

**Table C2**
**Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study of Triethanolamine: 630 mg/kg**
(continued)

| Number of Days on Study | 373 | 493 | 507 | 540 | 607 | 645 | 652 | 670 | 677 | 694 | 697 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 730 | 730 | 730 | 730 | 730 | 730 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 152 | 133 | 162 | 122 | 129 | 173 | 158 | 127 | 171 | 151 | 164 | 121 | 135 | 138 | 140 | 156 | 159 | 170 | 175 | 126 | 142 | 143 | 150 | 153 | 157 |
| **Integumentary System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Mammary gland | M | M | M | M | M | M | M | M | M | M | M | M | M | M | M | M | M | M | M | M | M | M | M | M | M |
| Skin | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Musculoskeletal System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Skeletal muscle | | | | | | | + | | | | | | | | | | | | | | | | | | |
| **Nervous System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Brain | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Peripheral nerve | | | | | | | | | | | | | | | | | | | | | | | | | |
| Spinal cord | | + | | | | | | | | | | | | | | | | | | | | | | | |
| **Respiratory System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lung | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Alveolar/bronchiolar adenoma | | | | | | | | | | | | X | | | | X | | X | | | X | | | X | |
| Alveolar/bronchiolar carcinoma | | | | | | | | | X | | | | | | | | | | | | | | | | |
| Hepatocellular carcinoma, metastatic, liver | | | | | | | | | | | | | X | | | | | | | | | | | | |
| Nose | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Trachea | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Special Senses System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Ear | | + | | | | | | | | | | | | | | | | | | | | | | | |
| Eye | | | | | | | | | | | | | | | | | | | | | | | | | |
| Harderian gland | | | | | | | | | | + | | | | | | | | | | | | | | | |
| Adenoma | | | | | | | | | | X | | | | | | | | | | | | | | | |
| **Urinary System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Kidney | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Urinary bladder | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Systemic Lesions** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Multiple organs | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Histiocytic sarcoma | | | | | | | | | | | | | | | | | | X | | | | | | | |
| Leukemia lymphocytic | | | | | | | X | | | | | | | | | | | | | | | | | | |
| Lymphoma malignant lymphocytic | | | | | | X | | | | | | | | | | | | | | X | | | | | |
| Lymphoma malignant mixed | | | | | | | | | | | | X | | | | | | X | | | | | X | | |
| Lymphoma malignant undifferentiated cell type | | | | | | | | | | | | | | | | | | | | | | | | | |

**TABLE C2**
**Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study of Triethanolamine: 630 mg/kg**
(continued)

| **Number of Days on Study** | 730 | 730 | 730 | 731 | 731 | 731 | 731 | 731 | 731 | 731 | 731 | 731 | 731 | 731 | 732 | 732 | 732 | 732 | 732 | 732 | 732 | 732 | 732 | 732 | 732 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 166 | 174 | 176 | 124 | 132 | 144 | 148 | 149 | 154 | 155 | 160 | 163 | 169 | 180 | 123 | 125 | 131 | 136 | 141 | 147 | 161 | 165 | 167 | 177 | 179 | Total Tissues/ Tumors |
| **Integumentary System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Mammary gland | M | M | M | M | M | M | M | M | M | M | M | M | M | M | M | M | M | M | M | M | M | M | M | M | M | |
| Skin | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Musculoskeletal System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | M | + | 48 |
| Skeletal muscle | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| **Nervous System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Brain | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Peripheral nerve | | | | | | + | | | | | | | | | | | | | | | | | | | | 1 |
| Spinal cord | | | | | | + | | | | | | | | | | | | | | | | | | | | 2 |
| **Respiratory System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lung | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Alveolar/bronchiolar adenoma | X | | X | | X | | | X | X | | | | X | | | | X | | | | X | X | | | | 14 |
| Alveolar/bronchiolar carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Hepatocellular carcinoma, metastatic, liver | X | | | | | | | | | X | | | | | | | | | | | | | | | | 3 |
| Nose | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | M | + | 48 |
| Trachea | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Special Senses System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Ear | | | | | | | | | | | | | + | | | | | | | | | | | | | 2 |
| Eye | | | | | | + | | | | | | | | | | | | | | | | | | | | 1 |
| Harderian gland | | + | | | | + | + | | | | | | | | | | + | | | + | | | | | | 6 |
| Adenoma | | | | | | X | X | | | | | | | | | | X | | | X | | | | | | 5 |
| **Urinary System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Kidney | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Urinary bladder | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Systemic Lesions** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Multiple organs | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Histiocytic sarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Leukemia lymphocytic | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Lymphoma malignant lymphocytic | | | | | | | | | | | | | | | | X | | | | | | | | | | 3 |
| Lymphoma malignant mixed | | | | | | X | | | | | | | | | | | | | X | | | | | | | 5 |
| Lymphoma malignant undifferentiated cell type | | | X | | | | | | | | | | | | | | | | | | | | | | | 1 |

**TABLE C2**
**Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study of Triethanolamine: 2,000 mg/kg**

| Number of Days on Study | 572 | 579 | 606 | 655 | 670 | 675 | 678 | 712 | 724 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 730 | 730 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 210 | 219 | 218 | 181 | 205 | 214 | 239 | 202 | 222 | 183 | 184 | 190 | 195 | 196 | 197 | 198 | 206 | 217 | 220 | 227 | 228 | 229 | 234 | 188 | 199 |
| **Alimentary System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Esophagus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Gallbladder | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine large, colon | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine large, rectum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine large, cecum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine small, duodenum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine small, jejunum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Intestine small, ileum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Liver | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Hemangioma | | | | | | | | | | | X | | | | | | | | | | | | | | |
| Hemangiosarcoma | | | | | | | | | | | | | | | | | | | X | | | | | | |
| Hepatoblastoma | | | | | | X | | | | | | | | | X | | | | | | | | | | |
| Hepatocellular carcinoma | X | | | | X | X | | | | | | | | | | | | | | | | | X | | |
| Hepatocellular carcinoma, multiple | | | X | | | | | X | | | | | | X | | | | | | | X | X | | | |
| Hepatocellular adenoma | X | | | X | | X | | | X | | | | | | | | | | | | X | | | | X |
| Hepatocellular adenoma, multiple | | X | | | | | | X | | X | | X | X | X | X | | X | X | | X | | X | | X | |
| Histiocytic sarcoma | | | | | | | X | | | | | | | | | | | | | | | | | | |
| Mesentery | | | | | | + | | | | | | | | | | | | | | | | | | | |
| Hepatoblastoma, metastatic, liver | | | | | | X | | | | | | | | | | | | | | | | | | | |
| Pancreas | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Salivary glands | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Stomach, forestomach | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Squamous cell carcinoma | | | | | | | | | | | | | | | | X | | | | | | | | | |
| Stomach, glandular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Cardiovascular System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Blood vessel | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Heart | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Endocrine System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Adrenal cortex | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Adrenal medulla | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Pheochromocytoma benign | | | | | | | | | | | | | | | | | | | | | | X | | | |
| Islets, pancreatic | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Parathyroid gland | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Pituitary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Thyroid gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Bilateral, follicular cell, adenoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| **General Body System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| None | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Genital System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Epididymis | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Preputial gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Prostate | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Hemangiosarcoma | | | | | | | | | | | | | | | | | | | X | | | | | | |
| Seminal vesicle | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Testes | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |

**TABLE C2**
**Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study of Triethanolamine: 2,000 mg/kg**
(continued)

| Number of Days on Study | 730 | 730 | 730 | 730 | 730 | 730 | 730 | 730 | 730 | 731 | 731 | 731 | 731 | 731 | 731 | 731 | 731 | 731 | 731 | 732 | 732 | 732 | 732 | 732 | 732 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 200 | 201 | 204 | 212 | 215 | 216 | 231 | 235 | 240 | 186 | 192 | 211 | 213 | 223 | 224 | 225 | 226 | 230 | 232 | 182 | 185 | 203 | 221 | 236 | 237 | Total Tissues/ Tumors |
| **Alimentary System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Esophagus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Gallbladder | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Intestine large, colon | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Intestine large, rectum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Intestine large, cecum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Intestine small, duodenum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Intestine small, jejunum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Carcinoma | | | | | | X | | | | | | | | | | | | | | | | | | | | 1 |
| Intestine small, ileum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Liver | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Hemangioma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Hemangiosarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Hepatoblastoma | | | | | | | | | | | | X | | | | | | | | | | | | | | 3 |
| Hepatocellular carcinoma | X | | X | | X | | | | | X | | | | | | | X | | | | | | | | | 9 |
| Hepatocellular carcinoma, multiple | | | | | | | | | | | | | | | | | | | | | | | | | | 5 |
| Hepatocellular adenoma | | | | X | | | | | | | | | | | | | | | | | X | | | | | 8 |
| Hepatocellular adenoma, multiple | | X | X | | | | | X | | X | X | X | X | X | X | X | X | X | X | X | | X | X | | X | 29 |
| Histiocytic sarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Mesentery | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Hepatoblastoma, metastatic, liver | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Pancreas | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Salivary glands | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Stomach, forestomach | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Squamous cell carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Stomach, glandular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Cardiovascular System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Blood vessel | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Heart | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Endocrine System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Adrenal cortex | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Adrenal medulla | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Pheochromocytoma benign | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Islets, pancreatic | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Parathyroid gland | M | M | + | + | + | + | M | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | 45 |
| Pituitary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | I | + | + | + | + | + | 49 |
| Thyroid gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Bilateral, follicular cell, adenoma | | | | | | | | X | | | | | | | | | | | | | | | | | | 1 |
| **General Body System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| None | | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Genital System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Epididymis | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Preputial gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Prostate | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Hemangiosarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Seminal vesicle | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Testes | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |

**TABLE C2**
**Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study of Triethanolamine: 2,000 mg/kg**
(continued)

| Number of Days on Study | 572 | 579 | 606 | 655 | 670 | 675 | 678 | 712 | 724 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 730 | 730 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 210 | 219 | 218 | 181 | 205 | 214 | 239 | 202 | 222 | 183 | 184 | 190 | 195 | 196 | 197 | 198 | 206 | 217 | 220 | 227 | 228 | 229 | 234 | 188 | 199 |
| **Hematopoietic System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone marrow | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Lymph node | | | | | | + | | | | | | | | | | | | | | | | | | | |
| Pancreatic, hepatoblastoma, metastatic, liver | | | | | | X | | | | | | | | | | | | | | | | | | | |
| Lymph node, mandibular | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Lymph node, mesenteric | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Hepatoblastoma, metastatic, liver | | | | | | X | | | | | | | | | | | | | | | | | | | |
| Histiocytic sarcoma | | | | | | | X | | | | | | | | | | | | | | | | | | |
| Spleen | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Hemangiosarcoma | | | | | | | | | | | | | | | | | | | X | | | | | | |
| Histiocytic sarcoma | | | | | | | X | | | | | | | | | | | | | | | | | | |
| Thymus | M | I | + | M | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Integumentary System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Mammary gland | M | M | M | M | M | M | M | M | M | M | M | M | M | M | M | M | M | M | M | M | M | M | M | M | M |
| Skin | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Neck, subcutaneous tissue, fat, hemangioma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Subcutaneous tissue, sarcoma | | | | | | | | | | | | | | | | | | | | | | | | X | |
| **Musculoskeletal System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Nervous System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Brain | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Peripheral nerve | | | | | + | | | | | | | | | | | | | | | | | | | | |
| Spinal cord | | | | | + | | | | | | | | | | | | | | | | | | | | |
| **Respiratory System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lung | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Alveolar/bronchiolar adenoma | | | | | | X | | | | | X | | | | | | | | | | | X | | | |
| Alveolar/bronchiolar adenoma, multiple | | | | | | | | | | | | | | | | | | | | | | | | | |
| Alveolar/bronchiolar carcinoma | | X | | | | | | | | | | | | | | | | | | | | | | | |
| Hepatocellular carcinoma, metastatic, liver | | | | | X | | | | | | | | | | | | | | | | | X | | | |
| Nose | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Trachea | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Special Senses System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Ear | | | | | + | | | | | | | | | | | + | | | | | | | | | |
| Harderian gland | | | + | | | | | | | | | | | | | | | | | | | | | | |
| Adenoma | | | X | | | | | | | | | | | | | | | | | | | | | | |
| **Urinary System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Kidney | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Histiocytic sarcoma | | | | | | | X | | | | | | | | | | | | | | | | | | |
| Renal tubule, adenoma | | | | | | | | | | | | | | | | | | | | | | | | X | |
| Urinary bladder | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Systemic Lesions** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Multiple organs | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Histiocytic sarcoma | | | | | | | X | | | | | | | | | | | | | | | | | | |
| Lymphoma malignant mixed | | | | | | | | | | | | | | | | | | | | | | | | | |

**TABLE C2**
**Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study of Triethanolamine: 2,000 mg/kg**
(continued)

| Number of Days on Study | 730 | 730 | 730 | 730 | 730 | 730 | 730 | 730 | 730 | 731 | 731 | 731 | 731 | 731 | 731 | 731 | 731 | 731 | 731 | 732 | 732 | 732 | 732 | 732 | 732 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 200 | 201 | 204 | 212 | 215 | 216 | 231 | 235 | 240 | 186 | 192 | 211 | 213 | 223 | 224 | 225 | 226 | 230 | 232 | 182 | 185 | 203 | 221 | 236 | 237 | Total Tissues/ Tumors |
| **Hematopoietic System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone marrow | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + | 49 |
| Lymph node | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Pancreatic, hepatoblastoma, metastatic, liver | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Lymph node, mandibular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | M | 48 |
| Lymph node, mesenteric | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 48 |
| Hepatoblastoma, metastatic, liver | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Histiocytic sarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Spleen | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Hemangiosarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Histiocytic sarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Thymus | M | + | M | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 43 |
| **Integumentary System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Mammary gland | M | M | M | M | M | M | M | M | M | M | M | M | M | M | M | M | M | M | M | M | M | M | M | M | M | |
| Skin | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Neck, subcutaneous tissue, fat, hemangioma | | | | | | X | | | | | | | | | | | | | | | | | | | | 1 |
| Subcutaneous tissue, sarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| **Musculoskeletal System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + | 49 |
| **Nervous System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Brain | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Peripheral nerve | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Spinal cord | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| **Respiratory System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lung | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Alveolar/bronchiolar adenoma | | | X | | | X | | | X | | | | | | | | X | | | X | | | | | | 8 |
| Alveolar/bronchiolar adenoma, multiple | | | | | | | | | | | | X | | | | | | | X | | | | | | | 2 |
| Alveolar/bronchiolar carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Hepatocellular carcinoma, metastatic, liver | | | | | | | | | | | | | | | | | | | | | | | | | | 2 |
| Nose | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + | 49 |
| Trachea | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Special Senses System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Ear | | | | | | | | | | | | | | | | | | | | | | | | | | 2 |
| Harderian gland | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Adenoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| **Urinary System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Kidney | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Histiocytic sarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Renal tubule, adenoma | | | X | | | | | | | | | | | | | | | | | | | | | | | 2 |
| Urinary bladder | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Systemic Lesions** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Multiple organs | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Histiocytic sarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Lymphoma malignant mixed | | | | | | | | | | | | | X | | | | | | | | | | | | | 1 |

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

| | 0 mg/kg | 200 mg/kg | 630 mg/kg | 2,000 mg/kg |
|---|---|---|---|---|
| **Harderian Gland: Adenoma** | | | | |
| Overall rate[a] | 4/50 (8%) | 5/50 (10%) | 5/50 (10%) | 1/50 (2%) |
| Adjusted rate[b] | 8.7% | 12.5% | 12.4% | 2.1% |
| Terminal rate[c] | 4/46 (9%) | 5/40 (13%) | 4/39 (10%) | 0/41 (0%) |
| First incidence (days) | 729 (T) | 729 (T) | 694 | 606 |
| Life table test[d] | P=0.113N | P=0.413 | P=0.400 | P=0.212N |
| Logistic regression test[d] | P=0.097N | P=0.413 | P=0.432 | P=0.180N |
| Cochran-Armitage test[d] | P=0.096N | | | |
| Fisher exact test[d] | | P=0.500 | P=0.500 | P=0.181N |
| **Liver: Hemangiosarcoma** | | | | |
| Overall rate | 2/50 (4%) | 3/50 (6%) | 1/50 (2%) | 1/50 (2%) |
| Adjusted rate | 4.3% | 7.5% | 2.6% | 2.4% |
| Terminal rate | 2/46 (4%) | 3/40 (8%) | 1/39 (3%) | 1/41 (2%) |
| First incidence (days) | 729 (T) | 729 (T) | 729 (T) | 729 (T) |
| Life table test | P=0.333N | P=0.436 | P=0.558N | P=0.540N |
| Logistic regression test | P=0.333N | P=0.436 | P=0.558N | P=0.540N |
| Cochran-Armitage test | P=0.311N | | | |
| Fisher exact test | | P=0.500 | P=0.500N | P=0.500N |
| **Liver: Hepatocellular Adenoma** | | | | |
| Overall rate | 27/50 (54%) | 27/50 (54%) | 29/50 (58%) | 37/50 (74%) |
| Adjusted rate | 54.0% | 62.7% | 67.4% | 78.6% |
| Terminal rate | 23/46 (50%) | 24/40 (60%) | 25/39 (64%) | 31/41 (76%) |
| First incidence (days) | 367 | 665 | 607 | 572 |
| Life table test | P=0.009 | P=0.320 | P=0.158 | P=0.013 |
| Logistic regression test | P=0.012 | P=0.571 | P=0.359 | P=0.034 |
| Cochran-Armitage test | P=0.013 | | | |
| Fisher exact test | | P=0.579N | P=0.420 | P=0.030 |
| **Liver: Hepatocellular Carcinoma** | | | | |
| Overall rate | 15/50 (30%) | 20/50 (40%) | 15/50 (30%) | 14/50 (28%) |
| Adjusted rate | 31.2% | 43.0% | 33.2% | 30.0% |
| Terminal rate | 13/46 (28%) | 14/40 (35%) | 9/39 (23%) | 9/41 (22%) |
| First incidence (days) | 678 | 537 | 507 | 572 |
| Life table test | P=0.347N | P=0.118 | P=0.396 | P=0.545 |
| Logistic regression test | P=0.175N | P=0.207 | P=0.585 | P=0.494N |
| Cochran-Armitage test | P=0.274N | | | |
| Fisher exact test | | P=0.201 | P=0.586N | P=0.500N |
| **Liver: Hepatoblastoma** | | | | |
| Overall rate | 0/50 (0%) | 0/50 (0%) | 0/50 (0%) | 3/50 (6%) |
| Adjusted rate | 0.0% | 0.0% | 0.0% | 7.0% |
| Terminal rate | 0/46 (0%) | 0/40 (0%) | 0/39 (0%) | 2/41 (5%) |
| First incidence (days) | —[e] | — | — | 675 |
| Life table test | P=0.008 | —[f] | — | P=0.106 |
| Logistic regression test | P=0.009 | — | — | P=0.121 |
| Cochran-Armitage test | P=0.009 | | | |
| Fisher exact test | | — | — | P=0.121 |

**TABLE C3**
**Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Dermal Study of Triethanolamine** (continued)

| | 0 mg/kg | 200 mg/kg | 630 mg/kg | 2,000 mg/kg |
|---|---|---|---|---|
| **Liver: Hepatocellular Carcinoma or Hepatoblastoma** | | | | |
| Overall rate | 15/50 (30%) | 20/50 (40%) | 15/50 (30%) | 16/50 (32%) |
| Adjusted rate | 31.2% | 43.0% | 33.2% | 34.4% |
| Terminal rate | 13/46 (28%) | 14/40 (35%) | 9/39 (23%) | 11/41 (27%) |
| First incidence (days) | 678 | 537 | 507 | 572 |
| Life table test | P=0.528N | P=0.118 | P=0.396 | P=0.376 |
| Logistic regression test | P=0.344N | P=0.207 | P=0.585 | P=0.505 |
| Cochran-Armitage test | P=0.462N | | | |
| Fisher exact test | | P=0.201 | P=0.586N | P=0.500 |
| **Liver: Hepatocellular Adenoma, Hepatocellular Carcinoma, or Hepatoblastoma** | | | | |
| Overall rate | 31/50 (62%) | 34/50 (68%) | 33/50 (66%) | 42/50 (84%) |
| Adjusted rate | 62.0% | 72.2% | 73.3% | 85.7% |
| Terminal rate | 27/46 (59%) | 27/40 (68%) | 27/39 (69%) | 34/41 (83%) |
| First incidence (days) | 367 | 537 | 507 | 572 |
| Life table test | P=0.011 | P=0.139 | P=0.137 | P=0.006 |
| Logistic regression test | P=0.009 | P=0.359 | P=0.377 | P=0.018 |
| Cochran-Armitage test | P=0.009 | | | |
| Fisher exact test | | P=0.338 | P=0.418 | P=0.012 |
| **Lung: Alveolar/bronchiolar Adenoma** | | | | |
| Overall rate | 15/50 (30%) | 15/50 (30%) | 14/50 (28%) | 10/50 (20%) |
| Adjusted rate | 32.6% | 36.4% | 35.9% | 23.7% |
| Terminal rate | 15/46 (33%) | 14/40 (35%) | 14/39 (36%) | 9/41 (22%) |
| First incidence (days) | 729 (T) | 621 | 729 (T) | 675 |
| Life table test | P=0.160N | P=0.410 | P=0.465 | P=0.274N |
| Logistic regression test | P=0.137N | P=0.503 | P=0.465 | P=0.224N |
| Cochran-Armitage test | P=0.123N | | | |
| Fisher exact test | | P=0.586N | P=0.500N | P=0.178N |
| **Lung: Alveolar/bronchiolar Carcinoma** | | | | |
| Overall rate | 2/50 (4%) | 5/50 (10%) | 1/50 (2%) | 1/50 (2%) |
| Adjusted rate | 4.3% | 11.7% | 2.4% | 2.0% |
| Terminal rate | 2/46 (4%) | 3/40 (8%) | 0/39 (0%) | 0/41 (0%) |
| First incidence (days) | 729 (T) | 666 | 677 | 579 |
| Life table test | P=0.210N | P=0.175 | P=0.554N | P=0.527N |
| Logistic regression test | P=0.194N | P=0.217 | P=0.505N | P=0.525N |
| Cochran-Armitage test | P=0.191N | | | |
| Fisher exact test | | P=0.218 | P=0.500N | P=0.500N |
| **Lung: Alveolar/bronchiolar Adenoma or Carcinoma** | | | | |
| Overall rate | 16/50 (32%) | 19/50 (38%) | 15/50 (30%) | 11/50 (22%) |
| Adjusted rate | 34.8% | 43.9% | 37.4% | 25.2% |
| Terminal rate | 16/46 (35%) | 16/40 (40%) | 14/39 (36%) | 9/41 (22%) |
| First incidence (days) | 729 (T) | 621 | 677 | 579 |
| Life table test | P=0.113N | P=0.186 | P=0.453 | P=0.286N |
| Logistic regression test | P=0.081N | P=0.287 | P=0.489 | P=0.193N |
| Cochran-Armitage test | P=0.078N | | | |
| Fisher exact test | | P=0.338 | P=0.500N | P=0.184N |

**Table C3**
**Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Dermal Study of Triethanolamine** (continued)

| | 0 mg/kg | 200 mg/kg | 630 mg/kg | 2,000 mg/kg |
|---|---|---|---|---|
| **All Organs: Hemangiosarcoma** | | | | |
| Overall rate | 2/50 (4%) | 4/50 (8%) | 1/50 (2%) | 1/50 (2%) |
| Adjusted rate | 4.3% | 10.0% | 2.6% | 2.4% |
| Terminal rate | 2/46 (4%) | 4/40 (10%) | 1/39 (3%) | 1/41 (2%) |
| First incidence (days) | 729 (T) | 729 (T) | 729 (T) | 729 (T) |
| Life table test | P=0.265N | P=0.275 | P=0.558N | P=0.540N |
| Logistic regression test | P=0.265N | P=0.275 | P=0.558N | P=0.540N |
| Cochran-Armitage test | P=0.244N | | | |
| Fisher exact test | | P=0.339 | P=0.500N | P=0.500N |
| **All Organs: Hemangioma or Hemangiosarcoma** | | | | |
| Overall rate | 3/50 (6%) | 5/50 (10%) | 1/50 (2%) | 3/50 (6%) |
| Adjusted rate | 6.5% | 12.0% | 2.6% | 7.3% |
| Terminal rate | 3/46 (7%) | 4/40 (10%) | 1/39 (3%) | 3/41 (7%) |
| First incidence (days) | 729 (T) | 667 | 729 (T) | 729 (T) |
| Life table test | P=0.513N | P=0.289 | P=0.366N | P=0.609 |
| Logistic regression test | P=0.493N | P=0.341 | P=0.366N | P=0.609 |
| Cochran-Armitage test | P=0.485N | | | |
| Fisher exact test | | P=0.357 | P=0.309N | P=0.661N |
| **All Organs: Malignant Lymphoma (Lymphocytic, Mixed, or Undifferentiated Cell Type)** | | | | |
| Overall rate | 4/50 (8%) | 1/50 (2%) | 9/50 (18%) | 1/50 (4%) |
| Adjusted rate | 8.7% | 2.5% | 22.3% | 2.4% |
| Terminal rate | 4/46 (9%) | 1/40 (3%) | 8/39 (21%) | 1/41 (2%) |
| First incidence (days) | 729 (T) | 729 (T) | 645 | 729 (T) |
| Life table test | P=0.251N | P=0.224N | P=0.068 | P=0.216N |
| Logistic regression test | P=0.232N | P=0.224N | P=0.086 | P=0.216N |
| Cochran-Armitage test | P=0.225N | | | |
| Fisher exact test | | P=0.181N | P=0.117 | P=0.181N |
| **All Organs: Benign Neoplasms** | | | | |
| Overall rate | 36/50 (72%) | 38/50 (76%) | 35/50 (70%) | 41/50 (82%) |
| Adjusted rate | 72.0% | 84.4% | 81.4% | 85.4% |
| Terminal rate | 32/46 (70%) | 33/40 (83%) | 31/39 (79%) | 34/41 (83%) |
| First incidence (days) | 367 | 621 | 607 | 572 |
| Life table test | P=0.093 | P=0.123 | P=0.231 | P=0.061 |
| Logistic regression test | P=0.152 | P=0.391 | P=0.551 | P=0.191 |
| Cochran-Armitage test | P=0.153 | | | |
| Fisher exact test | | P=0.410 | P=0.500N | P=0.171 |
| **All Organs: Malignant Neoplasms** | | | | |
| Overall rate | 20/50 (40%) | 28/50 (56%) | 25/50 (50%) | 23/50 (46%) |
| Adjusted rate | 41.7% | 58.2% | 53.2% | 47.7% |
| Terminal rate | 18/46 (39%) | 20/40 (50%) | 17/39 (44%) | 16/41 (39%) |
| First incidence (days) | 678 | 537 | 507 | 572 |
| Life table test | P=0.497 | P=0.038 | P=0.089 | P=0.222 |
| Logistic regression test | P=0.353N | P=0.163 | P=0.297 | P=0.351 |
| Cochran-Armitage test | P=0.507N | | | |
| Fisher exact test | | P=0.080 | P=0.211 | P=0.343 |

**TABLE C3**
**Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Dermal Study of Triethanolamine** (continued)

| | 0 mg/kg | 200 mg/kg | 630 mg/kg | 2,000 mg/kg |
|---|---|---|---|---|
| **All Organs: Benign or Malignant Neoplasms** | | | | |
| Overall rate | 40/50 (80%) | 45/50 (90%) | 42/50 (84%) | 48/50 (96%) |
| Adjusted rate | 80.0% | 91.8% | 89.4% | 96.0% |
| Terminal rate | 36/46 (78%) | 36/40 (90%) | 34/39 (87%) | 39/41 (95%) |
| First incidence (days) | 367 | 537 | 507 | 572 |
| Life table test | P=0.039 | P=0.029 | P=0.068 | P=0.008 |
| Logistic regression test | P=0.028 | P=0.130 | P=0.311 | P=0.025 |
| Cochran-Armitage test | P=0.028 | | | |
| Fisher exact test | | P=0.131 | P=0.398 | P=0.014 |

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

**TABLE C4**
**Historical Incidence of Liver Neoplasms in Control Male B6C3F$_1$ Mice[a]**

| Study | Incidence in Controls: Hepatocellular Adenoma | Hepatocellular Carcinoma | Hepatoblastoma | Hepatocellular Adenoma, Hepatocellular Carcinoma, or Hepatoblastoma |
|---|---|---|---|---|
| **Historical Incidence in Dermal Studies (with Acetone Vehicle) at Battelle Columbus Laboratories** | | | | |
| 4-Vinyl-1-cyclohexene diepoxide | 18/50 | 6/50 | 0/50 | 23/50 |
| Triethanolamine | 27/50 | 15/50 | 0/50 | 31/50 |
| **Overall Historical Incidence in Dermal Studies (with Acetone Vehicle)** | | | | |
| Total | 51/150 (34.0%) | 25/150 (16.7%) | 0/150 | 63/150 (42.0%) |
| Standard deviation | 21.1% | 11.7% | | 22.3% |
| Range | 12%-54% | 8%-30% | | 18%-62% |
| **Overall Historical Incidence in Feed Studies** | | | | |
| Total | 344/1,316 (26.1%) | 220/1,316 (16.7%) | 0/1,316 | 509/1,316 (38.7%) |
| Standard deviation | 13.2% | 7.2% | | 13.9% |
| Range | 4%-60% | 3%-29% | | 10%-68% |

[a] Data as of 17 June 1994

**TABLE C5**
**Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Dermal Study of Triethanolamine**[a]

| | 0 mg/kg | 200 mg/kg | 630 mg/kg | 2,000 mg/kg |
|---|---|---|---|---|
| **Disposition Summary** | | | | |
| Animals initially in study | 60 | 60 | 60 | 60 |
| ***15-Month interim evaluation*** | 10 | 10 | 10 | 10 |
| Early deaths | | | | |
| Moribund | 2 | 5 | 3 | 6 |
| Natural deaths | 2 | 5 | 8 | 3 |
| Survivors | | | | |
| Died last week of study | | 1 | | |
| Terminal sacrifice | 46 | 39 | 39 | 41 |
| Animals examined microscopically | 60 | 60 | 60 | 60 |
| ***15-Month Interim Evaluation*** | | | | |
| **Alimentary System** | | | | |
| Liver | (10) | (10) | (10) | (10) |
| Basophilic focus | | 1 (10%) | 1 (10%) | |
| Clear cell focus | | 1 (10%) | | |
| Eosinophilic focus | | | | 1 (10%) |
| Karyomegaly | 2 (20%) | 1 (10%) | 1 (10%) | 2 (20%) |
| Mixed cell focus | | | | 2 (20%) |
| Hepatocyte, cytoplasmic alteration | 2 (20%) | 1 (10%) | 1 (10%) | 2 (20%) |
| Hepatocyte, cytoplasmic alteration, focal | | | 1 (10%) | |
| Hepatocyte, vacuolization cytoplasmic, multifocal | 4 (40%) | 6 (60%) | 3 (30%) | 6 (60%) |
| Oval cell, hyperplasia | 2 (20%) | 1 (10%) | 1 (10%) | 3 (30%) |
| Pancreas | (10) | (10) | (10) | (10) |
| Acinus, atrophy | | | 1 (10%) | |
| Stomach, forestomach | (10) | (10) | (10) | (10) |
| Acanthosis | | | 1 (10%) | |
| Stomach, glandular | (10) | (10) | (10) | (10) |
| Dysplasia | 1 (10%) | | | |
| **Endocrine System** | | | | |
| Adrenal cortex | (10) | (10) | (10) | (10) |
| Capsule, accessory adrenal cortical nodule | | | 1 (10%) | |
| Capsule, hyperplasia | | 1 (10%) | | |
| Parathyroid gland | (8) | (8) | (8) | (9) |
| Cyst | 1 (13%) | | | |
| Pituitary gland | (10) | (10) | (10) | (10) |
| Pars distalis, cyst | | 1 (10%) | | |
| **Genital System** | | | | |
| Preputial gland | (10) | (10) | (10) | (10) |
| Duct, ectasia | 1 (10%) | 3 (30%) | 1 (10%) | 1 (10%) |

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

**TABLE C5**
**Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Dermal Study of Triethanolamine** (continued)

| | 0 mg/kg | 200 mg/kg | 630 mg/kg | 2,000 mg/kg |
|---|---|---|---|---|
| ***15-Month Interim Evaluation*** (continued) | | | | |
| **Integumentary System** | | | | |
| Skin | (10) | (10) | (10) | (10) |
| Ulcer | | | 1 (10%) | |
| Site of application-no mass, acanthosis | | 1 (10%) | 1 (10%) | 6 (60%) |
| Site of application-no mass, inflammation, chronic | | | 2 (20%) | 5 (50%) |
| **Respiratory System** | | | | |
| Lung | (10) | (10) | (10) | (10) |
| Alveolus, hemorrhage, multifocal | 1 (10%) | | | |
| **Urinary System** | | | | |
| Kidney | (10) | (10) | (10) | (10) |
| Nephropathy, chronic | 7 (70%) | 9 (90%) | 10 (100%) | 9 (90%) |
| ***Systems Examined with No Lesions Observed*** | | | | |
| **Cardiovascular System** | | | | |
| **General Body System** | | | | |
| **Hematopoietic System** | | | | |
| **Musculoskeletal System** | | | | |
| **Nervous System** | | | | |
| **Special Senses System** | | | | |
| ***2-Year Study*** | | | | |
| **Alimentary System** | | | | |
| Gallbladder | (50) | (48) | (49) | (49) |
| Cyst | 1 (2%) | | | |
| Intestine small, jejunum | (50) | (50) | (50) | (50) |
| Peyer's patch, hyperplasia, lymphoid | | | | 1 (2%) |
| Liver | (50) | (50) | (50) | (50) |
| Basophilic focus | 7 (14%) | 2 (4%) | 3 (6%) | 3 (6%) |
| Clear cell focus | 13 (26%) | 10 (20%) | 7 (14%) | 5 (10%) |
| Congestion | | 1 (2%) | | |
| Cyst | | | 1 (2%) | |
| Cytoplasmic alteration | 10 (20%) | 17 (34%) | 10 (20%) | 16 (32%) |
| Eosinophilic focus | 10 (20%) | 17 (34%) | 11 (22%) | 23 (46%) |
| Fatty change | | | 1 (2%) | |
| Hematopoietic cell proliferation | 1 (2%) | | 1 (2%) | 1 (2%) |
| Infiltration cellular, lymphocyte | | 1 (2%) | | |
| Karyomegaly | 11 (22%) | 17 (34%) | 9 (18%) | 16 (32%) |
| Mixed cell focus | 2 (4%) | | | 1 (2%) |
| Necrosis | 1 (2%) | | | 2 (4%) |
| Thrombosis | 1 (2%) | | | |
| Bile duct, hyperplasia | 2 (4%) | 2 (4%) | | 1 (2%) |
| Hepatocyte, cytoplasmic alteration | 1 (2%) | | | |
| Hepatocyte, necrosis | | 1 (2%) | | |
| Kupffer cell, hyperplasia | | 1 (2%) | | |
| Oval cell, hyperplasia | 10 (20%) | 14 (28%) | 9 (18%) | 16 (32%) |

**TABLE C5**
**Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Dermal Study of Triethanolamine**
(continued)

| | 0 mg/kg | 200 mg/kg | 630 mg/kg | 2,000 mg/kg |
|---|---|---|---|---|
| ***2-Year Study*** (continued) | | | | |
| **Alimentary System** (continued) | | | | |
| Mesentery | | (3) | | (1) |
| Fat, inflammation, chronic | | 2 (67%) | | |
| Pancreas | (50) | (50) | (50) | (50) |
| Infiltration cellular, histiocyte | | | | 1 (2%) |
| Acinus, atrophy | | 3 (6%) | | |
| Artery, inflammation, chronic | | 1 (2%) | | |
| Duct, cyst | | 1 (2%) | | |
| Stomach, forestomach | (50) | (49) | (50) | (50) |
| Acanthosis | 1 (2%) | | | 1 (2%) |
| Ulcer | 2 (4%) | | | |
| Stomach, glandular | (50) | (50) | (50) | (50) |
| Dysplasia | 1 (2%) | | | |
| Hyperplasia | | 1 (2%) | | |
| Pigmentation | | 1 (2%) | | |
| **Cardiovascular System** | | | | |
| Heart | (50) | (50) | (50) | (50) |
| Degeneration, chronic | 1 (2%) | 1 (2%) | | 1 (2%) |
| Atrium, thrombosis | | | | 1 (2%) |
| Coronary artery, polyarteritis, chronic | | 2 (4%) | | |
| **Endocrine System** | | | | |
| Adrenal cortex | (50) | (50) | (50) | (50) |
| Angiectasis | 1 (2%) | | | |
| Developmental malformation | 1 (2%) | | | 1 (2%) |
| Hyperplasia | 1 (2%) | 2 (4%) | 1 (2%) | 3 (6%) |
| Hypertrophy | 17 (34%) | 14 (28%) | 16 (32%) | 7 (14%) |
| Necrosis | | 1 (2%) | | 2 (4%) |
| Thrombosis | | | 1 (2%) | |
| Vacuolization cytoplasmic | 7 (14%) | 1 (2%) | | 2 (4%) |
| Capsule, accessory adrenal cortical nodule | | 1 (2%) | 1 (2%) | 1 (2%) |
| Capsule, cyst | | | 1 (2%) | |
| Capsule, spindle cell, hyperplasia | 10 (20%) | 4 (8%) | 7 (14%) | 4 (8%) |
| Adrenal medulla | (50) | (50) | (50) | (50) |
| Hyperplasia | 2 (4%) | 3 (6%) | | 1 (2%) |
| Necrosis | | | | 1 (2%) |
| Parathyroid gland | (47) | (44) | (48) | (45) |
| Cyst | | 1 (2%) | | |
| Pituitary gland | (48) | (49) | (46) | (49) |
| Pars distalis, cyst | 2 (4%) | | 1 (2%) | 3 (6%) |
| Pars distalis, hyperplasia | 2 (4%) | 1 (2%) | 1 (2%) | |
| Thyroid gland | (50) | (50) | (50) | (50) |
| Infiltration cellular, lymphocyte | | 1 (2%) | | |
| Polyarteritis, chronic | | 1 (2%) | | |
| Follicle, cyst | 1 (2%) | | | |
| Follicular cell, hyperplasia | 14 (28%) | 12 (24%) | 10 (20%) | 9 (18%) |
| **General Body System** | | | | |
| None | | | | |

**TABLE C5**
**Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Dermal Study of Triethanolamine**
(continued)

| | 0 mg/kg | 200 mg/kg | 630 mg/kg | 2,000 mg/kg |
|---|---|---|---|---|
| ***2-Year Study*** (continued) | | | | |
| **Genital System** | | | | |
| Epididymis | (50) | (50) | (50) | (50) |
| Granuloma sperm | 1 (2%) | 2 (4%) | 1 (2%) | 2 (4%) |
| Artery, inflammation, chronic | | 1 (2%) | | |
| Preputial gland | (50) | (50) | (50) | (50) |
| Inflammation, chronic | 2 (4%) | | 1 (2%) | 2 (4%) |
| Inflammation, chronic active | | | 1 (2%) | 2 (4%) |
| Duct, ectasia | 35 (70%) | 40 (80%) | 30 (60%) | 23 (46%) |
| Prostate | (50) | (50) | (50) | (50) |
| Infiltration cellular, histiocyte | | | | 1 (2%) |
| Inflammation, chronic | | 1 (2%) | | 1 (2%) |
| Seminal vesicle | (50) | (50) | (50) | (50) |
| Inflammation, chronic | 1 (2%) | | | 1 (2%) |
| Artery, inflammation, chronic | | 1 (2%) | | |
| Testes | (50) | (50) | (50) | (50) |
| Congestion | | 1 (2%) | | |
| Germinal epithelium, atrophy | 1 (2%) | 1 (2%) | | |
| Germinal epithelium, mineralization | | | | 1 (2%) |
| **Hematopoietic System** | | | | |
| Bone marrow | (50) | (49) | (48) | (49) |
| Myelofibrosis | 1 (2%) | 1 (2%) | | |
| Lymph node, mandibular | (47) | (47) | (48) | (48) |
| Hyperplasia, lymphoid | | | 1 (2%) | |
| Lymph node, mesenteric | (46) | (47) | (47) | (48) |
| Fibrosis | 1 (2%) | | | |
| Hematopoietic cell proliferation | 1 (2%) | 3 (6%) | 1 (2%) | 1 (2%) |
| Spleen | (50) | (50) | (50) | (50) |
| Congestion | | 1 (2%) | | |
| Hematopoietic cell proliferation | 4 (8%) | 6 (12%) | 4 (8%) | 8 (16%) |
| Thymus | (44) | (36) | (47) | (43) |
| Atrophy | 14 (32%) | 25 (69%) | 19 (40%) | 16 (37%) |
| Cyst | | | | 1 (2%) |
| Infiltration cellular, histiocyte | | | | 1 (2%) |
| **Integumentary System** | | | | |
| Skin | (50) | (50) | (50) | (50) |
| Ulcer | | | 1 (2%) | |
| Hair follicle, sebaceous gland, site of application-no mass, atrophy | | | 1 (2%) | 15 (30%) |
| Inguinal, acanthosis | | | | 1 (2%) |
| Inguinal, inflammation, chronic | | | | 2 (4%) |
| Inguinal, ulcer | | | | 1 (2%) |
| Inguinal, subcutaneous tissue, edema | | | | 1 (2%) |
| Site of application-no mass, acanthosis | 2 (4%) | 1 (2%) | 6 (12%) | 11 (22%) |
| Site of application-no mass, inflammation, chronic | 2 (4%) | | 7 (14%) | 11 (22%) |
| Site of application-no mass, ulcer | 1 (2%) | | 2 (4%) | 2 (4%) |

**Table C5**
**Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Dermal Study of Triethanolamine**
(continued)

| | 0 mg/kg | 200 mg/kg | 630 mg/kg | 2,000 mg/kg |
|---|---|---|---|---|
| ***2-Year Study*** (continued) | | | | |
| **Musculoskeletal System** | | | | |
| Bone | (50) | (49) | (48) | (49) |
| Cranium, hyperostosis | | 1 (2%) | | |
| **Nervous System** | | | | |
| Brain | (50) | (50) | (50) | (50) |
| Pons, necrosis, chronic, focal | | 1 (2%) | | |
| Peripheral nerve | | (1) | (1) | (1) |
| Sciatic, degeneration | | | 1 (100%) | 1 (100%) |
| Spinal cord | | (1) | (2) | (1) |
| Nerve, degeneration | | | 1 (50%) | 1 (100%) |
| White matter, degeneration | | 1 (100%) | | |
| **Respiratory System** | | | | |
| Lung | (50) | (50) | (50) | (50) |
| Inflammation, chronic | 1 (2%) | | 2 (4%) | |
| Alveolar epithelium, hyperplasia | 3 (6%) | 4 (8%) | 2 (4%) | 2 (4%) |
| Alveolar epithelium, hyperplasia, macrophage | 1 (2%) | | | 1 (2%) |
| Mediastinum, infiltration cellular, histiocyte | | | | 1 (2%) |
| **Special Senses System** | | | | |
| Eye | | (3) | (1) | |
| Cornea, inflammation, chronic | | 3 (100%) | | |
| Cornea, inflammation, chronic, proliferative | | | 1 (100%) | |
| Harderian gland | (4) | (5) | (6) | (1) |
| Hyperplasia | | | 1 (17%) | |
| **Urinary System** | | | | |
| Kidney | (50) | (50) | (50) | (50) |
| Hydronephrosis | 2 (4%) | | 1 (2%) | |
| Metaplasia, osseous | 1 (2%) | | | |
| Mineralization | | | 1 (2%) | |
| Nephropathy, chronic | 48 (96%) | 45 (90%) | 45 (90%) | 47 (94%) |
| Cortex, cyst | | 4 (8%) | 4 (8%) | 2 (4%) |

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


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**Table D1**
**Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Dermal Study of Triethanolamine**[a]

| | 0 mg/kg | 100 mg/kg | 300 mg/kg | 1,000 mg/kg |
|---|---|---|---|---|
| **Disposition Summary** | | | | |
| Animals initially in study | 60 | 60 | 60 | 60 |
| ***15-Month interim evaluation*** | 10 | 10 | 10 | 10 |
| Early deaths | | | | |
| Moribund | 7 | 4 | 5 | 11 |
| Natural deaths | 4 | 6 | 7 | 2 |
| Survivors | | | | |
| Died last week of study | 1 | | | |
| Terminal sacrifice | 38 | 40 | 38 | 37 |
| Animals examined microscopically | 60 | 60 | 60 | 60 |
| ***15-Month Interim Evaluation*** | | | | |
| **Alimentary System** | | | | |
| Liver | (10) | (10) | (10) | (10) |
| Hepatocellular adenoma | 2 (20%) | 2 (20%) | 1 (10%) | 1 (10%) |
| **Genital System** | | | | |
| Uterus | (10) | (10) | (9) | (10) |
| Polyp stromal | | | 1 (11%) | 2 (20%) |
| **Respiratory System** | | | | |
| Lung | (10) | (10) | (10) | (10) |
| Alveolar/bronchiolar adenoma | | 1 (10%) | | |
| ***Systems Examined with No Neoplasms Observed*** | | | | |
| **Cardiovascular System** | | | | |
| **Endocrine System** | | | | |
| **General Body System** | | | | |
| **Hematopoietic System** | | | | |
| **Integumentary System** | | | | |
| **Musculoskeletal System** | | | | |
| **Nervous System** | | | | |
| **Special Senses System** | | | | |
| **Urinary System** | | | | |
| ***2-Year Study*** | | | | |
| **Alimentary System** | | | | |
| Intestine small, duodenum | (50) | (50) | (50) | (50) |
| Intestine small, jejunum | (50) | (50) | (50) | (50) |
| Sarcoma, metastatic, skin | | 1 (2%) | | |

**Table D1**
**Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Dermal Study of Triethanolamine** (continued)

| | 0 mg/kg | 100 mg/kg | 300 mg/kg | 1,000 mg/kg |
|---|---|---|---|---|
| ***2-Year Study*** (continued) | | | | |
| **Alimentary System** (continued) | | | | |
| Liver | (50) | (50) | (50) | (50) |
| Hemangioma | | | 1 (2%) | |
| Hemangiosarcoma | | 3 (6%) | | |
| Hepatocellular carcinoma | 1 (2%) | 4 (8%) | 7 (14%) | 5 (10%) |
| Hepatocellular adenoma | 11 (22%) | 13 (26%) | 11 (22%) | 11 (22%) |
| Hepatocellular adenoma, multiple | 11 (22%) | 9 (18%) | 13 (26%) | 29 (58%) |
| Histiocytic sarcoma | | 2 (4%) | 1 (2%) | 3 (6%) |
| Ito cell tumor NOS, multiple | | 1 (2%) | | |
| Mesentery | (2) | (5) | (5) | (5) |
| Histiocytic sarcoma | | | | 1 (20%) |
| Fat, sarcoma, metastatic, skin | | 1 (20%) | | |
| Pancreas | (50) | (50) | (50) | (50) |
| Histiocytic sarcoma | | | | 1 (2%) |
| Sarcoma, metastatic, skin | | 1 (2%) | | |
| Salivary glands | (50) | (50) | (50) | (50) |
| Stomach, forestomach | (50) | (50) | (50) | (50) |
| Squamous cell papilloma | | 1 (2%) | | |
| Stomach, glandular | (50) | (50) | (50) | (50) |
| **Cardiovascular System** | | | | |
| Heart | (50) | (50) | (50) | (50) |
| Sarcoma, metastatic, skin | | | 1 (2%) | |
| **Endocrine System** | | | | |
| Adrenal cortex | (50) | (49) | (50) | (50) |
| Capsule, spindle cell, adenoma | 1 (2%) | | 1 (2%) | 1 (2%) |
| Adrenal medulla | (50) | (50) | (50) | (50) |
| Pheochromocytoma benign | | 1 (2%) | | |
| Islets, pancreatic | (50) | (50) | (50) | (50) |
| Carcinoma | | 1 (2%) | | |
| Pituitary gland | (44) | (49) | (49) | (49) |
| Adenoma | | 1 (2%) | | |
| Pars distalis, adenoma | 4 (9%) | 5 (10%) | 4 (8%) | 5 (10%) |
| Pars intermedia, adenoma | | 1 (2%) | | 2 (4%) |
| Thyroid gland | (50) | (50) | (50) | (50) |
| Bilateral, follicular cell, adenoma | | | | 1 (2%) |
| Follicular cell, adenoma | 4 (8%) | 2 (4%) | 5 (10%) | 5 (10%) |
| Follicular cell, carcinoma | | | 1 (2%) | |
| **General Body System** | | | | |
| None | | | | |

**Table D1**
**Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Dermal Study of Triethanolamine** (continued)

| | 0 mg/kg | 100 mg/kg | 300 mg/kg | 1,000 mg/kg |
|---|---|---|---|---|
| ***2-Year Study*** (continued) | | | | |
| **Genital System** | | | | |
| Ovary | (50) | (50) | (50) | (50) |
| Cystadenoma | 5 (10%) | | 3 (6%) | 2 (4%) |
| Granulosa cell tumor benign | 1 (2%) | 1 (2%) | | |
| Hemangioma | | 1 (2%) | | |
| Hemangiosarcoma | 1 (2%) | | | |
| Histiocytic sarcoma | | 1 (2%) | | 1 (2%) |
| Luteoma | 3 (6%) | 2 (4%) | | |
| Teratoma NOS | | 1 (2%) | 1 (2%) | |
| Follicle, cystadenoma | | | 1 (2%) | |
| Uterus | (50) | (50) | (50) | (50) |
| Histiocytic sarcoma | | 1 (2%) | 1 (2%) | 1 (2%) |
| Polyp stromal | 1 (2%) | 1 (2%) | | 1 (2%) |
| **Hematopoietic System** | | | | |
| Bone marrow | (50) | (50) | (50) | (50) |
| Hemangiosarcoma | 1 (2%) | | | |
| Lymph node | (4) | (8) | (6) | (9) |
| Bronchial, hemangiosarcoma, metastatic, uncertain primary site | 1 (25%) | | | |
| Bronchial, sarcoma, metastatic, skin | | | 1 (17%) | |
| Mediastinal, sarcoma, metastatic, skin | | | 1 (17%) | |
| Mediastinal, teratoma NOS, metastatic, ovary | | 1 (13%) | | |
| Pancreatic, histiocytic sarcoma | | | | 1 (11%) |
| Lymph node, mandibular | (47) | (49) | (49) | (49) |
| Histiocytic sarcoma | | 1 (2%) | | 2 (4%) |
| Lymph node, mesenteric | (46) | (49) | (48) | (49) |
| Histiocytic sarcoma | | | | 2 (4%) |
| Spleen | (50) | (50) | (50) | (50) |
| Hemangiosarcoma | 3 (6%) | 1 (2%) | | |
| Histiocytic sarcoma | | 2 (4%) | 1 (2%) | 2 (4%) |
| Capsule, sarcoma, metastatic, skin | | 1 (2%) | | |
| Thymus | (46) | (47) | (49) | (48) |
| Histiocytic sarcoma | | | 1 (2%) | 2 (4%) |
| Sarcoma, metastatic, skin | | 1 (2%) | 1 (2%) | |
| Thymoma NOS | | | | 1 (2%) |
| **Integumentary System** | | | | |
| Mammary gland | (48) | (48) | (50) | (47) |
| Adenoma | | | 1 (2%) | |
| Hemangiosarcoma | 1 (2%) | | | |
| Skin | (50) | (50) | (50) | (50) |
| Inguinal, subcutaneous tissue, osteosarcoma | | | 1 (2%) | |
| Neck, subcutaneous tissue, sarcoma | | | 1 (2%) | |
| Pinna, sarcoma | | 1 (2%) | 1 (2%) | |
| Subcutaneous tissue, fibrosarcoma, multiple | | | | 1 (2%) |
| Subcutaneous tissue, sarcoma | 1 (2%) | 2 (4%) | | |

**TABLE D1**
**Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Dermal Study of Triethanolamine** (continued)

| | 0 mg/kg | 100 mg/kg | 300 mg/kg | 1,000 mg/kg |
|---|---|---|---|---|
| ***2-Year Study*** (continued) | | | | |
| **Musculoskeletal System** | | | | |
| Bone | (50) | (50) | (50) | (50) |
| Lumbar, vertebra, sarcoma | | | 1 (2%) | |
| Scapula, osteosarcoma | | | | 1 (2%) |
| Vertebra, osteosarcoma | | | | 1 (2%) |
| Skeletal muscle | | (2) | (2) | |
| Fibrosarcoma | | 1 (50%) | | |
| Diaphragm, sarcoma, metastatic, skin | | 1 (50%) | 1 (50%) | |
| **Nervous System** | | | | |
| None | | | | |
| **Respiratory System** | | | | |
| Lung | (50) | (50) | (50) | (49) |
| Alveolar/bronchiolar adenoma | 2 (4%) | 4 (8%) | 2 (4%) | 5 (10%) |
| Alveolar/bronchiolar carcinoma | | | 1 (2%) | 2 (4%) |
| Fibrosarcoma, metastatic, skin | | | | 1 (2%) |
| Hemangiosarcoma, metastatic, uncertain primary site | 1 (2%) | | | |
| Hepatocellular carcinoma, metastatic, liver | | 1 (2%) | | |
| Histiocytic sarcoma | | 1 (2%) | 1 (2%) | 2 (4%) |
| Osteosarcoma, metastatic, bone | | | | 1 (2%) |
| Osteosarcoma, metastatic, skin | | | 1 (2%) | |
| Osteosarcoma, metastatic, tissue NOS | | | | 1 (2%) |
| Sarcoma, metastatic, bone | | | 1 (2%) | |
| Sarcoma, metastatic, skin | | 1 (2%) | 1 (2%) | |
| Mediastinum, sarcoma, metastatic, skin | | 1 (2%) | | |
| **Special Senses System** | | | | |
| Harderian gland | (1) | (2) | (1) | |
| Adenoma | 1 (100%) | 1 (50%) | 1 (100%) | |
| **Urinary System** | | | | |
| Kidney | (50) | (50) | (50) | (50) |
| Histiocytic sarcoma | | 1 (2%) | | |
| Urinary bladder | (50) | (50) | (50) | (50) |
| **Systemic Lesions** | | | | |
| Multiple organs[b] | (50) | (50) | (50) | (50) |
| Histiocytic sarcoma | | 2 (4%) | 2 (4%) | 3 (6%) |
| Leukemia lymphocytic | | | 1 (2%) | 1 (2%) |
| Lymphoma malignant | | | | 1 (2%) |
| Lymphoma malignant lymphocytic | 1 (2%) | 5 (10%) | 3 (6%) | 4 (8%) |
| Lymphoma malignant mixed | 4 (8%) | 4 (8%) | 1 (2%) | 7 (14%) |
| Lymphoma malignant undifferentiated cell | 1 (2%) | 1 (2%) | 2 (4%) | 3 (6%) |

**TABLE D1**
**Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Dermal Study of Triethanolamine** (continued)

| | 0 mg/kg | 100 mg/kg | 300 mg/kg | 1,000 mg/kg |
|---|---|---|---|---|
| **Neoplasm Summary** | | | | |
| Total animals with primary neoplasms[c] | | | | |
| 15-Month interim evaluation | 2 | 3 | 2 | 3 |
| 2-Year study | 37 | 43 | 42 | 49 |
| Total primary neoplasms | | | | |
| 15-Month interim evaluation | 2 | 3 | 2 | 3 |
| 2-Year study | 58 | 70 | 66 | 92 |
| Total animals with benign neoplasms | | | | |
| 15-Month interim evaluation | 2 | 3 | 2 | 3 |
| 2-Year study | 34 | 33 | 31 | 43 |
| Total benign neoplasms | | | | |
| 15-Month interim evaluation | 2 | 3 | 2 | 3 |
| 2-Year study | 44 | 43 | 43 | 62 |
| Total animals with malignant neoplasms | | | | |
| 2-Year study | 11 | 22 | 21 | 25 |
| Total malignant neoplasms | | | | |
| 2-Year study | 14 | 25 | 22 | 29 |
| Total animals with metastatic neoplasms | | | | |
| 2-Year study | 1 | 3 | 3 | 3 |
| Total metastatic neoplasms | | | | |
| 2-Year study | 2 | 10 | 8 | 3 |
| Total animals with malignant neoplasms of uncertain primary site | | | | |
| 2-Year study | 1 | | | |
| Total animals with uncertain neoplasms-benign or malignant | | | | |
| 2-Year study | | 2 | 1 | 1 |
| Total uncertain neoplasms | | | | |
| 2-Year study | | 2 | 1 | 1 |

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

**TABLE D2**
**Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Triethanolamine: 0 mg/kg**

| | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Number of Days on Study** | 009 | 197 | 289 | 350 | 487 | 512 | 534 | 572 | 681 | 698 | 700 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 730 | 730 | 730 | 730 | 730 | 730 |
| **Carcass ID Number** | 269 | 268 | 261 | 286 | 262 | 255 | 285 | 242 | 248 | 275 | 256 | 244 | 252 | 265 | 276 | 279 | 290 | 291 | 297 | 241 | 243 | 246 | 264 | 271 | 272 |
| **Alimentary System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Esophagus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Gallbladder | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine large, colon | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine large, rectum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine large, cecum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine small, duodenum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine small, jejunum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine small, ileum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Liver | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Hepatocellular carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Hepatocellular adenoma | | | | | | | | | X | | | | X | | X | | | | | | X | X | | | |
| Hepatocellular adenoma, multiple | | | | | | | | | | | | X | | X | | | | X | | | | | | X | |
| Mesentery | | | | | | | | + | | | | + | | | | | | | | | | | | | |
| Pancreas | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Salivary glands | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Stomach, forestomach | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Stomach, glandular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Cardiovascular System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Blood vessel | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Heart | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Endocrine System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Adrenal cortex | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Capsule, spindle cell, adenoma | | | | | | | | | | X | | | | | | | | | | | | | | | |
| Adrenal medulla | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Islets, pancreatic | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Parathyroid gland | + | + | + | + | + | + | + | + | + | M | M | + | + | + | + | + | + | + | M | + | M | + | + | + | + |
| Pituitary gland | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | M | + |
| Pars distalis, adenoma | | | | | X | | | | X | | | | | | | | | X | X | | | | | | |
| Thyroid gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Follicular cell, adenoma | | | | | | | | | | | | | | | | X | | | | | | | | | |
| **General Body System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| None | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Genital System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Clitoral gland | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Ovary | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Cystadenoma | | | | | | | | X | | | | | | | | | | | | | | | | | |
| Granulosa cell tumor benign | | | | | | | | | | | | | | | | | | | | | | | | | |
| Hemangiosarcoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Luteoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Uterus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Polyp stromal | | | | | | | | | | | | | | | | | | | | | | | | | |

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

**Table D2**
**Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Triethanolamine: 0 mg/kg** (continued)

| Number of Days on Study | 730 | 730 | 730 | 730 | 730 | 731 | 731 | 731 | 731 | 731 | 731 | 731 | 731 | 731 | 731 | 732 | 732 | 732 | 732 | 732 | 732 | 732 | 732 | 732 | 732 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 281 | 283 | 287 | 288 | 296 | 245 | 257 | 258 | 263 | 274 | 277 | 280 | 282 | 292 | 299 | 251 | 254 | 259 | 260 | 273 | 278 | 284 | 294 | 295 | 300 | Total Tissues/ Tumors |
| **Alimentary System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Esophagus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Gallbladder | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Intestine large, colon | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Intestine large, rectum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Intestine large, cecum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Intestine small, duodenum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Intestine small, jejunum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Intestine small, ileum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Liver | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Hepatocellular carcinoma | | | | | | | | | X | | | | | | | | | | | | | | | | | 1 |
| Hepatocellular adenoma | X | | | | | | | | | | X | | | X | | | | X | X | | | | X | | | 11 |
| Hepatocellular adenoma, multiple | | | X | | X | | | X | | | | | | | X | | | | | | X | X | | | X | 11 |
| Mesentery | | | | | | | | | | | | | | | | | | | | | | | | | | 2 |
| Pancreas | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Salivary glands | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Stomach, forestomach | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Stomach, glandular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Cardiovascular System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Blood vessel | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | M | M | + | + | + | 47 |
| Heart | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Endocrine System | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Adrenal cortex | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Capsule, spindle cell, adenoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Adrenal medulla | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Islets, pancreatic | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Parathyroid gland | + | + | + | + | M | + | + | M | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | 43 |
| Pituitary gland | + | + | + | M | + | + | + | M | I | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 44 |
| Pars distalis, adenoma | | | | | | | | | | | | | | | | | | | | | | | | | | 4 |
| Thyroid gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Follicular cell, adenoma | | | | X | | | | | | | | | | | | | | | X | | | | X | | | 4 |
| **General Body System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| None | | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Genital System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Clitoral gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Ovary | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Cystadenoma | | | | | | | | | | | X | X | | | | | | | | | X | X | | | | 5 |
| Granulosa cell tumor benign | | | | | | | | | X | | | | | | | | | | | | | | | | | 1 |
| Hemangiosarcoma | | | | | | | | | | | | | | | X | | | | | | | | | | | 1 |
| Luteoma | | | | | | | | | | | | | X | | | | X | | | | | | | X | | 3 |
| Uterus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Polyp stromal | | | | | | | | | | | | | | | | | X | | | | | | | | | 1 |

**Table D2**
**Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Triethanolamine: 0 mg/kg**
(continued)

| Number of Days on Study | 009 | 197 | 289 | 350 | 487 | 512 | 534 | 572 | 681 | 698 | 700 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 730 | 730 | 730 | 730 | 730 | 730 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 269 | 268 | 261 | 286 | 262 | 255 | 285 | 242 | 248 | 275 | 256 | 244 | 252 | 265 | 276 | 279 | 290 | 291 | 297 | 241 | 243 | 246 | 264 | 271 | 272 |
| **Hematopoietic System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone marrow | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Hemangiosarcoma | | | | | | | | | | | | | | | | | | | | | | | X | | |
| Lymph node | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bronchial, hemangiosarcoma, metastatic, uncertain primary site | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lymph node, mandibular | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + | M | + |
| Lymph node, mesenteric | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Spleen | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Hemangiosarcoma | | | | | | | | | | | | | | | | | | | | | | | X | | |
| Thymus | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | M | M | + |
| **Integumentary System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Mammary gland | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Hemangiosarcoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Skin | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Subcutaneous tissue, sarcoma | | | | | | | | | | X | | | | | | | | | | | | | | | |
| **Musculoskeletal System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Nervous System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Brain | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Peripheral nerve | | | + | | | | | | + | | | | | | | | | | | | | | | | |
| Spinal cord | | | + | | | | | | + | | | | | | | | | | | | | | | | |
| **Respiratory System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lung | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Alveolar/bronchiolar adenoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Hemangiosarcoma, metastatic, uncertain primary site | | | | | | | | | | | | | | | | | | | | | | | | | |
| Nose | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Trachea | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Special Senses System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Ear | | | + | | | | | | | | | | | | | | | | | | | | | | |
| Harderian gland | | | | | | | | | | | | | | | | | | | | | | | | | |
| Adenoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Urinary System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Kidney | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Urinary Bladder | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Systemic Lesions** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Multiple organs | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Lymphoma malignant lymphocytic | | | | | | | | | | | | | | | | X | | | | | | | | | |
| Lymphoma malignant mixed | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lymphoma malignant undifferentiated cell type | | | | | | | | | | | | | | | | | | | | | | | | | |

**TABLE D2**
**Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Triethanolamine: 0 mg/kg**
(continued)

| | | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Number of Days on Study** | 730 | 730 | 730 | 730 | 730 | 731 | 731 | 731 | 731 | 731 | 731 | 731 | 731 | 731 | 731 | 732 | 732 | 732 | 732 | 732 | 732 | 732 | 732 | 732 | 732 | |
| **Carcass ID Number** | 281 | 283 | 287 | 288 | 296 | 245 | 257 | 258 | 263 | 274 | 277 | 280 | 282 | 292 | 299 | 251 | 254 | 259 | 260 | 273 | 278 | 284 | 294 | 295 | 300 | Total Tissues/ Tumors |
| **Hematopoietic System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone marrow | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Hemangiosarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Lymph node | | | + | | | + | | | | | | | | + | + | | | | | | | | | | | 4 |
| Bronchial, hemangiosarcoma, metastatic, uncertain primary site | | | | | | | | | | | | | | X | | | | | | | | | | | | 1 |
| Lymph node, mandibular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 47 |
| Lymph node, mesenteric | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | M | + | M | + | 46 |
| Spleen | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Hemangiosarcoma | | | | | | | | | | X | | | | X | | | | | | | | | | | | 3 |
| Thymus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | | + | + | + | + | + | + | + | + | + | + | 46 |
| **Integumentary System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Mammary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | M | + | + | + | 48 |
| Hemangiosarcoma | | | | | | | | | | | | | | X | | | | | | | | | | | | 1 |
| Skin | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Subcutaneous tissue, sarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| **Musculoskeletal System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Nervous System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Brain | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Peripheral nerve | | | | | | | | | | | | | | | | | | | | | | | | | | 2 |
| Spinal cord | | | | | | | | | | | | | | | | | | | | | | | | | | 2 |
| **Respiratory System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lung | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Alveolar/bronchiolar adenoma | | | | | X | | | | | | | | | X | | | | | | | | | | | | 2 |
| Hemangiosarcoma, metastatic, uncertain primary site | | | | | | | | | | | | | | X | | | | | | | | | | | | 1 |
| Nose | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Trachea | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Special Senses System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Ear | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Harderian gland | | | | | | | | | | | | | | | | | | | | + | | | | | | 1 |
| Adenoma | | | | | | | | | | | | | | | | | | | | X | | | | | | 1 |
| **Urinary System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Kidney | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Urinary bladder | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Systemic Lesions** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Multiple organs | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Lymphoma malignant lymphocytic | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Lymphoma malignant mixed | | | X | | | X | | X | | | | | | | | | | | | | X | | | | | 4 |
| Lymphoma malignant undifferentiated cell type | | | | | | | | | | | | | | X | | | | | | | | | | | | 1 |

**TABLE D2**
**Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Triethanolamine: 100 mg/kg**

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

**Table D2**
**Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Triethanolamine: 100 mg/kg**
(continued)

| | | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Number of Days on Study** | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | |
| | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | |
| | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | |
| | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | Total |
| **Carcass ID Number** | 3 | 3 | 4 | 4 | 4 | 5 | 5 | 5 | 6 | 2 | 2 | 4 | 4 | 5 | 5 | 0 | 0 | 0 | 0 | 0 | 2 | 2 | 2 | 3 | 5 | Tissues/ |
| | 7 | 8 | 4 | 6 | 7 | 2 | 4 | 7 | 0 | 0 | 9 | 2 | 8 | 1 | 8 | 1 | 2 | 3 | 5 | 9 | 4 | 5 | 6 | 5 | 0 | Tumors |
| **Alimentary System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Esophagus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Gallbladder | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Intestine large, colon | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Intestine large, rectum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Intestine large, cecum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Intestine small, duodenum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Intestine small, jejunum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Sarcoma, metastatic, skin | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Intestine small, ileum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Liver | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Hemangiosarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | 3 |
| Hepatocellular carcinoma | | | | | | | | | | | | | | | | | | | X | | X | | | | | 4 |
| Hepatocellular adenoma | | | | | | | X | X | | | | | | | | | | X | | | | | X | X | | 13 |
| Hepatocellular adenoma, multiple | | X | | | | X | | | | | X | X | X | | | | | | | X | | | | | | 9 |
| Histiocytic sarcoma | | | X | | | | | | | | | | | | | | | | | | | | | | | 2 |
| Ito cell tumor NOS, multiple | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Mesentery | | | | | | | | | | + | | + | | | | | | | | + | | | | | | 5 |
| Fat, sarcoma, metastatic, skin | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Pancreas | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Sarcoma, metastatic, skin | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Salivary glands | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Stomach, forestomach | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Squamous cell papilloma | | | | | | | | | | | | | | | | | | | X | | | | | | | 1 |
| Stomach, glandular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Cardiovascular System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Blood vessel | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Heart | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Endocrine System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Adrenal cortex | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Adrenal medulla | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Pheochromocytoma benign | | | | | | | | | | | | | | | | | | | | | | | | | X | 1 |
| Islets, pancreatic | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Parathyroid gland | M | + | M | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | M | + | + | 43 |
| Pituitary gland | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Adenoma | | | | | | | | | | | | X | | | | | | | | | | | | | | 1 |
| Pars distalis, adenoma | X | | X | | | | | | | | | | | | | | | | X | | | | | | | 5 |
| Pars intermedia, adenoma | | | | | | | | | X | | | | | | | | | | | | | | | | | 1 |
| Thyroid gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Follicular cell, adenoma | | | | | | | | | | | | | | X | | | | | X | | | | | | | 2 |
| **General Body System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| None | | | | | | | | | | | | | | | | | | | | | | | | | | |

**Table D2**
**Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Triethanolamine: 100 mg/kg**
(continued)

| | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 0 | 4 | 5 | 5 | 6 | 6 | 6 | 6 | 6 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 |
| **Number of Days on Study** | 0 | 1 | 5 | 7 | 3 | 5 | 7 | 7 | 8 | 1 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 3 | 3 | 3 | 3 | 3 | 3 |
| | 9 | 4 | 7 | 8 | 9 | 0 | 5 | 5 | 5 | 3 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| **Carcass ID Number** | 0 | 1 | 4 | 5 | 3 | 4 | 1 | 3 | 2 | 1 | 1 | 1 | 3 | 3 | 4 | 4 | 5 | 5 | 5 | 0 | 1 | 2 | 2 | 2 | 3 |
| | 7 | 4 | 1 | 6 | 0 | 5 | 3 | 2 | 2 | 1 | 7 | 9 | 4 | 6 | 0 | 3 | 3 | 5 | 9 | 4 | 8 | 1 | 3 | 8 | 1 |
| **Genital System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Clitoral gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Ovary | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Granulosa cell tumor benign | | | | | | | | | | | | | | | | | | | | | | | | | |
| Hemangioma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Histiocytic sarcoma | | X | | | | | | | | | | | | | | | | | | | | | | | |
| Luteoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Teratoma NOS | | | | | | | | | | | | | | | | | | | | | | | | | |
| Uterus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Histiocytic sarcoma | | X | | | | | | | | | | | | | | | | | | | | | | | |
| Polyp stromal | | | | | | | | | | | | | | | | | | | | | | | X | | |
| **Hematopoietic System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone marrow | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Lymph node | | | | | + | | | | + | + | | | | | | | | | | | + | | | | |
| Mediastinal, teratoma NOS, metastatic, ovary | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lymph node, mandibular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Histiocytic sarcoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lymph node, mesenteric | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Spleen | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Hemangiosarcoma | | | | | | | | | | | | | | | | | | | X | | | | | | |
| Histiocytic sarcoma | | X | | | | | | | | | | | | | | | | | | | | | | | |
| Capsule, sarcoma, metastatic, skin | | | | X | | | | | | | | | | | | | | | | | | | | | |
| Thymus | + | + | M | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + |
| Sarcoma, metastatic, skin | | | | X | | | | | | | | | | | | | | | | | | | | | |
| **Integumentary System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Mammary gland | + | + | M | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Skin | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Pinna, sarcoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Subcutaneous tissue, sarcoma | | | | X | | | | | | | | | | | | | | X | | | | | | | |
| **Musculoskeletal System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Skeletal muscle | | | | + | | | + | | | | | | | | | | | | | | | | | | |
| Fibrosarcoma | | | | | | | X | | | | | | | | | | | | | | | | | | |
| Diaphragm, sarcoma, metastatic, skin | | | | X | | | | | | | | | | | | | | | | | | | | | |
| **Nervous System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Brain | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Peripheral nerve | | | | | | + | | | | | | | | | | | | | | | | | | | |
| Spinal cord | | | | | | + | | | | | | | | | | | | | | | | | | | |
| **Respiratory System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lung | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Alveolar/bronchiolar adenoma | | | | | | | | | | | | X | | | | | | | | | | X | | | |
| Hepatocellular carcinoma, metastatic, liver | | | X | | | | | | | | | | | | | | | | | | | | | | |
| Histiocytic sarcoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Sarcoma, metastatic, skin | | | | X | | | | | | | | | | | | | | | | | | | | | |
| Mediastinum, sarcoma, metastatic, skin | | | | X | | | | | | | | | | | | | | | | | | | | | |
| Nose | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Trachea | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |

**TABLE D2**
**Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Triethanolamine: 100 mg/kg**
(continued)

| Number of Days on Study | 730 | 730 | 730 | 730 | 730 | 730 | 730 | 730 | 730 | 731 | 731 | 731 | 731 | 731 | 731 | 732 | 732 | 732 | 732 | 732 | 732 | 732 | 732 | 732 | 732 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 337 | 338 | 344 | 346 | 347 | 352 | 354 | 357 | 360 | 320 | 329 | 342 | 348 | 351 | 358 | 301 | 302 | 303 | 305 | 309 | 324 | 325 | 326 | 335 | 350 | Total Tissues/ Tumors |
| **Genital System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Clitoral gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | M | M | + | 48 |
| Ovary | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Granulosa cell tumor benign | X | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Hemangioma | | | | | | | | | | | | | | | | X | | | | | | | | | | 1 |
| Histiocytic sarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Luteoma | | | | | | | | | | | | | | | | | | | X | | | | X | | | 2 |
| Teratoma NOS | | | | | | | | | | | | | X | | | | | | | | | | | | | 1 |
| Uterus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Histiocytic sarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Polyp stromal | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| **Hematopoietic System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone marrow | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Lymph node | | | | | + | | | + | | | | | + | | + | | | | | | | | | | | 8 |
| Mediastinal, teratoma NOS, metastatic, ovary | | | | | | | | | | | | | X | | | | | | | | | | | | | 1 |
| Lymph node, mandibular | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Histiocytic sarcoma | | | X | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Lymph node, mesenteric | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | M | + | + | + | + | 49 |
| Spleen | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Hemangiosarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Histiocytic sarcoma | | | X | | | | | | | | | | | | | | | | | | | | | | | 2 |
| Capsule, sarcoma, metastatic, skin | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Thymus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | 47 |
| Sarcoma, metastatic, skin | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| **Integumentary System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Mammary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 48 |
| Skin | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Pinna, sarcoma | | | | | | | | | | | | | | | | | | X | | | | | | | | 1 |
| Subcutaneous tissue, sarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | 2 |
| **Musculoskeletal System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Skeletal muscle | | | | | | | | | | | | | | | | | | | | | | | | | | 2 |
| Fibrosarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Diaphragm, sarcoma, metastatic, skin | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| **Nervous System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Brain | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Peripheral nerve | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Spinal cord | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| **Respiratory System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lung | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Alveolar/bronchiolar adenoma | | | | | X | | | | | | | | | | | | | | X | | | | | | | 4 |
| Hepatocellular carcinoma, metastatic, liver | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Histiocytic sarcoma | | | X | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Sarcoma, metastatic, skin | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Mediastinum, sarcoma, metastatic, skin | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Nose | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Trachea | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |

**TABLE D2**
**Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Triethanolamine: 100 mg/kg**
(continued)

| | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 0 | 4 | 5 | 5 | 6 | 6 | 6 | 6 | 6 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 |
| **Number of Days on Study** | 0 | 1 | 5 | 7 | 3 | 5 | 7 | 7 | 8 | 1 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 3 | 3 | 3 | 3 | 3 | 3 |
| | 9 | 4 | 7 | 8 | 9 | 0 | 5 | 5 | 5 | 3 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| **Carcass ID Number** | 0 | 1 | 4 | 5 | 3 | 4 | 1 | 3 | 2 | 1 | 1 | 1 | 3 | 3 | 4 | 4 | 5 | 5 | 5 | 0 | 1 | 2 | 2 | 2 | 3 |
| | 7 | 4 | 1 | 6 | 0 | 5 | 3 | 2 | 2 | 1 | 7 | 9 | 4 | 6 | 0 | 3 | 3 | 5 | 9 | 4 | 8 | 1 | 3 | 8 | 1 |
| **Special Senses System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Harderian gland | | | | | | | | | | | | | | | | | | | | | | | | | |
| Adenoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Urinary System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Kidney | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Histiocytic sarcoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Urinary bladder | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Systemic Lesions** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Multiple organs | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Histiocytic sarcoma | | X | | | | | | | | | | | | | | | | | | | | | | | |
| Lymphoma malignant lymphocytic | | | | | | | | | X | X | | | | | | | | X | | | X | | | | |
| Lymphoma malignant mixed | | | | | | | | | | | | X | | | | | | | | | | | | | |
| Lymphoma malignant undifferentiated cell type | | | | | X | | | | | | | | | | | | | | | | | | | | |

**TABLE D2**
**Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Triethanolamine: 100 mg/kg**
(continued)

| | | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | |
| **Number of Days on Study** | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | |
| | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | |
| | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | Total |
| **Carcass ID Number** | 3 | 3 | 4 | 4 | 4 | 5 | 5 | 5 | 6 | 2 | 2 | 4 | 4 | 5 | 5 | 0 | 0 | 0 | 0 | 0 | 2 | 2 | 2 | 3 | 5 | Tissues/ |
| | 7 | 8 | 4 | 6 | 7 | 2 | 4 | 7 | 0 | 0 | 9 | 2 | 8 | 1 | 8 | 1 | 2 | 3 | 5 | 9 | 4 | 5 | 6 | 5 | 0 | Tumors |
| **Special Senses System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Harderian gland | | + | | | | | | | | | | | | | | | | | | + | | | | | | 2 |
| Adenoma | | X | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| **Urinary System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Kidney | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Histiocytic sarcoma | | | X | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Urinary bladder | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Systemic Lesions** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Multiple organs | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Histiocytic sarcoma | | | X | | | | | | | | | | | | | | | | | | | | | | | 2 |
| Lymphoma malignant lymphocytic | | | | | | | | | | | X | | | | | | | | | | | | | | | 5 |
| Lymphoma malignant mixed | | | | | X | | | X | | | | | | | X | | | | | | | | | | | 4 |
| Lymphoma malignant undifferentiated cell type | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |

**TABLE D2**
**Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Triethanolamine: 300 mg/kg**

| | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Number of Days on Study** | 320 | 434 | 540 | 579 | 597 | 603 | 624 | 669 | 674 | 682 | 712 | 716 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 730 | 730 | 730 | 730 |
| **Carcass ID Number** | 396 | 392 | 411 | 414 | 382 | 418 | 395 | 399 | 406 | 375 | 383 | 409 | 362 | 376 | 377 | 378 | 379 | 390 | 400 | 404 | 420 | 368 | 372 | 384 | 385 |
| **Alimentary System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Esophagus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Gallbladder | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | M |
| Intestine large, colon | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine large, rectum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine large, cecum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine small, duodenum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine small, jejunum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine small, ileum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Liver | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Hemangioma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Hepatocellular carcinoma | | X | X | | X | | | | | | | | | | | | | | | | | | X | | |
| Hepatocellular adenoma | | | | | X | | X | | | | | | | | X | X | | | | | | X | | | |
| Hepatocellular adenoma, multiple | | | | | | | | | | | | X | | | | | X | | | X | X | | | | |
| Histiocytic sarcoma | | | | X | | | | | | | | | | | | | | | | | | | | | |
| Mesentery | | | | | | | + | | + | | + | | | | | | | + | | | | + | | | |
| Pancreas | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Salivary glands | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Stomach, forestomach | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Stomach, glandular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Cardiovascular System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Blood vessel | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Heart | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Sarcoma, metastatic, skin | | | | | | X | | | | | | | | | | | | | | | | | | | |
| **Endocrine System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Adrenal cortex | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Capsule, spindle cell, adenoma | | | | | | | | | | | | | | X | | | | | | | | | | | |
| Adrenal medulla | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Islets, pancreatic | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Parathyroid gland | M | + | + | + | + | M | M | + | + | M | + | + | + | + | M | + | + | + | + | M | M | M | + | + | + |
| Pituitary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Pars distalis, adenoma | | | | | | | | | | | | | | | | | | X | X | | | | | | |
| Thyroid gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Follicular cell, adenoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Follicular cell, carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| **General Body System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| None | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Genital System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Clitoral gland | + | + | + | + | + | + | M | M | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Ovary | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Cystadenoma | | | | | | | | | | | | | | | | | | X | | X | | | | | |
| Teratoma NOS | | | | | | | | | | | | | | | | | | | | | | | | | |
| Follicle, cystadenoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Uterus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Histiocytic sarcoma | | | | | | | | | | | | | | | | | | | | | | | | | |

**TABLE D2**
**Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Triethanolamine: 300 mg/kg**
(continued)

| | | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Number of Days on Study** | 730 | 730 | 730 | 730 | 730 | 730 | 730 | 730 | 731 | 731 | 731 | 731 | 731 | 731 | 731 | 732 | 732 | 732 | 732 | 732 | 732 | 732 | 732 | 732 | 736 | |
| **Carcass ID Number** | 389 | 393 | 401 | 402 | 405 | 408 | 412 | 415 | 361 | 363 | 365 | 366 | 371 | 380 | 381 | 364 | 397 | 398 | 403 | 407 | 410 | 416 | 417 | 419 | 394 | Total Tissues/ Tumors |
| **Alimentary System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Esophagus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Gallbladder | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Intestine large, colon | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Intestine large, rectum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Intestine large, cecum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Intestine small, duodenum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Intestine small, jejunum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Intestine small, ileum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Liver | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Hemangioma | | | | | | | | | | | | | | | | | | | | | | | X | | | 1 |
| Hepatocellular carcinoma | | | | X | | | | | | | | X | | | | | | | | | | | | X | | 7 |
| Hepatocellular adenoma | | | | | | X | X | | X | | | | | X | | | | | | | | | X | X | | 11 |
| Hepatocellular adenoma, multiple | | | X | X | X | | | | | X | X | | X | | | | | X | | X | | X | | | | 13 |
| Histiocytic sarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Mesentery | | | | | | | | | | | | | | | | | | | | | | | | | | 5 |
| Pancreas | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Salivary glands | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Stomach, forestomach | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Stomach, glandular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Cardiovascular System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Blood vessel | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Heart | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Sarcoma, metastatic, skin | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| **Endocrine System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Adrenal cortex | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Capsule, spindle cell, adenoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Adrenal medulla | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Islets, pancreatic | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Parathyroid gland | + | + | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | M | + | + | + | + | + | 40 |
| Pituitary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | 49 |
| Pars distalis, adenoma | | | | | | | X | | | | | | | | | | | X | | | | | | | | 4 |
| Thyroid gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Follicular cell, adenoma | X | | | | X | | X | | | | | X | | | | | | | | | | X | | | | 5 |
| Follicular cell, carcinoma | | | | | | | | | | | | | X | | | | | | | | | | | | | 1 |
| **General Body System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| None | | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Genital System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Clitoral gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 47 |
| Ovary | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Cystadenoma | | | | | | | | | | X | | | | | | | | | | | | | | | | 3 |
| Teratoma NOS | | | | | | | | | | | | | | | | | | | | | | | X | | | 1 |
| Follicle, cystadenoma | | | | | | | | | | | | | | | | X | | | | | | | | | | 1 |
| Uterus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Histiocytic sarcoma | | | | | | | | | | | | | | | X | | | | | | | | | | | 1 |

**Table D2**
**Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Triethanolamine: 300 mg/kg**
(continued)

| | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Number of Days on Study** | 320 | 434 | 540 | 579 | 597 | 603 | 624 | 669 | 674 | 682 | 712 | 716 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 730 | 730 | 730 | 730 |
| **Carcass ID Number** | 396 | 392 | 411 | 414 | 382 | 418 | 395 | 399 | 406 | 375 | 383 | 409 | 362 | 376 | 377 | 378 | 379 | 390 | 400 | 404 | 420 | 368 | 372 | 384 | 385 |
| **Hematopoietic System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone marrow | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Lymph node | | | | | | + | + | | | | | | | | | | | | | | | | | | |
| Bronchial, sarcoma, metastatic, skin | | | | | | X | | | | | | | | | | | | | | | | | | | |
| Mediastinal, sarcoma, metastatic, skin | | | | | | X | | | | | | | | | | | | | | | | | | | |
| Lymph node, mandibular | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Lymph node, mesenteric | + | M | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Spleen | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Histiocytic sarcoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Thymus | + | + | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Histiocytic sarcoma | | | | X | | | | | | | | | | | | | | | | | | | | | |
| Sarcoma, metastatic, skin | | | | | | X | | | | | | | | | | | | | | | | | | | |
| **Integumentary System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Mammary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Adenoma | | | | | | | | | | | | X | | | | | | | | | | | | | |
| Skin | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Inguinal, subcutaneous tissue, osteosarcoma | X | | | | | | | | | | | | | | | | | | | | | | | | |
| Neck, subcutaneous tissue, sarcoma | | | | | | X | | | | | | | | | | | | | | | | | | | |
| Pinna, sarcoma | | | | | | | | | | | | | | | | | | | | | | | | | X |
| **Musculoskeletal System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Lumbar, vertebra, sarcoma | | | | | | | | | X | | | | | | | | | | | | | | | | |
| Skeletal muscle | | | | | | + | + | | | | | | | | | | | | | | | | | | |
| Diaphragm, sarcoma, metastatic, skin | | | | | | X | | | | | | | | | | | | | | | | | | | |
| **Nervous System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Brain | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Respiratory System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lung | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Alveolar/bronchiolar adenoma | | | | | | | | | | | | | | | | X | | | | | | | | | X |
| Alveolar/bronchiolar carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Histiocytic sarcoma | | | | X | | | | | | | | | | | | | | | | | | | | | |
| Osteosarcoma, metastatic, skin | X | | | | | | | | | | | | | | | | | | | | | | | | |
| Sarcoma, metastatic, bone | | | | | | | | | X | | | | | | | | | | | | | | | | |
| Sarcoma, metastatic, skin | | | | | | X | | | | | | | | | | | | | | | | | | | |
| Nose | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Trachea | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Special Senses System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Ear | | | | | | | | | | | | | | | | | | | | | | | | | + |
| Harderian gland | | | | | | | | | | | | | | | + | | | | | | | | | | |
| Adenoma | | | | | | | | | | | | | | | X | | | | | | | | | | |

**TABLE D2**
**Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Triethanolamine: 300 mg/kg**
(continued)

| Number of Days on Study | 730 | 730 | 730 | 730 | 730 | 730 | 730 | 730 | 731 | 731 | 731 | 731 | 731 | 731 | 731 | 732 | 732 | 732 | 732 | 732 | 732 | 732 | 732 | 732 | 736 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 389 | 393 | 401 | 402 | 405 | 408 | 412 | 415 | 361 | 363 | 365 | 366 | 371 | 380 | 381 | 364 | 397 | 398 | 403 | 407 | 410 | 416 | 417 | 419 | 394 | Total Tissues/ Tumors |
| **Hematopoietic System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone marrow | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Lymph node | | + | + | | | | | | | | | | + | | | | | | | | | | | + | | 6 |
| Bronchial, sarcoma, metastatic, skin | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Mediastinal, sarcoma, metastatic, skin | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Lymph node, mandibular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Lymph node, mesenteric | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 48 |
| Spleen | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Histiocytic sarcoma | | | | | | | | | | | | | | | X | | | | | | | | | | | 1 |
| Thymus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Histiocytic sarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Sarcoma, metastatic, skin | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| **Integumentary System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Mammary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Adenoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Skin | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Inguinal, subcutaneous tissue, osteosarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Neck, subcutaneous tissue, sarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Pinna, sarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| **Musculoskeletal System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Lumbar, vertebra, sarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Skeletal muscle | | | | | | | | | | | | | | | | | | | | | | | | | | 2 |
| Diaphragm, sarcoma, metastatic, skin | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| **Nervous System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Brain | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Respiratory System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lung | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Alveolar/bronchiolar adenoma | | | | | | | | | | | | | | | | | | | | | | | | | | 2 |
| Alveolar/bronchiolar carcinoma | | | | | | X | | | | | | | | | | | | | | | | | | | | 1 |
| Histiocytic sarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Osteosarcoma, metastatic, skin | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Sarcoma, metastatic, bone | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Sarcoma, metastatic, skin | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Nose | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Trachea | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Special Senses System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Ear | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Harderian gland | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Adenoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |

**Table D2**
**Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Triethanolamine: 300 mg/kg**
(continued)

| | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Number of Days on Study** | 320 | 434 | 540 | 579 | 597 | 603 | 624 | 669 | 674 | 682 | 712 | 716 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 730 | 730 | 730 | 730 |
| **Carcass ID Number** | 396 | 392 | 411 | 414 | 382 | 418 | 395 | 399 | 406 | 375 | 383 | 409 | 362 | 376 | 377 | 378 | 379 | 390 | 400 | 404 | 420 | 368 | 372 | 384 | 385 |
| **Urinary System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Kidney | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Urinary bladder | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Systemic Lesions** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Multiple organs | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Histiocytic sarcoma | | | | X | | | | | | | | | | | | | | | | | | | | | |
| Leukemia lymphocytic | | | | | | | | X | | | | | | | | | | | | | | | | | |
| Lymphoma malignant lymphocytic | | | | | | | X | | | | | | | | | | | | | | | | | | |
| Lymphoma malignant mixed | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lymphoma malignant undifferentiated cell type | | | | | | | | | | | | | | | | | | | | | | | | | |

**TABLE D2**
**Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Triethanolamine: 300 mg/kg**
(continued)

| **Number of Days on Study** | 730 | 730 | 730 | 730 | 730 | 730 | 730 | 730 | 731 | 731 | 731 | 731 | 731 | 731 | 731 | 732 | 732 | 732 | 732 | 732 | 732 | 732 | 732 | 732 | 736 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 389 | 393 | 401 | 402 | 405 | 408 | 412 | 415 | 361 | 363 | 365 | 366 | 371 | 380 | 381 | 364 | 397 | 398 | 403 | 407 | 410 | 416 | 417 | 419 | 394 | Total Tissues/ Tumors |
| **Urinary System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Kidney | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Urinary bladder | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Systemic Lesions** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Multiple organs | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Histiocytic sarcoma | | | | | | | | | | | | | | | X | | | | | | | | | | | 2 |
| Leukemia lymphocytic | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Lymphoma malignant lymphocytic | | | X | | | | | | X | | | | | | | | | | | | | | | | | 3 |
| Lymphoma malignant mixed | | | | | | | | | | | | | | | | | | | X | | | | | | | 1 |
| Lymphoma malignant undifferentiated cell type | | X | | | | | | | | | | | | | | | | | | | | | | X | | 2 |

**TABLE D2**
**Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Triethanolamine: 1,000 mg/kg**

| Number of Days on Study | 317 | 415 | 521 | 537 | 551 | 591 | 647 | 661 | 670 | 680 | 699 | 712 | 712 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 730 | 730 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 423 | 479 | 464 | 436 | 461 | 473 | 458 | 476 | 428 | 480 | 447 | 456 | 462 | 421 | 425 | 439 | 440 | 441 | 454 | 468 | 469 | 475 | 478 | 426 | 430 |
| **Alimentary System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Esophagus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Gallbladder | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine large, colon | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine large, rectum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine large, cecum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine small, duodenum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine small, jejunum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine small, ileum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Liver | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Hepatocellular carcinoma | | | | | | X | | | | | | | | X | | | | | | X | | | | | |
| Hepatocellular adenoma | | | | | | | | | X | | | | X | X | | | | | | X | X | | X | | |
| Hepatocellular adenoma, multiple | | | | | | | X | | | X | X | | | | X | X | X | X | X | | | X | | X | X |
| Histiocytic sarcoma | | | X | | | X | | | | | | | X | | | | | | | | | | | | |
| Mesentery | | | | | | + | | | | | | | + | | | | | | | + | | | | + | |
| Histiocytic sarcoma | | | | | | X | | | | | | | | | | | | | | | | | | | |
| Pancreas | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Histiocytic sarcoma | | | | | | X | | | | | | | | | | | | | | | | | | | |
| Salivary glands | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Stomach, forestomach | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Stomach, glandular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Cardiovascular System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Blood vessel | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Heart | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Endocrine System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Adrenal cortex | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Capsule, spindle cell, adenoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Adrenal medulla | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Islets, pancreatic | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Parathyroid gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + |
| Pituitary gland | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Pars distalis, adenoma | | | | | | | X | | | | | | | | | X | X | | | | | | | | |
| Pars intermedia, adenoma | | | | | | | | | X | | | | | | | | | X | | | | | | | |
| Thyroid gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Bilateral, follicular cell, adenoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Follicular cell, adenoma | | | | | | | | | | | | | | | | | X | | | | | | | | X |
| **General Body System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| None | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Genital System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Clitoral gland | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Ovary | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Cystadenoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Histiocytic sarcoma | | | | | | X | | | | | | | | | | | | | | | | | | | |
| Uterus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Histiocytic sarcoma | | | | | | X | | | | | | | | | | | | | | | | | | | |
| Polyp stromal | | | | | | | | | | | | | X | | | | | | | | | | | | |

**Table D2**
**Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Triethanolamine: 1,000 mg/kg**
(continued)

| Number of Days on Study | 730 | 730 | 730 | 731 | 731 | 731 | 731 | 731 | 731 | 731 | 731 | 732 | 732 | 732 | 732 | 732 | 732 | 732 | 732 | 732 | 732 | 732 | 732 | 732 | 732 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 450 | 453 | 467 | 422 | 429 | 442 | 445 | 451 | 459 | 472 | 474 | 424 | 427 | 431 | 432 | 433 | 437 | 443 | 444 | 449 | 460 | 465 | 466 | 471 | 477 | Total Tissues/ Tumors |
| **Alimentary System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Esophagus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Gallbladder | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Intestine large, colon | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Intestine large, rectum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Intestine large, cecum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Intestine small, duodenum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Intestine small, jejunum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Intestine small, ileum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Liver | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Hepatocellular carcinoma | | | | | | | | | | | | | | | | | | | | | | | | X | X | 5 |
| Hepatocellular adenoma | | X | | | | X | | | | X | | | X | | | | | | X | | | | | | | 11 |
| Hepatocellular adenoma, multiple | X | | X | X | X | | X | X | X | | | X | | X | X | | X | X | | X | X | X | X | X | X | 29 |
| Histiocytic sarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | 3 |
| Mesentery | + | | | | | | | | | | | | | | | | | | | | | | | | | 5 |
| Histiocytic sarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Pancreas | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Histiocytic sarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Salivary glands | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Stomach, forestomach | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Stomach, glandular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Cardiovascular System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Blood vessel | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | 49 |
| Heart | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Endocrine System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Adrenal cortex | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Capsule, spindle cell, adenoma | | | X | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Adrenal medulla | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Islets, pancreatic | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Parathyroid gland | + | + | + | + | + | + | + | + | + | + | + | + | + | M | M | + | M | + | + | + | + | + | M | + | + | 45 |
| Pituitary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Pars distalis, adenoma | | | | | | | | | | X | | | | | | X | | | | | | | | | | 5 |
| Pars intermedia, adenoma | | | | | | | | | | | | | | | | | | | | | | | | | | 2 |
| Thyroid gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Bilateral, follicular cell, adenoma | | | | | | | | | | | | | | | | | | | | | | | | | X | 1 |
| Follicular cell, adenoma | | | | | | | | | | | X | | | X | X | | | | | | | | | | | 5 |
| **General Body System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| None | | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Genital System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Clitoral gland | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 48 |
| Ovary | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Cystadenoma | | | | | | | X | | | | | | X | | | | | | | | | | | | | 2 |
| Histiocytic sarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Uterus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Histiocytic sarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Polyp stromal | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |

**Table D2**
**Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Triethanolamine: 1,000 mg/kg**
(continued)

| | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Number of Days on Study** | 317 | 415 | 521 | 537 | 551 | 591 | 647 | 661 | 670 | 680 | 699 | 712 | 712 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 730 | 730 |
| **Carcass ID Number** | 423 | 479 | 464 | 436 | 461 | 473 | 458 | 476 | 428 | 480 | 447 | 456 | 462 | 421 | 425 | 439 | 440 | 441 | 454 | 468 | 469 | 475 | 478 | 426 | 430 |
| **Hematopoietic System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone marrow | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Lymph node | | | | | | + | | + | | | | + | | | | | | | | | | | | + | |
| Pancreatic, histiocytic sarcoma | | | | | | X | | | | | | | | | | | | | | | | | | | |
| Lymph node, mandibular | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Histiocytic sarcoma | | | X | | | X | | | | | | | | | | | | | | | | | | | |
| Lymph node, mesenteric | + | + | + | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + |
| Histiocytic sarcoma | | | X | | | X | | | | | | | | | | | | | | | | | | | |
| Spleen | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Histiocytic sarcoma | | | | | | X | | | | | | | X | | | | | | | | | | | | |
| Thymus | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Histiocytic sarcoma | | | X | | | X | | | | | | | | | | | | | | | | | | | |
| Thymoma NOS | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Integumentary System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Mammary gland | + | + | + | M | + | + | + | + | + | + | M | + | M | + | + | + | + | + | + | + | + | + | + | + | + |
| Skin | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Subcutaneous tissue, fibrosarcoma, multiple | | | | | | | | | | X | | | | | | | | | | | | | | | |
| **Musculoskeletal System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Scapula, osteosarcoma | | | | | | | | X | | | | | | | | | | | | | | | | | |
| Vertebra, osteosarcoma | | | | | X | | | | | | | | | | | | | | | | | | | | |
| **Nervous System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Brain | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Peripheral nerve | | | | | | | | | + | | | | | | | | | | | | | | | | |
| Spinal cord | | | | | | | | | + | | | | | | | | | | | | | | | | |
| **Respiratory System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lung | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Alveolar/bronchiolar adenoma | | | X | | | | | | | | | | | | | | | X | | | X | | | | |
| Alveolar/bronchiolar carcinoma | | X | | | | | | | | | | | | | | | | | | | | | | | |
| Fibrosarcoma, metastatic, skin | | | | | | | | | | X | | | | | | | | | | | | | | | |
| Histiocytic sarcoma | | | | | | X | | | | | | | X | | | | | | | | | | | | |
| Osteosarcoma, metastatic, bone | | | | | | | | X | | | | | | | | | | | | | | | | | |
| Osteosarcoma, metastatic, tissue NOS | | | | | X | | | | | | | | | | | | | | | | | | | | |
| Nose | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Trachea | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **Special Senses System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Ear | | | | | | | | | + | | | | | | | | | | | | | | | | |
| **Urinary System** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Kidney | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Urinary bladder | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |

**TABLE D2**
**Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Triethanolamine: 1,000 mg/kg**
(continued)

| Number of Days on Study | 7 3 0 | 7 3 0 | 7 3 0 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 1 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | 7 3 2 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carcass ID Number** | 4 5 0 | 4 5 3 | 4 6 7 | 4 2 2 | 4 2 9 | 4 4 2 | 4 4 5 | 4 5 1 | 4 5 9 | 4 7 2 | 4 7 4 | 4 2 4 | 4 2 7 | 4 3 1 | 4 3 2 | 4 3 3 | 4 3 7 | 4 4 3 | 4 4 4 | 4 4 9 | 4 6 0 | 4 6 5 | 4 6 6 | 4 7 1 | 4 7 7 | Total Tissues/ Tumors |
| **Hematopoietic System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone marrow | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Lymph node | | | | | | + | | | + | | | | | | | | + | | + | | | | | | + | 9 |
| Pancreatic, histiocytic sarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Lymph node, mandibular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Histiocytic sarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | 2 |
| Lymph node, mesenteric | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Histiocytic sarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | 2 |
| Spleen | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Histiocytic sarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | 2 |
| Thymus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | 48 |
| Histiocytic sarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | 2 |
| Thymoma NOS | | | X | | | | | | | | | | | | | | | | | | | | | | | 1 |
| **Integumentary System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Mammary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 47 |
| Skin | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Subcutaneous tissue, fibrosarcoma, multiple | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| **Musculoskeletal System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Scapula, osteosarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Vertebra, osteosarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| **Nervous System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Brain | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Peripheral nerve | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Spinal cord | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| **Respiratory System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lung | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Alveolar/bronchiolar adenoma | | | | | | | | | | | | | | | | | | | X | X | | | | | | 5 |
| Alveolar/bronchiolar carcinoma | | | | | X | | | | | | | | | | | | | | | | | | | | | 2 |
| Fibrosarcoma, metastatic, skin | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Histiocytic sarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | 2 |
| Osteosarcoma, metastatic, bone | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Osteosarcoma, metastatic, tissue NOS | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Nose | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Trachea | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **Special Senses System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Ear | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| **Urinary System** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Kidney | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Urinary bladder | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |

**TABLE D2**
**Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Triethanolamine: 1,000 mg/kg**
(continued)

| | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 3 | 4 | 5 | 5 | 5 | 5 | 6 | 6 | 6 | 6 | 6 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 |
| **Number of Days on Study** | 1 | 1 | 2 | 3 | 5 | 9 | 4 | 6 | 7 | 8 | 9 | 1 | 1 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 3 | 3 |
| | 7 | 5 | 1 | 7 | 1 | 1 | 7 | 1 | 0 | 0 | 9 | 2 | 2 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 0 | 0 |
| | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| **Carcass ID Number** | 2 | 7 | 6 | 3 | 6 | 7 | 5 | 7 | 2 | 8 | 4 | 5 | 6 | 2 | 2 | 3 | 4 | 4 | 5 | 6 | 6 | 7 | 7 | 2 | 3 |
| | 3 | 9 | 4 | 6 | 1 | 3 | 8 | 6 | 8 | 0 | 7 | 6 | 2 | 1 | 5 | 9 | 0 | 1 | 4 | 8 | 9 | 5 | 8 | 6 | 0 |
| **Systemic Lesions** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Multiple organs | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Histiocytic sarcoma | | | X | | | X | | | | | | | X | | | | | | | | | | | | |
| Leukemia lymphocytic | | | | | | | | | X | | | | | | | | | | | | | | | | |
| Lymphoma malignant | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lymphoma malignant lymphocytic | | | | | | | | | | | | X | | | | | | | | | | | | | |
| Lymphoma malignant mixed | X | | | | | | | | | | | | | | | | | | | | | | | X | |
| Lymphoma malignant undifferentiated cell type | | | | | | | | X | | | | | | | | | | | | | | | | | |

**TABLE D2**
**Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Triethanolamine: 1,000 mg/kg**
(continued)

| | | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | |
| **Number of Days on Study** | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | |
| | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | |
| | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | Total |
| **Carcass ID Number** | 5 | 5 | 6 | 2 | 2 | 4 | 4 | 5 | 5 | 7 | 7 | 2 | 2 | 3 | 3 | 3 | 3 | 4 | 4 | 4 | 6 | 6 | 6 | 7 | 7 | Tissues/ |
| | 0 | 3 | 7 | 2 | 9 | 2 | 5 | 1 | 9 | 2 | 4 | 4 | 7 | 1 | 2 | 3 | 7 | 3 | 4 | 9 | 0 | 5 | 6 | 1 | 7 | Tumors |
| **Systemic Lesions** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Multiple organs | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Histiocytic sarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | 3 |
| Leukemia lymphocytic | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Lymphoma malignant | | | | | | | | | | | | | X | | | | | | | | | | | | | 1 |
| Lymphoma malignant lymphocytic | | | | | X | X | | | | | | | | | | | X | | | | | | | | | 4 |
| Lymphoma malignant mixed | | X | | | | | | | X | | | | | X | | | | | X | | | | X | | | 7 |
| Lymphoma malignant undifferentiated cell type | | | | | | | | | | | | | | | X | | | | | | | | | X | | 3 |

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

| | 0 mg/kg | 100 mg/kg | 300 mg/kg | 1,000 mg/kg |
|---|---|---|---|---|
| **Liver: Hemangiosarcoma** | | | | |
| Overall rate[a] | 0/50 (0%) | 3/50 (6%) | 0/50 (0%) | 0/50 (0%) |
| Adjusted rate[b] | 0.0% | 7.5% | 0.0% | 0.0% |
| Terminal rate[c] | 0/39 (0%) | 3/40 (8%) | 0/38 (0%) | 0/37 (0%) |
| First incidence (days) | —[e] | 729 (T) | — | — |
| Life table test[d] | P=0.289N | P=0.126 | —[f] | — |
| Logistic regression test[d] | P=0.289N | P=0.126 | — | — |
| Cochran-Armitage test[d] | P=0.276N | | | |
| Fisher exact test[d] | | P=0.121 | — | — |
| **Liver: Hepatocellular Adenoma** | | | | |
| Overall rate | 22/50 (44%) | 22/50 (44%) | 24/50 (48%) | 40/50 (80%) |
| Adjusted rate | 54.9% | 53.6% | 58.3% | 95.2% |
| Terminal rate | 21/39 (54%) | 21/40 (53%) | 21/38 (55%) | 35/37 (95%) |
| First incidence (days) | 681 | 650 | 597 | 647 |
| Life table test | P<0.001 | P=0.537N | P=0.379 | P<0.001 |
| Logistic regression test | P<0.001 | P=0.496N | P=0.480 | P<0.001 |
| Cochran-Armitage test | P<0.001 | | | |
| Fisher exact test | | P=0.580N | P=0.421 | P<0.001 |
| **Liver: Hepatocellular Carcinoma** | | | | |
| Overall rate | 1/50 (2%) | 4/50 (8%) | 7/50 (14%) | 5/50 (10%) |
| Adjusted rate | 2.6% | 9.0% | 16.0% | 12.8% |
| Terminal rate | 1/39 (3%) | 2/40 (5%) | 4/38 (11%) | 4/37 (11%) |
| First incidence (days) | 729 (T) | 557 | 434 | 591 |
| Life table test | P=0.203 | P=0.201 | P=0.038 | P=0.098 |
| Logistic regression test | P=0.204 | P=0.176 | P=0.024 | P=0.110 |
| Cochran-Armitage test | P=0.218 | | | |
| Fisher exact test | | P=0.181 | P=0.030 | P=0.102 |
| **Liver: Hepatocellular Adenoma or Carcinoma** | | | | |
| Overall rate | 23/50 (46%) | 26/50 (52%) | 28/50 (56%) | 41/50 (82%) |
| Adjusted rate | 57.4% | 60.2% | 64.7% | 95.3% |
| Terminal rate | 22/39 (56%) | 23/40 (58%) | 23/38 (61%) | 35/37 (95%) |
| First incidence (days) | 681 | 557 | 434 | 591 |
| Life table test | P<0.001 | P=0.395 | P=0.187 | P<0.001 |
| Logistic regression test | P<0.001 | P=0.457 | P=0.276 | P<0.001 |
| Cochran-Armitage test | P<0.001 | | | |
| Fisher exact test | | P=0.345 | P=0.212 | P<0.001 |
| **Lung: Alveolar/bronchiolar Adenoma** | | | | |
| Overall rate | 2/50 (4%) | 4/50 (8%) | 2/50 (4%) | 5/49 (10%) |
| Adjusted rate | 5.1% | 10.0% | 5.3% | 13.0% |
| Terminal rate | 2/39 (5%) | 4/40 (10%) | 2/38 (5%) | 4/36 (11%) |
| First incidence (days) | 729 (T) | 729 (T) | 729 (T) | 521 |
| Life table test | P=0.173 | P=0.348 | P=0.686 | P=0.196 |
| Logistic regression test | P=0.201 | P=0.348 | P=0.686 | P=0.217 |
| Cochran-Armitage test | P=0.200 | | | |
| Fisher exact test | | P=0.339 | P=0.691N | P=0.210 |

**Table D3**
**Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Dermal Study of Triethanolamine** (continued)

| | 0 mg/kg | 100 mg/kg | 300 mg/kg | 1,000 mg/kg |
|---|---|---|---|---|
| **Lung: Alveolar/bronchiolar Adenoma or Carcinoma** | | | | |
| Overall rate | 2/50 (4%) | 4/50 (8%) | 3/50 (6%) | 7/49 (14%) |
| Adjusted rate | 5.1% | 10.0% | 7.9% | 17.4% |
| Terminal rate | 2/39 (5%) | 4/40 (10%) | 3/38 (8%) | 5/36 (14%) |
| First incidence (days) | 729 (T) | 729 (T) | 729 (T) | 415 |
| Life table test | P=0.044 | P=0.348 | P=0.488 | P=0.074 |
| Logistic regression test | P=0.055 | P=0.348 | P=0.488 | P=0.071 |
| Cochran-Armitage test | P=0.054 | | | |
| Fisher exact test | | P=0.339 | P=0.500 | P=0.075 |
| **Ovary: Cystadenoma** | | | | |
| Overall rate | 5/50 (10%) | 0/50 (0%) | 4/50 (8%) | 2/50 (4%) |
| Adjusted rate | 12.3% | 0.0% | 10.5% | 5.4% |
| Terminal rate | 4/39 (10%) | 0/40 (0%) | 4/38 (11%) | 2/37 (5%) |
| First incidence (days) | 572 | — | 729 (T) | 729 (T) |
| Life table test | P=0.435N | P=0.031N | P=0.508N | P=0.234N |
| Logistic regression test | P=0.402N | P=0.031N | P=0.476N | P=0.204N |
| Cochran-Armitage test | P=0.406N | | | |
| Fisher exact test | | P=0.028N | P=0.500N | P=0.218N |
| **Ovary: Luteoma** | | | | |
| Overall rate | 3/50 (6%) | 2/50 (4%) | 0/50 (0%) | 0/50 (0%) |
| Adjusted rate | 7.7% | 5.0% | 0.0% | 0.0% |
| Terminal rate | 3/39 (8%) | 2/40 (5%) | 0/38 (0%) | 0/37 (0%) |
| First incidence (days) | 729 (T) | 729 (T) | — | — |
| Life table test | P=0.088N | P=0.488N | P=0.126N | P=0.130N |
| Logistic regression test | P=0.088N | P=0.488N | P=0.126N | P=0.130N |
| Cochran-Armitage test | P=0.082N | | | |
| Fisher exact test | | P=0.500N | P=0.121N | P=0.121N |
| **Pituitary Gland (Pars Distalis or Unspecified Site): Adenoma** | | | | |
| Overall rate | 4/44 (9%) | 6/49 (12%) | 4/49 (8%) | 5/49 (10%) |
| Adjusted rate | 10.1% | 15.4% | 10.8% | 12.8% |
| Terminal rate | 2/34 (6%) | 6/39 (15%) | 4/37 (11%) | 4/37 (11%) |
| First incidence (days) | 487 | 729 (T) | 729 (T) | 647 |
| Life table test | P=0.563 | P=0.443 | P=0.606N | P=0.537 |
| Logistic regression test | P=0.571N | P=0.451 | P=0.579N | P=0.568 |
| Cochran-Armitage test | P=0.580N | | | |
| Fisher exact test | | P=0.441 | P=0.581N | P=0.569 |
| **Spleen: Hemangiosarcoma** | | | | |
| Overall rate | 3/50 (6%) | 1/50 (2%) | 0/50 (0%) | 0/50 (0%) |
| Adjusted rate | 7.7% | 2.5% | 0.0% | 0.0% |
| Terminal rate | 3/39 (8%) | 1/40 (3%) | 0/38 (0%) | 0/37 (0%) |
| First incidence (days) | 729 (T) | 729 (T) | — | — |
| Life table test | P=0.117N | P=0.296N | P=0.126N | P=0.130N |
| Logistic regression test | P=0.117N | P=0.296N | P=0.126N | P=0.130N |
| Cochran-Armitage test | P=0.110N | | | |
| Fisher exact test | | P=0.309N | P=0.121N | P=0.121N |

**TABLE D3**
**Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Dermal Study of Triethanolamine** (continued)

| | 0 mg/kg | 100 mg/kg | 300 mg/kg | 1,000 mg/kg |
|---|---|---|---|---|
| **Thyroid Gland (Follicular Cell): Adenoma** | | | | |
| Overall rate | 4/50 (8%) | 2/50 (4%) | 5/50 (10%) | 6/50 (12%) |
| Adjusted rate | 10.3% | 5.0% | 13.2% | 16.2% |
| Terminal rate | 4/39 (10%) | 2/40 (5%) | 5/38 (13%) | 6/37 (16%) |
| First incidence (days) | 729 (T) | 729 (T) | 729 (T) | 729 (T) |
| Life table test | P=0.150 | P=0.325N | P=0.484 | P=0.335 |
| Logistic regression test | P=0.149 | P=0.325N | P=0.484 | P=0.335 |
| Cochran-Armitage test | P=0.182 | | | |
| Fisher exact test | | P=0.339N | P=0.500 | P=0.370 |
| **Thyroid Gland (Follicular Cell): Adenoma or Carcinoma** | | | | |
| Overall rate | 4/50 (8%) | 2/50 (4%) | 6/50 (12%) | 6/50 (12%) |
| Adjusted rate | 10.3% | 5.0% | 15.8% | 16.2% |
| Terminal rate | 4/39 (10%) | 2/40 (5%) | 6/38 (16%) | 6/37 (16%) |
| First incidence (days) | 729 (T) | 729 (T) | 729 (T) | 729 (T) |
| Life table test | P=0.162 | P=0.325N | P=0.352 | P=0.335 |
| Logistic regression test | P=0.162 | P=0.325N | P=0.352 | P=0.335 |
| Cochran-Armitage test | P=0.197 | | | |
| Fisher exact test | | P=0.339N | P=0.370 | P=0.370 |
| **All Organs: Hemangiosarcoma** | | | | |
| Overall rate | 4/50 (8%) | 3/50 (6%) | 0/50 (0%) | 0/50 (0%) |
| Adjusted rate | 10.3% | 7.5% | 0.0% | 0.0% |
| Terminal rate | 4/39 (10%) | 3/40 (8%) | 0/38 (0%) | 0/37 (0%) |
| First incidence (days) | 729 (T) | 729 (T) | — | — |
| Life table test | P=0.042N | P=0.486N | P=0.066N | P=0.070N |
| Logistic regression test | P=0.042N | P=0.486N | P=0.066N | P=0.070N |
| Cochran-Armitage test | P=0.038N | | | |
| Fisher exact test | | P=0.500N | P=0.059N | P=0.059N |
| **All Organs: Hemangioma or Hemangiosarcoma** | | | | |
| Overall rate | 4/50 (8%) | 4/50 (8%) | 1/50 (2%) | 0/50 (0%) |
| Adjusted rate | 10.3% | 10.0% | 2.6% | 0.0% |
| Terminal rate | 4/39 (10%) | 4/40 (10%) | 1/38 (3%) | 0/37 (0%) |
| First incidence (days) | 729 (T) | 729 (T) | 729 (T) | — |
| Life table test | P=0.037N | P=0.630N | P=0.187N | P=0.070N |
| Logistic regression test | P=0.037N | P=0.630N | P=0.187N | P=0.070N |
| Cochran-Armitage test | P=0.033N | | | |
| Fisher exact test | | P=0.643N | P=0.181N | P=0.059N |
| **All Organs: Malignant Lymphoma (Lymphocytic, Mixed, NOS, or Undifferentiated Cell Type)** | | | | |
| Overall rate | 6/50 (12%) | 10/50 (20%) | 6/50 (12%) | 15/50 (30%) |
| Adjusted rate | 15.4% | 23.1% | 15.1% | 37.0% |
| Terminal rate | 6/39 (15%) | 7/40 (18%) | 5/38 (13%) | 12/37 (32%) |
| First incidence (days) | 729 (T) | 639 | 624 | 317 |
| Life table test | P=0.013 | P=0.231 | P=0.607 | P=0.020 |
| Logistic regression test | P=0.019 | P=0.241 | P=0.597N | P=0.029 |
| Cochran-Armitage test | P=0.018 | | | |
| Fisher exact test | | P=0.207 | P=0.620N | P=0.024 |

**Table D3**
**Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Dermal Study of Triethanolamine** (continued)

| | 0 mg/kg | 100 mg/kg | 300 mg/kg | 1,000 mg/kg |
|---|---|---|---|---|
| **All Organs: Histiocytic Sarcoma** | | | | |
| Overall rate | 0/50 (0%) | 2/50 (4%) | 2/50 (4%) | 3/50 (6%) |
| Adjusted rate | 0.0% | 4.5% | 4.7% | 6.7% |
| Terminal rate | 0/39 (0%) | 1/40 (3%) | 1/38 (3%) | 0/37 (0%) |
| First incidence (days) | — | 414 | 579 | 521 |
| Life table test | P=0.165 | P=0.250 | P=0.249 | P=0.133 |
| Logistic regression test | P=0.123 | P=0.206 | P=0.220 | P=0.087 |
| Cochran-Armitage test | P=0.162 | | | |
| Fisher exact test | | P=0.247 | P=0.247 | P=0.121 |
| **All Organs: Benign Neoplasms** | | | | |
| Overall rate | 34/50 (68%) | 34/50 (68%) | 32/50 (64%) | 44/50 (88%) |
| Adjusted rate | 79.0% | 80.9% | 76.0% | 100.0% |
| Terminal rate | 30/39 (77%) | 32/40 (80%) | 28/38 (74%) | 37/37 (100%) |
| First incidence (days) | 487 | 650 | 579 | 521 |
| Life table test | P=0.001 | P=0.508N | P=0.465N | P=0.007 |
| Logistic regression test | P=0.003 | P=0.385N | P=0.275N | P=0.019 |
| Cochran-Armitage test | P=0.006 | | | |
| Fisher exact test | | P=0.585N | P=0.417N | P=0.014 |
| **All Organs: Malignant Neoplasms** | | | | |
| Overall rate | 11/50 (22%) | 22/50 (44%) | 21/50 (42%) | 25/50 (50%) |
| Adjusted rate | 27.5% | 46.6% | 43.9% | 52.8% |
| Terminal rate | 10/39 (26%) | 15/40 (38%) | 12/38 (32%) | 15/37 (41%) |
| First incidence (days) | 698 | 414 | 320 | 317 |
| Life table test | P=0.024 | P=0.030 | P=0.038 | P=0.005 |
| Logistic regression test | P=0.037 | P=0.021 | P=0.025 | P=0.004 |
| Cochran-Armitage test | P=0.021 | | | |
| Fisher exact test | | P=0.016 | P=0.026 | P=0.003 |
| **All Organs: Benign or Malignant Neoplasms** | | | | |
| Overall rate | 37/50 (74%) | 43/50 (86%) | 42/50 (84%) | 50/50 (100%) |
| Adjusted rate | 86.0% | 89.6% | 87.4% | 100.0% |
| Terminal rate | 33/39 (85%) | 35/40 (88%) | 32/38 (84%) | 37/37 (100%) |
| First incidence (days) | 487 | 414 | 320 | 317 |
| Life table test | P=0.003 | P=0.207 | P=0.180 | P=0.002 |
| Logistic regression test | P<0.001 | P=0.202 | P=0.266 | P<0.001 |
| Cochran-Armitage test | P<0.001 | | | |
| Fisher exact test | | P=0.105 | P=0.163 | P<0.001 |

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

**TABLE D4**
**Historical Incidence of Hepatocellular Neoplasms in Control Female B6C3F$_1$ Mice[a]**

| Study | Incidence in Controls | | |
|---|---|---|---|
| | Adenoma | Carcinoma | Adenoma or Carcinoma |
| **Historical Incidence in Dermal Studies (with Acetone Vehicle) at Battelle Columbus Laboratories** | | | |
| 4-Vinyl-1-cyclohexene diepoxide | 8/50 | 2/50 | 10/50 |
| Triethanolamine | 22/50 | 1/50 | 23/50 |
| **Overall Historical Incidence in Dermal Studies (with Acetone Vehicle)** | | | |
| Total | 34/150 (22.7%) | 7/150 (4.7%) | 40/150 (26.7%) |
| Standard deviation | 18.9% | 3.1% | 17.0% |
| Range | 8%-44% | 2%-8% | 14%-46% |
| **Overall Historical Incidence in Feed Studies** | | | |
| Total | 194/1,312 (14.8%) | 90/1,312 (6.9%) | 260/1,312 (19.8%) |
| Standard deviation | 10.5% | 6.1% | 12.8% |
| Range | 2%-50% | 0%-20% | 3%-56% |

[a] Data as of 17 June 1994

**Table D5**
**Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Dermal Study of Triethanolamine[a]**

| | 0 mg/kg | 100 mg/kg | 300 mg/kg | 1,000 mg/kg |
|---|---|---|---|---|
| **Disposition Summary** | | | | |
| Animals initially in study | 60 | 60 | 60 | 60 |
| ***15-Month interim evaluation*** | 10 | 10 | 10 | 10 |
| Early deaths | | | | |
| Moribund | 7 | 4 | 5 | 11 |
| Natural deaths | 4 | 6 | 7 | 2 |
| Survivors | | | | |
| Died last week of study | 1 | | | |
| Terminal sacrifice | 38 | 40 | 38 | 37 |
| Animals examined microscopically | 60 | 60 | 60 | 60 |
| ***15-Month Interim Evaluation*** | | | | |
| **Alimentary System** | | | | |
| Liver | (10) | (10) | (10) | (10) |
| Basophilic focus | | | 1 (10%) | |
| Clear cell focus | | 1 (10%) | | |
| Eosinophilic focus | 2 (20%) | | | 1 (10%) |
| Pancreas | (10) | (10) | (10) | (10) |
| Acinus, atrophy | 2 (20%) | | | |
| Stomach, forestomach | (10) | (10) | (10) | (10) |
| Acanthosis | 1 (10%) | | | |
| **Endocrine System** | | | | |
| Thyroid gland | (10) | (10) | (10) | (10) |
| Follicular cell, hyperplasia | | | | 3 (30%) |
| **Genital System** | | | | |
| Ovary | (9) | (10) | (9) | (10) |
| Thrombosis | | 1 (10%) | | |
| Follicle, cyst | 2 (22%) | 2 (20%) | 2 (22%) | |
| Follicle, cyst, multiple | | | 1 (11%) | |
| Uterus | (10) | (10) | (9) | (10) |
| Endometrium, hyperplasia, cystic, glandular | 10 (100%) | 10 (100%) | 9 (100%) | 9 (90%) |
| **Hematopoietic System** | | | | |
| Bone marrow | (10) | (10) | (10) | (10) |
| Myelofibrosis | 1 (10%) | 1 (10%) | | 1 (10%) |
| Lymph node, mesenteric | (8) | (10) | (8) | (10) |
| Hyperplasia, lymphoid | | | 1 (13%) | |
| Spleen | (10) | (10) | (10) | (10) |
| Hyperplasia, lymphoid | | | 1 (10%) | |
| Thymus | (9) | (10) | (9) | (10) |
| Hyperplasia, lymphoid | | | 1 (11%) | |

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

**TABLE D5**
**Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Dermal Study of Triethanolamine**
(continued)

| | 0 mg/kg | 100 mg/kg | 300 mg/kg | 1,000 mg/kg |
|---|---|---|---|---|
| ***15-Month Interim Evaluation*** (continued) | | | | |
| **Integumentary System** | | | | |
| Skin | (10) | (10) | (10) | (10) |
| Site of application-no mass, acanthosis | | 1 (10%) | | 2 (20%) |
| Site of application-no mass, inflammation, chronic | | | | 3 (30%) |
| **Urinary System** | | | | |
| Kidney | (10) | (10) | (10) | (10) |
| Nephropathy, chronic | 6 (60%) | 3 (30%) | 2 (20%) | 4 (40%) |
| ***Systems Examined with No Lesions Observed*** | | | | |
| **Cardiovascular System** | | | | |
| **General Body System** | | | | |
| **Musculoskeletal System** | | | | |
| **Nervous System** | | | | |
| **Respiratory System** | | | | |
| **Special Senses System** | | | | |
| ***2-Year Study*** | | | | |
| **Alimentary System** | | | | |
| Intestine large, colon | (50) | (50) | (50) | (50) |
| Inflammation, chronic active | 1 (2%) | | | |
| Intestine small, jejunum | (50) | (50) | (50) | (50) |
| Peyer's patch, hyperplasia, lymphoid | | 2 (4%) | | |
| Liver | (50) | (50) | (50) | (50) |
| Basophilic focus | | 2 (4%) | 1 (2%) | 1 (2%) |
| Clear cell focus | 1 (2%) | | | 1 (2%) |
| Congestion | | | 1 (2%) | |
| Cytoplasmic alteration | | 1 (2%) | | |
| Eosinophilic focus | 9 (18%) | 10 (20%) | 18 (36%) | 16 (32%) |
| Fatty change | | | | 1 (2%) |
| Hematopoietic cell proliferation | | 1 (2%) | | |
| Hepatodiaphragmatic nodule | | 1 (2%) | | |
| Hypertrophy | 1 (2%) | | | |
| Infiltration cellular, lymphocyte | | | 2 (4%) | |
| Inflammation, chronic active | | 1 (2%) | 1 (2%) | |
| Karyomegaly | | 1 (2%) | | |
| Leukocytosis | 1 (2%) | | | |
| Necrosis | 2 (4%) | 3 (6%) | 2 (4%) | 1 (2%) |
| Kupffer cell, hyperplasia | | | | 1 (2%) |
| Mesentery | (2) | (5) | (5) | (5) |
| Fat, infiltration cellular, lymphocyte | | | 1 (20%) | |
| Fat, inflammation, chronic | 2 (100%) | 4 (80%) | 3 (60%) | 3 (60%) |

**Table D5**
**Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Dermal Study of Triethanolamine** (continued)

| | 0 mg/kg | 100 mg/kg | 300 mg/kg | 1,000 mg/kg |
|---|---|---|---|---|
| ***2-Year Study*** (continued) | | | | |
| **Alimentary System** (continued) | | | | |
| Pancreas | (50) | (50) | (50) | (50) |
| Cyst | | 1 (2%) | | |
| Inflammation, chronic active | 1 (2%) | 1 (2%) | | |
| Acinus, atrophy | 2 (4%) | 2 (4%) | 1 (2%) | |
| Artery, inflammation, chronic | | 1 (2%) | | |
| Duct, cyst | | | 1 (2%) | |
| Stomach, forestomach | (50) | (50) | (50) | (50) |
| Acanthosis | | | 1 (2%) | 1 (2%) |
| Stomach, glandular | (50) | (50) | (50) | (50) |
| Hyperplasia | 1 (2%) | 1 (2%) | | 1 (2%) |
| Inflammation, chronic active | | 1 (2%) | | |
| Pigmentation | | 1 (2%) | | 1 (2%) |
| Ulcer | 1 (2%) | | | |
| **Cardiovascular System** | | | | |
| Heart | (50) | (50) | (50) | (50) |
| Artery, thrombosis | 1 (2%) | | | |
| Coronary artery, inflammation, chronic | 1 (2%) | | | |
| **Endocrine System** | | | | |
| Adrenal cortex | (50) | (49) | (50) | (50) |
| Hyperplasia | | | | 1 (2%) |
| Hypertrophy | 3 (6%) | 2 (4%) | 3 (6%) | 1 (2%) |
| Infiltration cellular, lymphocyte | | | 1 (2%) | |
| Necrosis | | 1 (2%) | | |
| Capsule, accessory adrenal cortical nodule | 2 (4%) | | | 2 (4%) |
| Capsule, cyst | | 1 (2%) | 1 (2%) | |
| Capsule, spindle cell, hyperplasia | | 1 (2%) | 1 (2%) | |
| Adrenal medulla | (50) | (50) | (50) | (50) |
| Cyst | | | 1 (2%) | |
| Hyperplasia | 1 (2%) | 3 (6%) | | 3 (6%) |
| Pituitary gland | (44) | (49) | (49) | (49) |
| Pars distalis, angiectasis | | | | 1 (2%) |
| Pars distalis, cyst | 1 (2%) | 2 (4%) | | 1 (2%) |
| Pars distalis, hyperplasia | 3 (7%) | 7 (14%) | 8 (16%) | 5 (10%) |
| Pars intermedia, hyperplasia | | | 1 (2%) | |
| Rathke's cleft, cyst | 1 (2%) | | | |
| Rathke's cleft, hemorrhage | | | | 1 (2%) |
| Thyroid gland | (50) | (50) | (50) | (50) |
| Infiltration cellular, lymphocyte | | 1 (2%) | | |
| Inflammation, chronic active | | 1 (2%) | | |
| Follicle, cyst | | 1 (2%) | | 2 (4%) |
| Follicular cell, hyperplasia | 23 (46%) | 20 (40%) | 18 (36%) | 24 (48%) |
| **General Body System** | | | | |
| None | | | | |

**Table D5**
**Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Dermal Study of Triethanolamine** (continued)

| | 0 mg/kg | 100 mg/kg | 300 mg/kg | 1,000 mg/kg |
|---|---|---|---|---|
| ***2-Year Study*** (continued) | | | | |
| **Genital System** | | | | |
| Clitoral gland | (49) | (48) | (47) | (48) |
| Inflammation, chronic | | | | 1 (2%) |
| Duct, ectasia | 3 (6%) | 1 (2%) | 2 (4%) | 3 (6%) |
| Ovary | (50) | (50) | (50) | (50) |
| Atrophy | 34 (68%) | 37 (74%) | 34 (68%) | 29 (58%) |
| Cyst | | 1 (2%) | | |
| Thrombosis | | 1 (2%) | 2 (4%) | 1 (2%) |
| Follicle, cyst | 13 (26%) | 17 (34%) | 16 (32%) | 14 (28%) |
| Periovarian tissue, cyst | | 1 (2%) | 1 (2%) | |
| Periovarian tissue, infiltration cellular, lymphocyte | | | 1 (2%) | |
| Periovarian tissue, inflammation, chronic active | | 1 (2%) | | |
| Uterus | (50) | (50) | (50) | (50) |
| Hemorrhage | 1 (2%) | | | |
| Infiltration cellular, lymphocyte | | | 1 (2%) | |
| Inflammation, chronic | 1 (2%) | | | |
| Endometrium, hyperplasia, cystic, glandular | 47 (94%) | 48 (96%) | 47 (94%) | 44 (88%) |
| Lymphatic, ectasia | 1 (2%) | | | |
| **Hematopoietic System** | | | | |
| Bone marrow | (50) | (50) | (50) | (50) |
| Myelofibrosis | 6 (12%) | 15 (30%) | 4 (8%) | 6 (12%) |
| Myeloid cell, atrophy | | | | 1 (2%) |
| Lymph node | (4) | (8) | (6) | (9) |
| Mediastinal, hyperplasia, lymphoid | 1 (25%) | | 1 (17%) | |
| Lymph node, mandibular | (47) | (49) | (49) | (49) |
| Hyperplasia, lymphoid | | 1 (2%) | 2 (4%) | 1 (2%) |
| Lymph node, mesenteric | (46) | (49) | (48) | (49) |
| Hematopoietic cell proliferation | 1 (2%) | | | |
| Hyperplasia, lymphoid | | 1 (2%) | | |
| Spleen | (50) | (50) | (50) | (50) |
| Hematopoietic cell proliferation | 3 (6%) | 9 (18%) | 3 (6%) | 6 (12%) |
| Hyperplasia, lymphoid | | 5 (10%) | 4 (8%) | |
| Necrosis | | | 1 (2%) | |
| Thymus | (46) | (47) | (49) | (48) |
| Atrophy | 19 (41%) | 28 (60%) | 28 (57%) | 22 (46%) |
| Cyst | | | | 1 (2%) |
| Hyperplasia, lymphoid | | 1 (2%) | 1 (2%) | |
| **Integumentary System** | | | | |
| Mammary gland | (48) | (48) | (50) | (47) |
| Hyperplasia, glandular | | | | 1 (2%) |
| Skin | (50) | (50) | (50) | (50) |
| Acanthosis | | | 1 (2%) | |
| Inguinal, inflammation, chronic | | | | 1 (2%) |
| Site of application-no mass, acanthosis | | 2 (4%) | 1 (2%) | 3 (6%) |
| Site of application-no mass, inflammation, chronic | | 2 (4%) | 2 (4%) | 5 (10%) |

**TABLE D5**
**Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Dermal Study of Triethanolamine**
(continued)

| | 0 mg/kg | 100 mg/kg | 300 mg/kg | 1,000 mg/kg |
|---|---|---|---|---|
| ***2-Year Study*** (continued) | | | | |
| **Musculoskeletal System** | | | | |
| Bone | (50) | (50) | (50) | (50) |
| Vertebra, coccygeal, fracture | | | | 1 (2%) |
| **Nervous System** | | | | |
| Brain | (50) | (50) | (50) | (50) |
| Compression | 3 (6%) | 3 (6%) | 1 (2%) | 1 (2%) |
| Hemorrhage | | | | 2 (4%) |
| Medulla, hemorrhage | | | 1 (2%) | |
| Peripheral nerve | (2) | (1) | | (1) |
| Sciatic, degeneration | | | | 1 (100%) |
| Spinal cord | (2) | (1) | | (1) |
| Nerve, degeneration | 1 (50%) | 1 (100%) | | 1 (100%) |
| White matter, degeneration | | 1 (100%) | | |
| **Respiratory System** | | | | |
| Lung | (50) | (50) | (50) | (49) |
| Hemorrhage, focal | | | 1 (2%) | |
| Inflammation, chronic active | | 1 (2%) | | 1 (2%) |
| Mineralization, focal | | | | 1 (2%) |
| Alveolar epithelium, hyperplasia | 1 (2%) | | | 1 (2%) |
| Alveolar epithelium, hyperplasia, macrophage | | 1 (2%) | | |
| Pleura, hyperplasia | | | 1 (2%) | |
| **Special Senses System** | | | | |
| Ear | (1) | | (1) | (1) |
| Internal ear, hyperplasia, glandular | | | 1 (100%) | |
| Harderian gland | (1) | (2) | (1) | |
| Acinus, hyperplasia | | 1 (50%) | | |
| **Urinary System** | | | | |
| Kidney | (50) | (50) | (50) | (50) |
| Amyloid deposition | 1 (2%) | | | |
| Inflammation, chronic active | | 1 (2%) | | |
| Nephropathy, chronic | 16 (32%) | 27 (54%) | 28 (56%) | 21 (42%) |
| Cortex, cyst | 1 (2%) | | | |
| Cortex, infarct | | 3 (6%) | 2 (4%) | |
| Pelvis, inflammation, acute | 1 (2%) | | | |
| Renal tubule, hyperplasia, cystic | | | | 1 (2%) |
| Renal tubule, necrosis | | 1 (2%) | | |
| Urinary bladder | (50) | (50) | (50) | (50) |
| Inflammation, chronic active | | 1 (2%) | | 1 (2%) |

# APPENDIX E
# GENETIC TOXICOLOGY

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# GENETIC TOXICOLOGY

## *SALMONELLA TYPHIMURIUM* MUTAGENICITY TEST PROTOCOL

Testing was performed as reported by Mortelmans *et al.* (1986). Triethanolamine was sent to the laboratory as a coded aliquot from Radian Corporation (Austin, TX). It was incubated with the *Salmonella typhimurium* tester strains TA98, TA100, TA1535, and TA1537 either in buffer or S9 mix (metabolic activation enzymes and cofactors from Aroclor 1254-induced male Sprague-Dawley rat or Syrian hamster liver) for 20 minutes at 37° C. Top agar supplemented with L-histidine and d-biotin was added, and the contents of the tubes were mixed and poured onto the surfaces of minimal glucose agar plates. Histidine-independent mutant colonies arising on these plates were counted following incubation for 2 days at 37° C.

Each trial consisted of triplicate plates of concurrent positive and negative controls and five doses of triethanolamine. The high dose was limited by toxicity. All trials were repeated.

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

## CHINESE HAMSTER OVARY CELL CYTOGENETICS PROTOCOLS

Testing was performed as reported by Galloway *et al.* (1987). Triethanolamine was sent to the laboratory as a coded aliquot by Radian Corporation. It was tested in cultured Chinese hamster ovary (CHO) cells for induction of sister chromatid exchanges (SCEs) and chromosomal aberrations (Abs), both in the presence and absence of Aroclor 1254-induced male Sprague-Dawley rat liver S9 and cofactor mix. Cultures were handled under gold lights to prevent photolysis of bromodeoxyuridine-substituted DNA. Each test consisted of concurrent solvent and positive controls and of at least three doses of triethanolamine. In the trials conducted without S9, the high dose was limited by toxicity; in the trials with S9, the high dose was limited to 10,100 $\mu$g/mL. A single flask per dose was used, and tests yielding equivocal or positive results were repeated.

***Sister Chromatid Exchange Test:*** In the SCE test without S9, CHO cells were incubated for up to 26 hours with triethanolamine in supplemented McCoy's 5A medium. Bromodeoxyuridine (BrdU) was added 2 hours after culture initiation. After 26 hours, the medium containing triethanolamine was removed and replaced with fresh medium plus BrdU and Colcemid, and incubation was continued for up to 2 hours. Cells were then harvested by mitotic shake-off, fixed, and stained with Hoechst 33258 and Giemsa. In the SCE test with S9, cells were incubated with triethanolamine, serum-free medium, and S9 for 2 hours. The medium was then removed and replaced with medium containing serum and BrdU and no triethanolamine and incubation proceeded for an additional 25.8 hours, with Colcemid present for the final 2 hours. Harvesting and staining were the same as for cells treated without S9. All slides were scored blind and those from a single test were read by the same person. Fifty second-division metaphase cells were scored for frequency of SCEs/cell from each dose level.

Statistical analyses were conducted on the slopes of the dose-response curves and the individual dose points (Galloway *et al.*, 1987). An SCE frequency 20% above the concurrent solvent control value was chosen as a statistically conservative positive response. The probability of this level of difference occurring by chance at one dose point is less than 0.01; the probability for such a chance occurrence at two dose points is less than 0.001. An increase of 20% or greater at any single dose was considered weak evidence of activity;

increases at two or more doses resulted in a determination that the trial was positive. A statistically significant trend ($P<0.005$) in the absence of any responses reaching 20% above background led to a call of equivocal.

***Chromosomal Aberrations Test:*** In the Abs test without S9, cells were incubated in McCoy's 5A medium with triethanolamine for 8.5 hours; Colcemid was added, and incubation continued for 2 hours. The cells were then harvested by mitotic shake-off, fixed, and stained with Giemsa. For the Abs test with S9, cells were treated with triethanolamine and S9 for 2 hours, after which the treatment medium was removed and the cells were incubated for 8.5 hours in fresh medium, with Colcemid present for the final 2 hours. Cells were harvested in the same manner as for the treatment without S9.

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

Chromosomal aberration data are presented as percentage of cells with aberrations. To arrive at a statistical call for a trial, analyses were conducted on both the dose response curve and individual dose points. For a single trial, a statistically significant ($P\leq0.05$) difference for one dose point and a significant trend ($P\leq0.015$) were considered weak evidence for a positive response; significant differences for two or more doses indicated the trial was positive. A positive trend test in the absence of a statistically significant increase at any one dose resulted in an equivocal call (Galloway *et al.*, 1987). Ultimately, the trial calls were based on a consideration of the statistical analyses as well as the biological information available to the reviewers.

## *DROSOPHILA MELANOGASTER* TEST PROTOCOL

The assays for induction of sex-linked recessive lethal (SLRL) mutations were performed with adult flies as described by Yoon *et al.* (1985). Triethanolamine was supplied as a coded aliquot by Radian Corporation. It was assayed in the SLRL test by feeding for 3 days to adult Canton-S wild-type males no more than 24 hours old at the beginning of treatment. Because no response was obtained, triethanolamine was retested by injection into adult males. Three dose levels were tested to ensure adequate testing of the chemical.

To administer a chemical by injection, a glass Pasteur pipette was drawn out in a flame to a microfine filament, and the tip was broken off to allow delivery of the test solution. Injection was performed either manually, by attaching a rubber bulb to the other end of the pipette and forcing through sufficient solution (0.2 to 0.3 $\mu$L) to slightly distend the abdomen of the fly, or by attaching the pipette to a microinjector which automatically delivered a calibrated volume. Flies were anesthetized with ether and immobilized on a strip of tape. Injection into the thorax, under the wing, was performed with the aid of a dissecting microscope.

Toxicity tests were performed to set concentrations of triethanolamine at a level that would induce 30% mortality after 72 hours of feeding or 24 hours after injection, while keeping induced sterility at an acceptable level. Oral exposure was achieved by allowing Canton-S males to feed for 72 hours on a solution of triethanolamine in 5% sucrose. In the injection experiments, 24- to 72-hour-old Canton-S males were treated with a solution of triethanolamine dissolved in saline or peanut oil and allowed to recover for 24 hours. A concurrent saline or peanut oil control group was also included. In the adult exposures, treated males were mated to three *Basc* females for 3 days and given fresh females at 2-day intervals to produce three matings of 3, 2, and 2 days (in each case, sample sperm from successive matings were treated at successively earlier post-meiotic stages). $F_1$ heterozygous females were mated with their siblings and

then placed in individual vials. $F_1$ daughters from the same parental male were kept together to identify clusters. (A cluster occurs when a number of mutants from a given male result from a single spontaneous premeiotic mutation event and is identified when the number of mutants from that male exceeds the number predicted by a Poisson distribution.) If a cluster was identified, all data from the male in question were discarded. Clusters were identified in four dose groups in this series of experiments. These are noted in Table E4. Presumptive lethal mutations were identified as vials containing fewer than 5% of the expected number of wild-type males after 17 days; these were retested to confirm the response.

SLRL data were analyzed by simultaneous comparison with the concurrent and historical controls, using a normal approximation to the binomial test (Margolin *et al.*, 1983). A test result was considered positive if the P value was less than or equal to 0.01 and the mutation frequency in the tested group is greater than 0.10%, or if the P value was less than or equal to 0.05 and the frequency in the treatment group was greater than 0.15%. A test was considered to be inconclusive if (a) the P value was between 0.05 and 0.01 but the frequency in the treatment group was between 0.10% and 0.15% or (b) the P value was between 0.10 and 0.05 but the frequency in the treatment group was greater than 0.10%. A test was considered negative if the P value was greater than or equal to 0.10 or if the frequency in the treatment group was less than 0.10%.

## MOUSE PERIPHERAL BLOOD MICRONUCLEUS TEST PROTOCOL

A detailed discussion of this assay is presented by MacGregor *et al.* (1990). Peripheral blood samples were obtained from male and female B6C3$F_1$ mice at the end of the 13-week toxicity study. Smears were immediately prepared and fixed in absolute methanol and were later stained with a chromatin-specific fluorescent dye mixture of Hoechst 33258/pyronin Y (MacGregor *et al.*, 1983) and coded. Slides were scanned to determine the frequency of micronuclei in 2,000 polychromatic erythrocytes (PCEs) and 10,000 normochromatic erythrocytes (NCEs) in each animal per dose group.

Log transformation of the NCE data, testing for normality by the Shapiro-Wilk test, and testing for heterogeneity of variance by Cochran's test were performed before statistical analyses. The frequency of micronucleated cells among NCEs was analyzed by analysis of variance using the SAS GLM procedure. The NCE data for each dose group were compared with the concurrent solvent control with a Student's *t*-test. The frequency of micronucleated cells among PCEs was analyzed by the Cochran-Armitage trend test, and individual dose groups were compared to the concurrent solvent control by Kastenbaum-Bowman's binomial test.

## EVALUATION PROTOCOL

These are the basic guidelines for arriving at an overall assay result for assays performed by the National Toxicology Program. Statistical as well as biological factors are considered. For an individual assay, the statistical procedures for data analysis have been described in the preceding protocols. There have been instances, however, in which multiple aliquots of a chemical were tested in the same assay, and differing results were obtained among aliquots and/or among laboratories. Results from more than one aliquot or from more than one laboratory are not simply combined into an overall result. Rather, all the data are critically evaluated, particularly with regard to pertinent protocol variations, in determining the weight of evidence for an overall conclusion of chemical activity in an assay. In addition to multiple aliquots, the *in vitro* assays have another variable that must be considered in arriving at an overall test result. *In vitro* assays are conducted with and without exogenous metabolic activation. Results obtained in the absence of activation are not combined with results obtained in the presence of activation; each testing condition is evaluated separately. The summary table in the Abstract of this Technical Report presents a result that represents a scientific judgement of the overall evidence for activity of the chemical in an assay.

## RESULTS

Triethanolamine (33 to 3,333 μg/plate) was negative for induction of mutations in *S. typhimurium* strains TA98, TA100, TA1535, and TA1537 when tested with or without S9 metabolic activation (Table E1; Mortelmans *et al.*, 1986). In cytogenetic tests with cultured CHO cells, no induction of SCEs (Table E2) or Abs (Table E3) was observed with or without S9 (Galloway *et al.*, 1987). In the SCE test without S9, the first of two trials was negative. In the second trial, a significant increase in SCEs was observed at the highest dose tested (2,520 μg/mL), but the trend test was negative ($P \geq 0.025$), and the trial was concluded to be equivocal. Severe cytotoxicity limited the number of cells that could be scored at this high dose. Overall, the SCE test was considered to be negative. Cytotoxicity was also noted at the highest dose tested (4,030 μg/mL) in the Abs test without S9.

Triethanolamine administered by feeding or injection at doses up to 30,000 ppm did not induce SLRL mutations in germ cells of male *D. melanogaster* (Table E4; Yoon *et al.*, 1985). Results of an *in vivo* peripheral blood micronucleus test in mice were also negative (Table E5). In this test, blood samples were obtained from male and female mice after 13 weeks of dermal applications of 1,000 to 4,000 mg/kg triethanolamine. No significant increases in the frequencies of micronucleated NCEs or PCEs were observed at any dose tested.

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

| Strain | Dose (μg/plate) | Revertants/Plate[b] -S9 Trial 1 | -S9 Trial 2 | +10% hamster S9 Trial 1 | +10% hamster S9 Trial 2 | +10% rat S9 Trial 1 | +10% rat S9 Trial 2 |
|---|---|---|---|---|---|---|---|
| **TA100** | 0 | 89 ± 2.6 | 104 ± 11.8 | 192 ± 13.5 | 163 ± 14.8 | 159 ± 15.2 | 164 ± 8.4 |
| | 33 | 96 ± 8.5 | 112 ± 6.1 | 180 ± 7.9 | 145 ± 4.2 | 162 ± 9.9 | 143 ± 14.5 |
| | 100 | 87 ± 3.1 | 98 ± 2.2 | 215 ± 26.7 | 162 ± 11.0 | 151 ± 6.1 | 157 ± 4.4 |
| | 333 | 74 ± 12.7 | 93 ± 5.2 | 188 ± 10.0 | 154 ± 4.6 | 165 ± 3.7 | 147 ± 12.2 |
| | 1,000 | 73 ± 3.2 | 106 ± 10.6 | 145 ± 5.2 | 148 ± 13.6 | 152 ± 6.1 | 149 ± 5.4 |
| | 3,333 | 74 ± 4.8 | 96 ± 5.3 | 155 ± 3.8 | 137 ± 2.6 | 153 ± 14.2 | 122 ± 20.8 |
| Trial summary | | Negative | Negative | Negative | Negative | Negative | Negative |
| Positive control[c] | | 359 ± 21.0 | 425 ± 29.6 | 668 ± 41.6 | 935 ± 188.8 | 299 ± 30.2 | 293 ± 1.2 |
| **TA1535** | 0 | 7 ± 0.9 | 4 ± 1.3 | 9 ± 1.5 | 6 ± 1.5 | 11 ± 1.9 | 7 ± 2.0 |
| | 33 | 5 ± 1.7 | 2 ± 0.3 | 9 ± 0.9 | 4 ± 1.2 | 8 ± 2.2 | 3 ± 1.2 |
| | 100 | 5 ± 2.1 | 3 ± 0.3 | 6 ± 0.9 | 2 ± 1.2 | 8 ± 2.3 | 4 ± 1.0 |
| | 333 | 10 ± 1.5 | 3 ± 1.5 | 6 ± 1.8 | 4 ± 0.0 | 9 ± 1.5 | 7 ± 2.1 |
| | 1,000 | 7 ± 0.9 | 3 ± 0.7 | 7 ± 1.8 | 6 ± 0.7 | 9 ± 1.9 | 4 ± 1.2 |
| | 3,333 | 7 ± 0.6 | 4 ± 0.6 | 8 ± 1.8 | 3 ± 1.5 | 8 ± 2.1 | 5 ± 1.5 |
| Trial summary | | Negative | Negative | Negative | Negative | Negative | Negative |
| Positive control | | 193 ± 19.5 | 291 ± 39.0 | 61 ± 11.8 | 47 ± 7.7 | 71 ± 4.6 | 19 ± 2.0 |
| **TA1537** | 0 | 9 ± 2.4 | 6 ± 1.5 | 8 ± 1.5 | 9 ± 0.3 | 8 ± 2.0 | 5 ± 1.8 |
| | 33 | 6 ± 2.2 | 5 ± 0.7 | 10 ± 1.3 | 9 ± 2.5 | 11 ± 1.8 | 5 ± 1.2 |
| | 100 | 7 ± 1.2 | 6 ± 0.6 | 10 ± 3.0 | 10 ± 1.0 | 8 ± 1.2 | 4 ± 1.2 |
| | 333 | 7 ± 1.2 | 6 ± 1.3 | 8 ± 3.5 | 8 ± 1.3 | 12 ± 2.5 | 5 ± 1.7 |
| | 1,000 | 9 ± 0.9 | 6 ± 0.9 | 7 ± 2.4 | 7 ± 1.0 | 7 ± 0.9 | 6 ± 0.9 |
| | 3,333 | 3 ± 0.3 | 5 ± 2.7 | 9 ± 1.8 | 8 ± 1.5 | 9 ± 1.5 | 8 ± 1.9 |
| Trial summary | | Negative | Negative | Negative | Negative | Negative | Negative |
| Positive control | | 300 ± 35.1 | 198 ± 22.5 | 37 ± 10.7 | 44 ± 3.2 | 35 ± 5.8 | 19 ± 1.2 |
| **TA98** | 0 | 18 ± 2.3 | 15 ± 2.0 | 23 ± 2.7 | 18 ± 2.9 | 23 ± 1.0 | 19 ± 2.1 |
| | 33 | 13 ± 1.7 | 12 ± 2.6 | 18 ± 1.0 | 15 ± 1.3 | 20 ± 3.7 | 15 ± 1.5 |
| | 100 | 14 ± 2.3 | 11 ± 0.7 | 31 ± 9.4 | 18 ± 3.1 | 27 ± 1.7 | 18 ± 3.5 |
| | 333 | 15 ± 1.5 | 12 ± 0.9 | 23 ± 4.4 | 17 ± 0.3 | 17 ± 1.7 | 13 ± 2.6 |
| | 1,000 | 9 ± 1.5 | 12 ± 2.2 | 25 ± 2.0 | 19 ± 0.6 | 18 ± 3.4 | 15 ± 0.9 |
| | 3,333 | 14 ± 1.9 | 12 ± 1.2 | 17 ± 3.5 | 13 ± 0.9 | 16 ± 0.7 | 11 ± 0.9 |
| Trial summary | | Negative | Negative | Negative | Negative | Negative | Negative |
| Positive control | | 261 ± 25.1 | 245 ± 30.7 | 330 ± 15.5 | 420 ± 7.1 | 94 ± 2.5 | 166 ± 1.2 |

[a] The study was performed at Case Western Reserve University. The detailed protocol and these data are presented by Mortelmans *et al.* (1986).
[b] Revertants are presented as mean ± standard error from three plates.
[c] The positive controls in the absence of metabolic activation were sodium azide (TA100 and TA1535), 9-aminoacridine (TA1537), and 4-nitro-*o*-phenylenediamine (TA98). The positive control for metabolic activation with all strains was 2-aminoanthracene.

**Table E2**
**Induction of Sister Chromatid Exchanges in Chinese Hamster Ovary Cells by Triethanolamine[a]**

| Compound | Dose (μg/mL) | Total Cells Scored | No. of Chromo-somes | No. of SCEs | SCEs/ Chromo-some | SCEs/ Cell | Hrs in BrdU | Relative Change of SCEs/ Chromosome[b] (%) |
|---|---|---|---|---|---|---|---|---|
| **-S9** | | | | | | | | |
| **Trial 1** | | | | | | | | |
| Summary: Negative | | | | | | | | |
| Medium[c] | | 50 | 1,047 | 398 | 0.38 | 8.0 | 25.8 | |
| Mitomycin-C[d] | 0 | 50 | 1,049 | 1,887 | 1.79 | 37.7 | 25.8 | 373.22 |
| Triethanolamine | 100 | 50 | 1,050 | 443 | 0.42 | 8.9 | 25.8 | 10.99 |
| | 330 | 50 | 1,050 | 417 | 0.39 | 8.3 | 25.8 | 4.47 |
| | 1,010 | 50 | 1,048 | 387 | 0.36 | 7.7 | 25.8 | -2.86 |
| | | | | | P=0.745[e] | | | |
| **Trial 2** | | | | | | | | |
| Summary: Equivocal | | | | | | | | |
| Medium | | 50 | 1,043 | 435 | 0.41 | 8.7 | 25.5 | |
| Mitomycin-C | 0.005 | 50 | 1,036 | 1,648 | 1.59 | 33.0 | 25.5 | 281.42 |
| Triethanolamine | 630 | 50 | 1,041 | 447 | 0.42 | 8.9 | 25.5 | 2.96 |
| | 1,260 | 50 | 1,043 | 438 | 0.41 | 8.8 | 25.5 | 0.69 |
| | 2,520 | 8 | 163 | 84 | 0.51 | 10.5 | 28.0 | 23.56* |
| | | | | | P=0.174 | | | |
| **+S9** | | | | | | | | |
| Summary: Negative | | | | | | | | |
| Medium | | 50 | 1,034 | 426 | 0.41 | 8.5 | 25.8 | |
| Cyclophosphamide[d] | 1.5 | 50 | 1,039 | 1,389 | 1.33 | 27.8 | 25.8 | 224.49 |
| Triethanolamine | 330 | 50 | 1,031 | 446 | 0.43 | 8.9 | 25.8 | 5.00 |
| | 1,010 | 50 | 1,045 | 453 | 0.43 | 9.1 | 25.8 | 5.22 |
| | 10,100 | 50 | 1,039 | 463 | 0.44 | 9.3 | 25.8 | 8.16 |
| | | | | | P=0.130 | | | |

* Positive response (≥20% increase over solvent control)
[a] The study was performed at Litton Bionetics, Inc. A detailed description of the protocol and these data are presented by Galloway *et al.* (1987). SCE=sister chromatid exchange; BrdU=bromodeoxyuridine
[b] SCEs/chromosome in treated cells versus SCEs/chromosome in solvent control cells
[c] Solvent control
[d] Positive control
[e] Significance of SCEs/chromosome tested by the linear regression trend test versus log of the dose

**TABLE E3**
**Induction of Chromosomal Aberrations in Chinese Hamster Ovary Cells by Triethanolamine[a]**

| -S9 | | | | | +S9 | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Dose (μg/mL) | Total Cells Scored | No. of Abs | Abs/ Cell | Cells with Abs (%) | Dose (μg/mL) | Total Cells Scored | No. of Abs | Abs/ Cell | Cells with Abs (%) |
| Harvest time: 10.5 hours | | | | | Harvest time: 10.5 hours | | | | |
| Summary: Negative | | | | | Summary: Negative | | | | |
| Dimethylsulfoxide[b] | | | | | Dimethylsulfoxide | | | | |
| | 100 | 7 | 0.07 | 5.0 | | 100 | 2 | 0.02 | 2.0 |
| Mitomycin-C[c] | | | | | Cyclophosphamide[c] | | | | |
| 0.5 | 100 | 24 | 0.24 | 20.0 | 25 | 100 | 32 | 0.32 | 26.0 |
| Triethanolamine | | | | | Triethanolamine | | | | |
| 1,510 | 100 | 2 | 0.02 | 2.0 | 6,040 | 100 | 3 | 0.03 | 3.0 |
| 2,010 | 100 | 1 | 0.01 | 1.0 | 8,060 | 100 | 6 | 0.06 | 5.0 |
| 4,030 | 56 | 0 | 0.00 | 1.0 | 10,070 | 100 | 2 | 0.02 | 2.0 |
| | | | | P=0.985[d] | | | | | P=0.373 |

[a] The study was performed at Litton Bionetics, Inc. The detailed protocol and these data are presented by Galloway *et al*. (1987). Abs=aberrations
[b] Solvent control
[c] Positive control
[d] Significance of percent cells with aberrations tested by the linear regression trend test versus log of the dose

**TABLE E4**
**Induction of Sex-Linked Recessive Lethal Mutations in *Drosophila melanogaster* by Triethanolamine[a]**

| Route of Exposure | Dose (ppm) | Incidence of Death (%) | Incidence of Sterility (%) | No. of Lethals/No. of X Chromosomes Tested: Mating 1 | Mating 2 | Mating 3 | Total[b] |
|---|---|---|---|---|---|---|---|
| Injection | 10,000 | 12 | 0 | 0/1,016 | 0/1,185 | 2/1,000 | 2/3,201 (0.06%) |
| | 0[c] | | | 0/1,024 | 0/1,179 | 0/981 | 0/3,184 (0.00%) |
| Feeding | 20,000[c] | 2 | 3 | 0/1,011 | 1/1,262 | 1/570 | 2/2,843 (0.07%) |
| | 0[c] | | | 1/909 | 2/1,467 | 1/735 | 4/3,111 (0.13%) |
| Injection | 20,000 | 8 | 0 | 0/524 | 0/1,127 | 1/984 | 1/2,635 (0.04%) |
| | 0 | | | 0/374 | 0/1,268 | 2/871 | 2/2,513 (0.08%) |
| Feeding | 30,000 | 48 | 20 | 0/1,190 | 1/1,924 | 0/739 | 1/3,853 (0.03%) |
| | 0[c] | | | 2/2,091 | 2/2,509 | 2/1,989 | 6/6,589 (0.09%) |
| Injection | 30,000 | 56 | 30 | 1/247 | 0/113 | 1/108 | 2/468 (0.43%) |
| | 0 | | | 1/864 | 2/1,078 | 1/1,091 | 4/3,033 (0.13%) |

[a] The study was performed at Brown University. A detailed protocol of the sex-linked recessive lethal assay is presented by Yoon *et al.* (1985). Results were not significant at the 5% level (Margolin *et al.*, 1983).
[b] Combined total number of lethal mutations/number of X chromosomes tested for three mating trials
[c] Data were corrected for the occurrence of spontaneous clusters.

**TABLE E5**
**Frequency of Micronuclei in Peripheral Blood Erythrocytes of Mice Following Treatment with Triethanolamine by Dermal Application for 13 Weeks[a]**

| | Dose (mg/kg) | Micronucleated Cells/1,000 Cells[b] | | Number of Mice |
|---|---|---|---|---|
| | | PCEs | NCEs | |
| **Male** | | | | |
| | 0 | 2.13 ± 0.40 | 1.75 ± 0.20 | 10 |
| | 1,000 | 1.04 ± 0.36 | 1.88 ± 0.17 | 10 |
| | 2,000 | 2.41 ± 0.40 | 1.36 ± 0.10 | 10 |
| | 4,000 | 2.00 ± 0.48 | 1.90 ± 0.30 | 10 |
| Trend test | | P=0.337[c] | P=0.785[c] | |
| **Female** | | | | |
| | 0 | 2.06 ± 0.35 | 1.16 ± 0.12 | 10 |
| | 1,000 | 1.60 ± 0.34 | 1.20 ± 0.08 | 10 |
| | 2,000 | 2.38 ± 0.43 | 1.08 ± 0.12 | 10 |
| | 4,000 | 2.12 ± 0.39 | 0.99 ± 0.11 | 10 |
| Trend test | | P=0.355 | P=0.145 | |

[a] The detailed protocol is presented by MacGregor *et al*. (1990); 10,000 NCEs (normochromatic erythrocytes) and 2,000 PCEs (polychromatic erythrocytes) were scored per animal.
[b] Data are presented as mean ± standard error.
[c] Cochran-Armitage trend test for PCEs and analysis of variance by the SAS GLM procedure for NCEs

# APPENDIX F
# ORGAN WEIGHTS
# AND ORGAN-WEIGHT-TO-BODY-WEIGHT RATIOS

**TABLE F1** Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats in the 13-Week Dermal Study of Triethanolamine . . . . . . . . . . . . . . . . . . . . . . . . . . . . 230

**TABLE F2** Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats at the 15-Month Interim Evaluation in the 2-Year Dermal Study of Triethanolamine . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . 232

**TABLE F3** Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 13-Week Dermal Study of Triethanolamine . . . . . . . . . . . . . . . . . . . . . . . . . . . . 233

**TABLE F4** Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice at the 15-Month Interim Evaluation in the 2-Year Dermal Study of Triethanolamine . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . 235

**TABLE F1**
**Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats in the 13-Week Dermal Study of Triethanolamine[a]**

| | 0 mg/kg | 125 mg/kg | 250 mg/kg | 500 mg/kg | 1,000 mg/kg | 2,000 mg/kg |
|---|---|---|---|---|---|---|
| **Male** | | | | | | |
| n | 10 | 10 | 10 | 10 | 10 | 10 |
| Necropsy body wt | 299 ± 6 | 284 ± 7 | 286 ± 6 | 287 ± 7 | 295 ± 11 | 248 ± 11** |
| Brain | | | | | | |
| Absolute | 1.911 ± 0.021 | 1.867 ± 0.021 | 1.868 ± 0.019 | 1.900 ± 0.011 | 1.919 ± 0.018 | 1.880 ± 0.030 |
| Relative | 6.41 ± 0.11 | 6.60 ± 0.15 | 6.55 ± 0.12 | 6.65 ± 0.18 | 6.58 ± 0.19 | 7.74 ± 0.39** |
| L. Epididymis | | | | | | |
| Absolute | 0.443 ± 0.008 | 0.438 ± 0.011 | 0.442 ± 0.007 | 0.453 ± 0.010 | 0.449 ± 0.012 | 0.411 ± 0.014 |
| Relative | 1.49 ± 0.03 | 1.55 ± 0.05 | 1.55 ± 0.04 | 1.59 ± 0.06 | 1.53 ± 0.04 | 1.68 ± 0.08 |
| Heart | | | | | | |
| Absolute | 0.993 ± 0.030 | 0.907 ± 0.017 | 0.961 ± 0.037 | 0.953 ± 0.023 | 0.983 ± 0.032 | 0.898 ± 0.022 |
| Relative | 3.32 ± 0.06 | 3.20 ± 0.07 | 3.36 ± 0.09 | 3.33 ± 0.08 | 3.35 ± 0.10 | 3.68 ± 0.17 |
| R. Kidney | | | | | | |
| Absolute | 1.187 ± 0.025 | 1.134 ± 0.026 | 1.188 ± 0.031 | 1.264 ± 0.028 | 1.366 ± 0.039** | 1.366 ± 0.051** |
| Relative | 3.97 ± 0.05 | 4.00 ± 0.06 | 4.16 ± 0.06 | 4.41 ± 0.06* | 4.65 ± 0.09** | 5.58 ± 0.24** |
| Liver | | | | | | |
| Absolute | 13.949 ± 0.446 | 12.404 ± 0.443 | 13.418 ± 0.693 | 15.174 ± 0.382 | 15.516 ± 0.421 | 12.517 ± 0.405 |
| Relative | 46.58 ± 0.86 | 43.68 ± 1.14 | 46.73 ± 1.61 | 53.12 ± 1.90* | 52.92 ± 1.05* | 51.18 ± 2.14* |
| Lung | | | | | | |
| Absolute | 1.870 ± 0.054 | 1.740 ± 0.062 | 1.761 ± 0.083 | 1.674 ± 0.037 | 1.817 ± 0.060 | 1.569 ± 0.039** |
| Relative | 6.28 ± 0.23 | 6.15 ± 0.25 | 6.15 ± 0.25 | 5.88 ± 0.25 | 6.18 ± 0.08 | 6.49 ± 0.41 |
| Spleen | | | | | | |
| Absolute | 0.666 ± 0.016 | 0.646 ± 0.013 | 0.626 ± 0.009 | 0.666 ± 0.013 | 0.690 ± 0.028 | 0.612 ± 0.024 |
| Relative | 2.23 ± 0.03 | 2.28 ± 0.05 | 2.19 ± 0.04 | 2.33 ± 0.05 | 2.34 ± 0.03 | 2.50 ± 0.11** |
| L. Testis | | | | | | |
| Absolute | 1.409 ± 0.028 | 1.362 ± 0.026 | 1.349 ± 0.019 | 1.369 ± 0.013 | 1.394 ± 0.033 | 1.372 ± 0.032 |
| Relative | 4.71 ± 0.06 | 4.82 ± 0.13 | 4.73 ± 0.09 | 4.79 ± 0.10 | 4.76 ± 0.09 | 5.61 ± 0.22** |
| Thymus | | | | | | |
| Absolute | 0.326 ± 0.015 | 0.298 ± 0.010 | 0.318 ± 0.013 | 0.330 ± 0.014[b] | 0.338 ± 0.020 | 0.256 ± 0.017** |
| Relative | 1.09 ± 0.04 | 1.06 ± 0.05 | 1.12 ± 0.05 | 1.13 ± 0.05[b] | 1.14 ± 0.04 | 1.03 ± 0.04 |

**TABLE F1**
**Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats in the 13-Week Dermal Study of Triethanolamine**
(continued)

| | 0 mg/kg | 125 mg/kg | 250 mg/kg | 500 mg/kg | 1,000 mg/kg | 2,000 mg/kg |
|---|---|---|---|---|---|---|
| **Female** | | | | | | |
| n | 10 | 10 | 10 | 10 | 10 | 10 |
| Necropsy body wt | 174 ± 4 | 170 ± 4 | 174 ± 4 | 174 ± 3 | 170 ± 3 | 158 ± 4** |
| Brain | | | | | | |
| Absolute | 1.748 ± 0.020 | 1.712 ± 0.023 | 1.754 ± 0.014 | 1.759 ± 0.024 | 1.761 ± 0.022 | 1.770 ± 0.013 |
| Relative | 10.14 ± 0.35 | 10.17 ± 0.33 | 10.14 ± 0.23 | 10.11 ± 0.12 | 10.35 ± 0.14 | 11.27 ± 0.19** |
| Heart | | | | | | |
| Absolute | 0.649 ± 0.016 | 0.659 ± 0.014 | 0.661 ± 0.015 | 0.652 ± 0.016[b] | 0.673 ± 0.022 | 0.619 ± 0.011 |
| Relative | 3.76 ± 0.12 | 3.91 ± 0.13 | 3.81 ± 0.06 | 3.75 ± 0.08[b] | 3.95 ± 0.11 | 3.95 ± 0.10 |
| R. Kidney | | | | | | |
| Absolute | 0.744 ± 0.017 | 0.745 ± 0.017 | 0.758 ± 0.019 | 0.810 ± 0.015* | 0.847 ± 0.019** | 0.891 ± 0.019** |
| Relative | 4.31 ± 0.14 | 4.41 ± 0.11 | 4.37 ± 0.08 | 4.66 ± 0.08* | 4.98 ± 0.12** | 5.67 ± 0.15** |
| Liver | | | | | | |
| Absolute | 6.982 ± 0.290 | 6.860 ± 0.188 | 7.154 ± 0.222 | 7.340 ± 0.289 | 7.483 ± 0.342 | 7.067 ± 0.272 |
| Relative | 40.28 ± 1.52 | 40.52 ± 0.71 | 41.15 ± 0.68 | 42.10 ± 1.37 | 43.88 ± 1.76 | 44.96 ± 1.64* |
| Lung | | | | | | |
| Absolute | 1.199 ± 0.032 | 1.283 ± 0.023 | 1.357 ± 0.072 | 1.253 ± 0.055 | 1.261 ± 0.037 | 1.146 ± 0.039 |
| Relative | 6.94 ± 0.23 | 7.60 ± 0.20 | 7.82 ± 0.37 | 7.18 ± 0.23 | 7.40 ± 0.17 | 7.31 ± 0.30 |
| Spleen | | | | | | |
| Absolute | 0.468 ± 0.010 | 0.461 ± 0.010 | 0.462 ± 0.009 | 0.456 ± 0.011 | 0.461 ± 0.013 | 0.427 ± 0.009* |
| Relative | 2.71 ± 0.08 | 2.73 ± 0.08 | 2.67 ± 0.03 | 2.62 ± 0.04 | 2.71 ± 0.09 | 2.72 ± 0.07 |
| Thymus | | | | | | |
| Absolute | 0.261 ± 0.013 | 0.269 ± 0.011 | 0.279 ± 0.022 | 0.268 ± 0.010 | 0.275 ± 0.019 | 0.250 ± 0.009 |
| Relative | 1.51 ± 0.08 | 1.59 ± 0.07 | 1.60 ± 0.11 | 1.54 ± 0.06 | 1.61 ± 0.09 | 1.59 ± 0.06 |

* Significantly different (P≤0.05) from the control group by Williams' or Dunnett's test
** P≤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=9

**TABLE F2**
**Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats at the 15-Month Interim Evaluation in the 2-Year Dermal Study of Triethanolamine[a]**

| | 0 mg/kg | 32 mg/kg | 63 mg/kg | 125 mg/kg |
|---|---|---|---|---|
| n | 10 | 10 | 10 | 10 |
| **Male** | | | | |
| Necropsy body wt | 423 ± 13 | 440 ± 8 | 429 ± 13 | 408 ± 13 |
| L. Kidney | | | | |
| Absolute | 1.652 ± 0.044 | 1.726 ± 0.035 | 1.690 ± 0.047 | 1.619 ± 0.047 |
| Relative | 3.92 ± 0.09 | 3.93 ± 0.06 | 3.95 ± 0.08 | 3.97 ± 0.06 |
| R. Kidney | | | | |
| Absolute | 1.627 ± 0.030 | 1.717 ± 0.045 | 1.680 ± 0.057 | 1.574 ± 0.046 |
| Relative | 3.86 ± 0.07 | 3.90 ± 0.08 | 3.92 ± 0.08 | 3.86 ± 0.05 |
| Liver | | | | |
| Absolute | 17.991 ± 0.709 | 18.037 ± 0.687 | 17.809 ± 0.609 | 16.669 ± 0.695 |
| Relative | 42.92 ± 2.43 | 40.90 ± 1.03 | 41.55 ± 0.75 | 40.82 ± 1.01 |
| | **0 mg/kg** | **63 mg/kg** | **125 mg/kg** | **250 mg/kg** |
| **Female** | | | | |
| Necropsy body wt | 242 ± 6 | 260 ± 6 | 245 ± 9 | 255 ± 6 |
| L. Kidney | | | | |
| Absolute | 1.008 ± 0.017 | 1.058 ± 0.018 | 1.064 ± 0.034 | 1.133 ± 0.020** |
| Relative | 4.18 ± 0.12 | 4.09 ± 0.10 | 4.36 ± 0.09 | 4.46 ± 0.09 |
| R. Kidney | | | | |
| Absolute | 0.982 ± 0.021 | 1.026 ± 0.016 | 1.031 ± 0.027 | 1.113 ± 0.022** |
| Relative | 4.06 ± 0.10 | 3.96 ± 0.06 | 4.23 ± 0.08 | 4.38 ± 0.10* |
| Liver | | | | |
| Absolute | 9.735 ± 0.189 | 10.217 ± 0.213 | 9.952 ± 0.300 | 10.393 ± 0.228 |
| Relative | 40.22 ± 0.41 | 39.42 ± 0.48 | 40.77 ± 0.79 | 40.85 ± 0.72 |

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

**Table F3**
**Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 13-Week Dermal Study of Triethanolamine[a]**

| | 0 mg/kg | 250 mg/kg | 500 mg/kg | 1,000 mg/kg | 2,000 mg/kg | 4,000 mg/kg |
|---|---|---|---|---|---|---|
| **Male** | | | | | | |
| n | 10 | 10 | 10 | 10 | 10 | 10 |
| Necropsy body wt | 34.2 ± 0.7 | 30.9 ± 0.7** | 32.1 ± 0.7 | 32.5 ± 0.7 | 32.0 ± 0.8 | 32.0 ± 0.6 |
| Brain | | | | | | |
| Absolute | 0.455 ± 0.007 | 0.446 ± 0.003 | 0.448 ± 0.006 | 0.449 ± 0.004 | 0.446 ± 0.009 | 0.458 ± 0.005 |
| Relative | 13.37 ± 0.35 | 14.49 ± 0.30 | 14.03 ± 0.29 | 13.90 ± 0.28 | 14.02 ± 0.45 | 14.35 ± 0.30 |
| L. Epididymis | | | | | | |
| Absolute | 0.052 ± 0.002 | 0.054 ± 0.003 | 0.055 ± 0.003 | 0.053 ± 0.003 | 0.053 ± 0.002 | 0.051 ± 0.002 |
| Relative | 1.52 ± 0.06 | 1.75 ± 0.12 | 1.71 ± 0.08 | 1.62 ± 0.07 | 1.67 ± 0.07 | 1.61 ± 0.07 |
| Heart | | | | | | |
| Absolute | 0.171 ± 0.007 | 0.158 ± 0.003 | 0.158 ± 0.005 | 0.168 ± 0.004 | 0.176 ± 0.004 | 0.186 ± 0.008 |
| Relative | 5.01 ± 0.19 | 5.13 ± 0.11 | 4.97 ± 0.21 | 5.21 ± 0.21 | 5.51 ± 0.14 | 5.82 ± 0.25** |
| R. Kidney | | | | | | |
| Absolute | 0.320 ± 0.009 | 0.306 ± 0.005 | 0.311 ± 0.010 | 0.326 ± 0.006 | 0.325 ± 0.008 | 0.347 ± 0.010* |
| Relative | 9.37 ± 0.18 | 9.93 ± 0.12 | 9.73 ± 0.26 | 10.07 ± 0.20* | 10.17 ± 0.16* | 10.85 ± 0.30** |
| Liver | | | | | | |
| Absolute | 1.685 ± 0.041 | 1.633 ± 0.054 | 1.667 ± 0.033 | 1.654 ± 0.041 | 1.719 ± 0.035 | 1.875 ± 0.041** |
| Relative | 49.37 ± 1.03 | 52.81 ± 0.82* | 52.08 ± 0.73* | 51.01 ± 0.91* | 53.78 ± 0.47** | 58.60 ± 0.89** |
| Lung | | | | | | |
| Absolute | 0.350 ± 0.014 | 0.327 ± 0.012 | 0.309 ± 0.010 | 0.319 ± 0.017 | 0.334 ± 0.019 | 0.328 ± 0.013 |
| Relative | 10.22 ± 0.30 | 10.59 ± 0.29 | 9.71 ± 0.41 | 9.82 ± 0.44 | 10.44 ± 0.57 | 10.27 ± 0.41 |
| Spleen | | | | | | |
| Absolute | 0.073 ± 0.002 | 0.068 ± 0.002 | 0.071 ± 0.002 | 0.073 ± 0.002 | 0.074 ± 0.003 | 0.077 ± 0.003 |
| Relative | 2.14 ± 0.09 | 2.19 ± 0.06 | 2.21 ± 0.06 | 2.25 ± 0.05 | 2.32 ± 0.09 | 2.42 ± 0.10 |
| L. Testis | | | | | | |
| Absolute | 0.112 ± 0.004 | 0.109 ± 0.003 | 0.113 ± 0.002 | 0.113 ± 0.003 | 0.109 ± 0.002 | 0.110 ± 0.004 |
| Relative | 3.29 ± 0.13 | 3.54 ± 0.09 | 3.52 ± 0.07 | 3.48 ± 0.09 | 3.41 ± 0.05 | 3.43 ± 0.09 |
| Thymus | | | | | | |
| Absolute | 0.044 ± 0.002 | 0.035 ± 0.003 | 0.043 ± 0.003 | 0.046 ± 0.005 | 0.044 ± 0.003 | 0.043 ± 0.002 |
| Relative | 1.30 ± 0.06 | 1.14 ± 0.10 | 1.33 ± 0.10 | 1.43 ± 0.17 | 1.38 ± 0.08 | 1.33 ± 0.06 |

**Table F3**
**Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 13-Week Dermal Study of Triethanolamine** (continued)

| | 0 mg/kg | 250 mg/kg | 500 mg/kg | 1,000 mg/kg | 2,000 mg/kg | 4,000 mg/kg |
|---|---|---|---|---|---|---|
| **Female** | | | | | | |
| n | 10 | 10 | 10 | 10 | 10 | 10 |
| Necropsy body wt | 28.2 ± 0.6 | 28.2 ± 0.5 | 28.7 ± 0.6 | 28.2 ± 0.7 | 27.4 ± 0.5 | 28.2 ± 0.5 |
| Brain | | | | | | |
| Absolute | 0.469 ± 0.006 | 0.459 ± 0.004 | 0.473 ± 0.005 | 0.478 ± 0.006 | 0.469 ± 0.004 | 0.467 ± 0.004 |
| Relative | 16.70 ± 0.38 | 16.29 ± 0.25 | 16.58 ± 0.34 | 17.03 ± 0.47 | 17.19 ± 0.28 | 16.60 ± 0.32 |
| Heart | | | | | | |
| Absolute | 0.149 ± 0.007 | 0.161 ± 0.008 | 0.150 ± 0.005 | 0.156 ± 0.008 | 0.159 ± 0.006 | 0.167 ± 0.005 |
| Relative | 5.30 ± 0.23 | 5.74 ± 0.34 | 5.23 ± 0.12 | 5.55 ± 0.25 | 5.80 ± 0.15 | 5.93 ± 0.15 |
| R. Kidney | | | | | | |
| Absolute | 0.217 ± 0.005 | 0.234 ± 0.004* | 0.230 ± 0.006 | 0.231 ± 0.004 | 0.230 ± 0.003 | 0.253 ± 0.008** |
| Relative | 7.69 ± 0.11 | 8.32 ± 0.15* | 8.03 ± 0.15* | 8.22 ± 0.17* | 8.41 ± 0.15** | 8.95 ± 0.21** |
| Liver | | | | | | |
| Absolute | 1.590 ± 0.061 | 1.548 ± 0.027 | 1.600 ± 0.041 | 1.566 ± 0.031 | 1.576 ± 0.051 | 1.833 ± 0.047** |
| Relative | 56.37 ± 1.78 | 54.96 ± 1.00 | 55.81 ± 0.79 | 55.63 ± 1.09 | 57.58 ± 1.19 | 64.92 ± 1.11** |
| Lung | | | | | | |
| Absolute | 0.314 ± 0.020 | 0.305 ± 0.018 | 0.329 ± 0.014 | 0.326 ± 0.013 | 0.310 ± 0.013 | 0.302 ± 0.018 |
| Relative | 11.11 ± 0.62 | 10.86 ± 0.71 | 11.53 ± 0.53 | 11.56 ± 0.43 | 11.34 ± 0.42 | 10.70 ± 0.63 |
| Spleen | | | | | | |
| Absolute | 0.093 ± 0.004 | 0.095 ± 0.003 | 0.098 ± 0.003 | 0.099 ± 0.005 | 0.100 ± 0.003 | 0.109 ± 0.005** |
| Relative | 3.32 ± 0.16 | 3.37 ± 0.11 | 3.42 ± 0.08 | 3.53 ± 0.17 | 3.66 ± 0.12 | 3.85 ± 0.18* |
| Thymus | | | | | | |
| Absolute | 0.049 ± 0.004 | 0.056 ± 0.003 | 0.052 ± 0.002 | 0.052 ± 0.004 | 0.059 ± 0.002 | 0.056 ± 0.002 |
| Relative | 1.76 ± 0.15 | 1.98 ± 0.07 | 1.80 ± 0.06 | 1.85 ± 0.13 | 2.16 ± 0.08* | 1.97 ± 0.07 |

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

**Table F4**
**Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice at the 15-Month Interim Evaluation in the 2-Year Dermal Study of Triethanolamine[a]**

| | 0 mg/kg | 200 mg/kg | 630 mg/kg | 2,000 mg/kg |
|---|---|---|---|---|
| n | 10 | 10 | 10 | 10 |
| **Male** | | | | |
| Necropsy body wt | 49.5 ± 1.9 | 49.5 ± 1.5 | 50.0 ± 1.9 | 52.0 ± 1.2 |
| L. Kidney | | | | |
| Absolute | 0.439 ± 0.013 | 0.459 ± 0.012 | 0.476 ± 0.015 | 0.517 ± 0.014** |
| Relative | 8.92 ± 0.13 | 9.32 ± 0.26 | 9.58 ± 0.25 | 9.98 ± 0.26** |
| R. Kidney | | | | |
| Absolute | 0.452 ± 0.015 | 0.473 ± 0.014 | 0.504 ± 0.015* | 0.549 ± 0.016** |
| Relative | 9.19 ± 0.23 | 9.61 ± 0.32 | 10.14 ± 0.27* | 10.56 ± 0.23** |
| Liver | | | | |
| Absolute | 2.850 ± 0.330 | 2.950 ± 0.216 | 2.538 ± 0.149 | 3.088 ± 0.197 |
| Relative | 57.29 ± 5.93 | 59.82 ± 4.16 | 50.53 ± 1.38 | 59.37 ± 3.59 |
| | **0 mg/kg** | **100 mg/kg** | **300 mg/kg** | **1,000 mg/kg** |
| **Female** | | | | |
| Necropsy body wt | 50.9 ± 1.8 | 48.4 ± 1.3 | 47.7 ± 1.3 | 49.8 ± 1.9 |
| L. Kidney | | | | |
| Absolute | 0.292 ± 0.008 | 0.294 ± 0.006 | 0.311 ± 0.005 | 0.308 ± 0.007 |
| Relative | 5.76 ± 0.13 | 6.11 ± 0.18 | 6.58 ± 0.20* | 6.26 ± 0.26 |
| R. Kidney | | | | |
| Absolute | 0.312 ± 0.010 | 0.318 ± 0.006 | 0.330 ± 0.004 | 0.328 ± 0.005 |
| Relative | 6.16 ± 0.11 | 6.60 ± 0.15 | 6.96 ± 0.18** | 6.67 ± 0.24 |
| Liver | | | | |
| Absolute | 2.074 ± 0.066 | 2.104 ± 0.100 | 2.098 ± 0.032 | 2.178 ± 0.077 |
| Relative | 40.89 ± 0.79 | 43.52 ± 1.53 | 44.34 ± 1.45 | 43.93 ± 1.27 |

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

# APPENDIX G
# HEMATOLOGY, CLINICAL CHEMISTRY, AND URINALYSIS RESULTS

TABLE G1 Hematology, Clinical Chemistry, and Urinalysis Data for Rats in the 13-Week Dermal Study of Triethanolamine . . . . . . . . . . . . . . . . . . . . . . . . . . . . 238
TABLE G2 Hematology, Clinical Chemistry, and Urinalysis Data for Mice in the 13-Week Dermal Study of Triethanolamine . . . . . . . . . . . . . . . . . . . . . . . . . . . . 241

**Table G1**
**Hematology, Clinical Chemistry, and Urinalysis Data for Rats in the 13-Week Dermal Study of Triethanolamine[a]**

| | 0 mg/kg | 125 mg/kg | 250 mg/kg | 500 mg/kg | 1,000 mg/kg | 2,000 mg/kg |
|---|---|---|---|---|---|---|
| n | 10 | 10 | 10 | 10 | 10 | 10 |
| **Male** | | | | | | |
| Hematology | | | | | | |
| Hematocrit (%) | 50.6 ± 0.5 | 50.0 ± 0.5 | 51.0 ± 0.8 | 50.8 ± 1.0 | 50.1 ± 1.0 | 49.2 ± 1.0 |
| Hemoglobin (g/dL) | 15.6 ± 0.1 | 15.5 ± 0.1 | 15.8 ± 0.2 | 15.9 ± 0.3 | 15.6 ± 0.2 | 15.2 ± 0.3 |
| Erythrocytes ($10^6/\mu L$) | 9.58 ± 0.09 | 9.50 ± 0.08 | 9.70 ± 0.15 | 9.67 ± 0.17 | 9.55 ± 0.16 | 9.53 ± 0.16 |
| Mean cell volume (fL) | 52.8 ± 0.2 | 52.6 ± 0.2 | 52.5 ± 0.2 | 52.4 ± 0.2 | 52.3 ± 0.4 | 51.8 ± 0.3** |
| Mean cell hemoglobin (pg) | 16.3 ± 0.1 | 16.3 ± 0.1 | 16.3 ± 0.1 | 16.5 ± 0.1 | 16.4 ± 0.2 | 16.0 ± 0.1 |
| Mean cell hemoglobin concentration (g/dL) | 30.8 ± 0.2 | 30.9 ± 0.1 | 31.0 ± 0.2 | 31.3 ± 0.3 | 31.3 ± 0.4 | 31.0 ± 0.2 |
| Platelets ($10^3/\mu L$) | 638.4 ± 9.0 | 617.4 ± 17.4 | 615.4 ± 7.7 | 599.3 ± 18.8[b] | 637.6 ± 12.9 | 647.6 ± 10.1 |
| Reticulocytes ($10^6/\mu L$) | 0.1 ± 0.0 | 0.1 ± 0.0 | 0.2 ± 0.0 | 0.1 ± 0.0 | 0.2 ± 0.0 | 0.1 ± 0.0 |
| Leukocytes ($10^3/\mu L$) | 6.26 ± 0.34 | 7.22 ± 0.39 | 7.32 ± 0.50 | 7.30 ± 0.42 | 7.04 ± 0.34 | 9.04 ± 0.40** |
| Segmented neutrophils ($10^3/\mu L$) | 1.21 ± 0.13 | 1.16 ± 0.15 | 1.26 ± 0.12 | 1.18 ± 0.12 | 1.24 ± 0.13 | 2.64 ± 0.20** |
| Lymphocytes ($10^3/\mu L$) | 4.98 ± 0.30 | 5.94 ± 0.38 | 6.01 ± 0.47 | 6.00 ± 0.38 | 5.69 ± 0.32 | 6.14 ± 0.40 |
| Monocytes ($10^3/\mu L$) | 0.01 ± 0.01 | 0.02 ± 0.01 | 0.00 ± 0.00 | 0.00 ± 0.00 | 0.02 ± 0.01 | 0.00 ± 0.00 |
| Eosinophils ($10^3/\mu L$) | 0.06 ± 0.02 | 0.10 ± 0.04 | 0.06 ± 0.02 | 0.12 ± 0.04 | 0.09 ± 0.02 | 0.26 ± 0.05** |
| Nucleated erythrocytes ($10^3/\mu L$) | 0.00 ± 0.00 | 0.01 ± 0.01 | 0.00 ± 0.00 | 0.00 ± 0.00 | 0.01 ± 0.01 | 0.01 ± 0.01 |
| Clinical Chemistry | | | | | | |
| Urea nitrogen (mg/dL) | 20.8 ± 0.4 | 19.5 ± 0.3 | 19.7 ± 0.5 | 19.9 ± 0.6 | 20.6 ± 0.5 | 21.2 ± 0.4 |
| Creatinine (mg/dL) | 0.58 ± 0.02 | 0.56 ± 0.02 | 0.57 ± 0.02 | 0.57 ± 0.03 | 0.58 ± 0.02 | 0.54 ± 0.02 |
| Glucose (mg/dL) | 112 ± 2 | 111 ± 2 | 110 ± 3 | 113 ± 7 | 111 ± 3 | 107 ± 3 |
| Total protein (g/dL) | 6.7 ± 0.1 | 6.7 ± 0.2 | 6.9 ± 0.1 | 6.8 ± 0.2 | 7.0 ± 0.2 | 6.7 ± 0.1 |
| Albumin (g/dL) | 5.0 ± 0.1 | 5.0 ± 0.1 | 5.1 ± 0.1 | 5.2 ± 0.1 | 5.2 ± 0.1 | 4.9 ± 0.1 |
| Alanine aminotransferase (IU/L) | 45 ± 2 | 45 ± 2 | 51 ± 3 | 53 ± 4 | 52 ± 4* | 69 ± 5** |
| Aspartate aminotransferase (IU/L) | 76 ± 4 | 74 ± 2 | 96 ± 7* | 98 ± 10* | 90 ± 7* | 127 ± 7** |
| Sorbitol dehydrogenase (IU/L) | 16 ± 1 | 14 ± 1 | 16 ± 2 | 15 ± 1 | 15 ± 1 | 15 ± 2 |

**TABLE G1**
**Hematology, Clinical Chemistry, and Urinalysis Data for Rats in the 13-Week Dermal Study of Triethanolamine** (continued)

| | 0 mg/kg | 125 mg/kg | 250 mg/kg | 500 mg/kg | 1,000 mg/kg | 2,000 mg/kg |
|---|---|---|---|---|---|---|
| n | 10 | 10 | 10 | 10 | 10 | 10 |
| **Male** (continued) | | | | | | |
| Urinalysis | | | | | | |
| Glucose (mg/hr) | | | | | | |
| Day 3 | 0.018 ± 0.003 | 0.016 ± 0.003 | 0.017 ± 0.004 | 0.014 ± 0.003 | 0.012 ± 0.004 | 0.015 ± 0.003 |
| Day 16 | 0.039 ± 0.002 | 0.041 ± 0.002 | 0.042 ± 0.007 | 0.042 ± 0.003 | 0.040 ± 0.002 | 0.042 ± 0.002 |
| Day 44 | 0.037 ± 0.005 | 0.021 ± 0.005 | 0.031 ± 0.007 | 0.029 ± 0.006 | 0.029 ± 0.007 | 0.031 ± 0.005 |
| Week 13 | 0.054 ± 0.003[b] | 0.055 ± 0.004 | 0.051 ± 0.003 | 0.035 ± 0.007 | 0.033 ± 0.007* | 0.036 ± 0.007 |
| Protein (mg/hr) | | | | | | |
| Day 3 | 0.013 ± 0.001 | 0.014 ± 0.002 | 0.018 ± 0.002 | 0.024 ± 0.004 | 0.016 ± 0.002 | 0.014 ± 0.002 |
| Day 16 | 0.085 ± 0.012 | 0.090 ± 0.010 | 0.080 ± 0.008 | 0.065 ± 0.004 | 0.063 ± 0.009 | 0.046 ± 0.009* |
| Day 44 | 0.104 ± 0.008 | 0.087 ± 0.008 | 0.102 ± 0.007 | 0.062 ± 0.009** | 0.066 ± 0.010** | 0.045 ± 0.008** |
| Week 13 | 0.598 ± 0.024[b] | 0.663 ± 0.045 | 0.637 ± 0.019 | 0.510 ± 0.060 | 0.407 ± 0.050** | 0.269 ± 0.029** |
| Volume (mL/16 hr) | | | | | | |
| Day 3 | 9.2 ± 1.2 | 8.7 ± 1.4 | 8.9 ± 1.1 | 11.2 ± 1.6 | 10.1 ± 0.9 | 7.8 ± 1.1 |
| Day 16 | 14.1 ± 1.3 | 12.7 ± 1.9 | 12.7 ± 1.8 | 15.2 ± 1.3 | 16.3 ± 1.3 | 14.7 ± 1.9 |
| Day 44 | 13.3 ± 1.3 | 13.2 ± 2.3 | 15.5 ± 1.8 | 14.9 ± 1.6 | 16.1 ± 1.3 | 15.3 ± 1.9 |
| Week 13 | 9.2 ± 0.7[b] | 8.2 ± 1.0[b] | 12.2 ± 1.8 | 11.8 ± 1.0 | 11.2 ± 1.5[b] | 9.5 ± 1.6 |
| Specific gravity | | | | | | |
| Day 3 | 1.017 ± 0.002 | 1.018 ± 0.002 | 1.016 ± 0.002 | 1.015 ± 0.002 | 1.015 ± 0.001 | 1.023 ± 0.002 |
| Day 16 | 1.012 ± 0.001 | 1.016 ± 0.003 | 1.014 ± 0.002 | 1.012 ± 0.001 | 1.012 ± 0.001 | 1.017 ± 0.002 |
| Day 44 | 1.016 ± 0.001 | 1.017 ± 0.003 | 1.015 ± 0.002 | 1.014 ± 0.001 | 1.015 ± 0.001 | 1.023 ± 0.002 |
| Week 13 | 1.021 ± 0.001 | 1.026 ± 0.003 | 1.023 ± 0.003 | 1.019 ± 0.001 | 1.023 ± 0.002 | 1.035 ± 0.004* |
| **Female** | | | | | | |
| Hematology | | | | | | |
| Hematocrit (%) | 50.5 ± 0.4 | 50.7 ± 0.6 | 51.0 ± 0.7 | 50.2 ± 0.4 | 49.3 ± 0.6 | 48.4 ± 0.6* |
| Hemoglobin (g/dL) | 15.7 ± 0.2 | 15.6 ± 0.2 | 15.7 ± 0.3 | 15.5 ± 0.1 | 15.4 ± 0.2 | 15.0 ± 0.2 |
| Erythrocytes ($10^6/\mu L$) | 8.87 ± 0.08 | 8.87 ± 0.11 | 8.96 ± 0.14 | 8.83 ± 0.07 | 8.77 ± 0.10 | 8.67 ± 0.11 |
| Mean cell volume (fL) | 56.9 ± 0.3 | 57.3 ± 0.3 | 57.0 ± 0.3 | 56.9 ± 0.3 | 56.4 ± 0.2 | 55.7 ± 0.3** |
| Mean cell hemoglobin (pg) | 17.7 ± 0.1 | 17.6 ± 0.1 | 17.6 ± 0.2 | 17.6 ± 0.1 | 17.5 ± 0.1 | 17.3 ± 0.1 |
| Mean cell hemoglobin concentration (g/dL) | 31.1 ± 0.1 | 30.8 ± 0.2 | 30.8 ± 0.2 | 30.9 ± 0.2 | 31.2 ± 0.1 | 31.1 ± 0.1 |
| Platelets ($10^3/\mu L$) | 613.8 ± 19.2 | 601.2 ± 22.3 | 640.2 ± 16.4 | 606.0 ± 35.8 | 609.0 ± 17.4 | 641.4 ± 18.7 |
| Reticulocytes ($10^6/\mu L$) | 0.1 ± 0.0 | 0.1 ± 0.0 | 0.1 ± 0.0 | 0.1 ± 0.0 | 0.1 ± 0.0 | 0.1 ± 0.0 |
| Leukocytes ($10^3/\mu L$) | 5.08 ± 0.38 | 5.14 ± 0.36 | 5.96 ± 0.40 | 5.86 ± 0.49 | 5.38 ± 0.23 | 6.36 ± 0.44 |
| Segmented neutrophils ($10^3/\mu L$) | 0.68 ± 0.07 | 0.67 ± 0.10 | 0.74 ± 0.08 | 0.87 ± 0.16 | 0.84 ± 0.11 | 1.46 ± 0.24** |
| Lymphocytes ($10^3/\mu L$) | 4.31 ± 0.40 | 4.38 ± 0.33 | 5.16 ± 0.34 | 4.92 ± 0.44 | 4.42 ± 0.15 | 4.77 ± 0.29 |
| Monocytes ($10^3/\mu L$) | 0.02 ± 0.01 | 0.00 ± 0.00 | 0.01 ± 0.01 | 0.01 ± 0.01 | 0.03 ± 0.01 | 0.02 ± 0.01 |
| Eosinophils ($10^3/\mu L$) | 0.07 ± 0.03 | 0.08 ± 0.01 | 0.05 ± 0.01 | 0.09 ± 0.02 | 0.10 ± 0.03 | 0.12 ± 0.03 |
| Nucleated erythrocytes ($10^3/\mu L$) | 0.02 ± 0.01 | 0.00 ± 0.00 | 0.00 ± 0.00 | 0.01 ± 0.01 | 0.02 ± 0.01 | 0.01 ± 0.01 |

**TABLE G1**
**Hematology, Clinical Chemistry, and Urinalysis Data for Rats in the 13-Week Dermal Study of Triethanolamine** (continued)

| | 0 mg/kg | 125 mg/kg | 250 mg/kg | 500 mg/kg | 1,000 mg/kg | 2,000 mg/kg |
|---|---|---|---|---|---|---|
| n | 10 | 10 | 10 | 10 | 10 | 10 |
| **Female** (continued) | | | | | | |
| Clinical Chemistry | | | | | | |
| Urea nitrogen (mg/dL) | 20.5 ± 0.6 | 19.9 ± 0.5 | 21.1 ± 0.4 | 21.5 ± 0.5 | 20.5 ± 0.4 | 23.0 ± 0.6** |
| Creatinine (mg/dL) | 0.60 ± 0.02 | 0.57 ± 0.02 | 0.58 ± 0.02 | 0.59 ± 0.02 | 0.57 ± 0.02 | 0.58 ± 0.02 |
| Glucose (mg/dL) | 113 ± 6 | 110 ± 6 | 102 ± 2 | 107 ± 3 | 105 ± 3 | 103 ± 3 |
| Total protein (g/dL) | 6.4 ± 0.1 | 6.5 ± 0.1 | 6.5 ± 0.1 | 6.5 ± 0.1 | 6.5 ± 0.1 | 6.7 ± 0.1 |
| Albumin (g/dL) | 4.9 ± 0.1 | 4.9 ± 0.1 | 4.9 ± 0.1 | 5.0 ± 0.1 | 5.0 ± 0.1 | 5.2 ± 0.1* |
| Alanine aminotransferase (IU/L) | 43 ± 2 | 43 ± 3 | 45 ± 2 | 45 ± 2 | 42 ± 2 | 53 ± 3 |
| Aspartate aminotransferase (IU/L) | 85 ± 6 | 88 ± 10 | 96 ± 6 | 84 ± 4 | 87 ± 4 | 126 ± 12** |
| Sorbitol dehydrogenase (IU/L) | 21 ± 1 | 19 ± 1 | 18 ± 1 | 16 ± 1* | 16 ± 1* | 18 ± 1 |
| Urinalysis | | | | | | |
| Glucose (mg/hr) | | | | | | |
| Day 3 | 0.011 ± 0.003 | 0.013 ± 0.002 | 0.013 ± 0.004 | 0.011 ± 0.003 | 0.012 ± 0.004 | 0.010 ± 0.003 |
| Day 16 | 0.029 ± 0.002 | 0.025 ± 0.002 | 0.025 ± 0.003 | 0.024 ± 0.003 | 0.025 ± 0.003 | 0.017 ± 0.003* |
| Day 44 | 0.013 ± 0.004 | 0.013 ± 0.003 | 0.016 ± 0.007 | 0.018 ± 0.006 | 0.028 ± 0.005 | 0.027 ± 0.008 |
| Week 13 | 0.009 ± 0.003 | 0.011 ± 0.003 | 0.021 ± 0.002** | 0.023 ± 0.003** | 0.026 ± 0.002** | 0.025 ± 0.003** |
| Protein (mg/hr) | | | | | | |
| Day 3 | 0.016 ± 0.002 | 0.014 ± 0.004 | 0.007 ± 0.001** | 0.008 ± 0.001* | 0.005 ± 0.000** | 0.008 ± 0.001** |
| Day 16 | 0.008 ± 0.003 | 0.005 ± 0.001 | 0.009 ± 0.001 | 0.008 ± 0.001 | 0.009 ± 0.002 | 0.010 ± 0.002 |
| Day 44 | 0.004 ± 0.002 | 0.004 ± 0.001 | 0.012 ± 0.005 | 0.013 ± 0.002* | 0.005 ± 0.001 | 0.010 ± 0.002 |
| Week 13 | 0.029 ± 0.005[b] | 0.051 ± 0.006 | 0.036 ± 0.008 | 0.042 ± 0.008 | 0.039 ± 0.006 | 0.039 ± 0.009 |
| Volume (mL/16 hr) | | | | | | |
| Day 3 | 9.1 ± 0.9 | 8.6 ± 1.1 | 10.8 ± 1.1 | 9.6 ± 1.3 | 8.2 ± 0.6 | 9.8 ± 1.3 |
| Day 16 | 11.4 ± 1.6 | 7.6 ± 1.3 | 9.6 ± 0.7 | 10.4 ± 0.9 | 8.3 ± 0.7 | 8.3 ± 1.3 |
| Day 44 | 10.1 ± 1.4 | 10.0 ± 1.7 | 11.3 ± 1.2 | 9.2 ± 1.2 | 7.4 ± 0.9 | 7.6 ± 0.8 |
| Week 13 | 6.0 ± 1.0 | 7.5 ± 1.2 | 6.3 ± 0.7 | 8.1 ± 1.0 | 6.2 ± 0.6 | 5.4 ± 0.9 |
| Specific gravity | | | | | | |
| Day 3 | 1.013 ± 0.002 | 1.016 ± 0.002 | 1.012 ± 0.001 | 1.015 ± 0.001 | 1.016 ± 0.001 | 1.018 ± 0.002 |
| Day 16 | 1.013 ± 0.002 | 1.017 ± 0.002 | 1.014 ± 0.001 | 1.013 ± 0.001 | 1.018 ± 0.001* | 1.021 ± 0.004[c] |
| Day 44 | 1.016 ± 0.002 | 1.015 ± 0.002 | 1.013 ± 0.002 | 1.016 ± 0.002 | 1.024 ± 0.003* | 1.026 ± 0.002** |
| Week 13 | 1.017 ± 0.001 | 1.016 ± 0.002 | 1.020 ± 0.003 | 1.017 ± 0.002 | 1.023 ± 0.002* | 1.032 ± 0.005** |

* Significantly different (P≤0.05) from the control group by Dunn's or Shirley's test
** P≤0.01
a Mean ± standard error. Statistical tests were performed on unrounded data.
b n=9
c n=6

**TABLE G2**
**Hematology, Clinical Chemistry, and Urinalysis Data for Mice in the 13-Week Dermal Study of Triethanolamine[a]**

| | 0 mg/kg | 250 mg/kg | 500 mg/kg | 1,000 mg/kg | 2,000 mg/kg | 4,000 mg/kg |
|---|---|---|---|---|---|---|
| **Male** | | | | | | |
| Hematology | | | | | | |
| n | 10 | 10 | 10 | 10 | 10 | 10 |
| Hematocrit (%) | 53.6 ± 0.6 | 53.5 ± 0.7 | 55.4 ± 0.5 | 54.1 ± 0.9 | 53.7 ± 0.4 | 51.5 ± 0.5 |
| Hemoglobin (g/dL) | 15.6 ± 0.3 | 15.3 ± 0.2 | 16.0 ± 0.3 | 15.4 ± 0.3 | 15.4 ± 0.2 | 14.8 ± 0.2 |
| Erythrocytes ($10^6/\mu L$) | 10.02 ± 0.12 | 9.85 ± 0.16 | 10.33 ± 0.10 | 10.08 ± 0.15 | 9.91 ± 0.08 | 9.64 ± 0.10 |
| Mean cell volume (fL) | 53.5 ± 0.2 | 54.3 ± 0.3 | 53.7 ± 0.3 | 53.4 ± 0.3 | 54.2 ± 0.3 | 53.5 ± 0.3 |
| Mean cell hemoglobin (pg) | 15.6 ± 0.2 | 15.6 ± 0.2 | 15.5 ± 0.1 | 15.3 ± 0.1 | 15.6 ± 0.1 | 15.4 ± 0.1 |
| Mean cell hemoglobin concentration (g/dL) | 29.0 ± 0.2 | 28.6 ± 0.3 | 28.9 ± 0.3 | 28.5 ± 0.2 | 28.7 ± 0.2 | 28.7 ± 0.3 |
| Platelets ($10^3/\mu L$) | 721.6 ± 37.9 | 785.6 ± 30.9 | 741.8 ± 42.6 | 773.0 ± 32.3 | 767.8 ± 31.0 | 855.6 ± 40.1 |
| Reticulocytes ($10^6/\mu L$) | 0.2 ± 0.0 | 0.2 ± 0.0 | 0.2 ± 0.0 | 0.2 ± 0.0 | 0.2 ± 0.0 | 0.2 ± 0.0 |
| Leukocytes ($10^3/\mu L$) | 6.40 ± 0.28 | 5.64 ± 0.30 | 6.22 ± 0.37 | 5.90 ± 0.63 | 5.74 ± 0.25 | 5.22 ± 0.72* |
| Segmented neutrophils ($10^3/\mu L$) | 1.01 ± 0.14 | 0.86 ± 0.07 | 1.12 ± 0.22 | 1.02 ± 0.13 | 0.85 ± 0.10 | 0.74 ± 0.10 |
| Lymphocytes ($10^3/\mu L$) | 5.15 ± 0.23 | 4.60 ± 0.24 | 4.91 ± 0.31 | 4.75 ± 0.56 | 4.77 ± 0.22 | 4.33 ± 0.60 |
| Monocytes ($10^3/\mu L$) | 0.01 ± 0.01 | 0.02 ± 0.01 | 0.01 ± 0.01 | 0.01 ± 0.01 | 0.01 ± 0.01 | 0.01 ± 0.01 |
| Eosinophils ($10^3/\mu L$) | 0.24 ± 0.05 | 0.15 ± 0.05 | 0.18 ± 0.06 | 0.12 ± 0.02 | 0.12 ± 0.03 | 0.15 ± 0.04 |
| Nucleated erythrocytes ($10^3/\mu L$) | 0.00 ± 0.00 | 0.00 ± 0.00 | 0.00 ± 0.00 | 0.01 ± 0.01 | 0.01 ± 0.01 | 0.00 ± 0.00 |
| Clinical Chemistry | | | | | | |
| n | 9 | 9 | 10 | 9 | 8 | 10 |
| Urea nitrogen (mg/dL) | 25.7 ± 2.4 | 23.7 ± 1.2 | 22.5 ± 0.9 | 23.0 ± 1.1 | 22.5 ± 0.9 | 24.0 ± 1.9 |
| Creatinine (mg/dL) | 0.39 ± 0.03 | 0.36 ± 0.02 | 0.40 ± 0.02 | 0.37 ± 0.02 | 0.35 ± 0.02 | 0.40 ± 0.02 |
| Glucose (mg/dL) | 151 ± 7 | 159 ± 5 | 149 ± 6 | 149 ± 5 | 150 ± 6 | 168 ± 15 |
| Total protein (g/dL) | 5.6 ± 0.1 | 5.5 ± 0.1 | 5.6 ± 0.1 | 5.5 ± 0.1 | 5.7 ± 0.1 | 5.6 ± 0.1 |
| Albumin (g/dL) | 3.9 ± 0.1 | 3.8 ± 0.0 | 3.9 ± 0.1 | 3.7 ± 0.1 | 4.0 ± 0.1 | 3.8 ± 0.1 |
| Alanine aminotransferase (IU/L) | 33 ± 4[b] | 34 ± 2 | 41 ± 3 | 37 ± 4[c] | 38 ± 6[d] | 31 ± 2[d] |
| Aspartate aminotransferase (IU/L) | 59 ± 11 | 57 ± 10 | 59 ± 5 | 53 ± 6[c] | 65 ± 11 | 63 ± 9[d] |
| Sorbitol dehydrogenase (IU/L) | 49 ± 3 | 36 ± 1** | 34 ± 2** | 30 ± 2**[c] | 30 ± 2**[d] | 25 ± 2** |

**TABLE G2**
**Hematology, Clinical Chemistry, and Urinalysis Data for Mice in the 13-Week Dermal Study of Triethanolamine**
(continued)

| | 0 mg/kg | 250 mg/kg | 500 mg/kg | 1,000 mg/kg | 2,000 mg/kg | 4,000 mg/kg |
|---|---|---|---|---|---|---|
| **Male** (continued) | | | | | | |
| Urinalysis | | | | | | |
| n | 10 | 10 | 9 | 10 | 10 | 10 |
| Glucose (mg/hr) | | | | | | |
| Day 46 | 0.006 ± 0.001 | 0.008 ± 0.003[d] | 0.006 ± 0.001 | 0.005 ± 0.001 | 0.004 ± 0.001 | 0.004 ± 0.001[d] |
| Week 13 | 0.007 ± 0.001 | 0.006 ± 0.001 | 0.007 ± 0.002[c] | 0.010 ± 0.002 | 0.007 ± 0.001 | 0.010 ± 0.002 |
| Protein (mg/hr) | | | | | | |
| Day 46 | 0.175 ± 0.041 | 0.168 ± 0.051[d] | 0.162 ± 0.041 | 0.139 ± 0.041 | 0.129 ± 0.035 | 0.108 ± 0.026[d] |
| Week 13 | 0.198 ± 0.032 | 0.148 ± 0.026 | 0.173 ± 0.053[c] | 0.187 ± 0.028 | 0.160 ± 0.027 | 0.238 ± 0.043 |
| Volume (mL/16 hr) | | | | | | |
| Day 46 | 1.1 ± 0.2 | 1.0 ± 0.3[d] | 1.6 ± 0.5 | 0.9 ± 0.2 | 0.8 ± 0.2 | 0.7 ± 0.2[d] |
| Week 13 | 1.2 ± 0.2 | 0.7 ± 0.1 | 1.0 ± 0.3 | 1.3 ± 0.3 | 1.1 ± 0.2 | 1.3 ± 0.2 |
| Specific gravity | | | | | | |
| Day 46 | 1.029 ± 0.004 | 1.028 ± 0.002[d] | 1.020 ± 0.004 | 1.026 ± 0.004 | 1.029 ± 0.003[b] | 1.031 ± 0.006[e] |
| Week 13 | 1.028 ± 0.002 | 1.039 ± 0.005 | 1.025 ± 0.006[c] | 1.029 ± 0.003 | 1.027 ± 0.003 | 1.038 ± 0.005 |
| **Female** | | | | | | |
| Hematology | | | | | | |
| n | 10 | 10 | 10 | 9 | 9 | 10 |
| Hematocrit (%) | 53.6 ± 1.2 | 53.1 ± 0.7 | 53.9 ± 0.5 | 53.9 ± 1.0 | 54.2 ± 0.5 | 53.8 ± 1.3 |
| Hemoglobin (g/dL) | 14.7 ± 0.4 | 15.0 ± 0.2 | 15.4 ± 0.1 | 15.4 ± 0.2 | 15.5 ± 0.2 | 15.7 ± 0.3 |
| Erythrocytes ($10^6/\mu L$) | 9.76 ± 0.26 | 9.71 ± 0.15 | 9.80 ± 0.12 | 9.86 ± 0.19 | 10.03 ± 0.12 | 9.88 ± 0.30 |
| Mean cell volume (fL) | 55.1 ± 0.3 | 54.8 ± 0.4 | 55.1 ± 0.5 | 54.6 ± 0.3 | 54.1 ± 0.3* | 54.6 ± 1.0* |
| Mean cell hemoglobin (pg) | 15.1 ± 0.4 | 15.5 ± 0.1 | 15.7 ± 0.1 | 15.7 ± 0.2 | 15.5 ± 0.1 | 16.0 ± 0.4 |
| Mean cell hemoglobin concentration (g/dL) | 27.6 ± 0.6 | 28.3 ± 0.2 | 28.5 ± 0.2 | 28.7 ± 0.4 | 28.6 ± 0.2 | 29.3 ± 0.2** |
| Platelets ($10^3/\mu L$) | 620.6 ± 46.9 | 655.6 ± 41.6 | 627.8 ± 45.3 | 684.2 ± 27.4 | 714.4 ± 24.1 | 722.0 ± 53.5 |
| Reticulocytes ($10^6/\mu L$) | 0.2 ± 0.0 | 0.2 ± 0.0 | 0.2 ± 0.0 | 0.2 ± 0.0 | 0.2 ± 0.0 | 0.2 ± 0.0 |
| Leukocytes ($10^3/\mu L$) | 4.40 ± 0.32 | 4.72 ± 0.34 | 4.04 ± 0.34 | 4.96 ± 0.29 | 5.16 ± 0.29 | 5.68 ± 0.43 |
| Segmented neutrophils ($10^3/\mu L$) | 0.56 ± 0.07 | 0.62 ± 0.07 | 0.49 ± 0.09 | 0.58 ± 0.07 | 0.66 ± 0.07 | 0.75 ± 0.15 |
| Lymphocytes ($10^3/\mu L$) | 3.78 ± 0.27 | 4.02 ± 0.29 | 3.46 ± 0.31 | 4.28 ± 0.25 | 4.37 ± 0.25 | 4.80 ± 0.33 |
| Monocytes ($10^3/\mu L$) | 0.00 ± 0.00 | 0.01 ± 0.01 | 0.01 ± 0.01 | 0.01 ± 0.01 | 0.02 ± 0.01 | 0.01 ± 0.01 |
| Eosinophils ($10^3/\mu L$) | 0.05 ± 0.02 | 0.08 ± 0.01 | 0.07 ± 0.02 | 0.10 ± 0.02 | 0.11 ± 0.02 | 0.13 ± 0.02* |
| Nucleated erythrocytes ($10^3/\mu L$) | 0.00 ± 0.00 | 0.00 ± 0.00 | 0.00 ± 0.00 | 0.00 ± 0.00 | 0.00 ± 0.00 | 0.00 ± 0.00 |

**Table G2**
**Hematology, Clinical Chemistry, and Urinalysis Data for Mice in the 13-Week Dermal Study of Triethanolamine**
(continued)

| | 0 mg/kg | 250 mg/kg | 500 mg/kg | 1,000 mg/kg | 2,000 mg/kg | 4,000 mg/kg |
|---|---|---|---|---|---|---|
| **Female** (continued) | | | | | | |
| Clinical Chemistry | | | | | | |
| n | 10 | 10 | 9 | 9 | 10 | 10 |
| Urea nitrogen (mg/dL) | 23.9 ± 1.6 | 18.8 ± 1.1 | 20.0 ± 1.8 | 20.4 ± 1.4[b] | 18.4 ± 1.6 | 19.6 ± 1.5 |
| Creatinine (mg/dL) | 0.41 ± 0.02 | 0.39 ± 0.01[d] | 0.42 ± 0.02 | 0.41 ± 0.01[b] | 0.42 ± 0.02 | 0.40 ± 0.02 |
| Glucose (mg/dL) | 138 ± 5 | 151 ± 7 | 153 ± 11 | 145 ± 5[b] | 143 ± 4 | 144 ± 5 |
| Total protein (g/dL) | 5.5 ± 0.1 | 5.7 ± 0.1 | 5.7 ± 0.1 | 5.7 ± 0.1 | 5.8 ± 0.1* | 5.6 ± 0.1 |
| Albumin (g/dL) | 4.1 ± 0.1 | 4.2 ± 0.1 | 4.2 ± 0.1 | 4.1 ± 0.0 | 4.3 ± 0.1 | 4.2 ± 0.1 |
| Alanine aminotransferase (IU/L) | 35 ± 4 | 44 ± 9[d] | 32 ± 4[c] | 24 ± 1 | 27 ± 2 | 42 ± 9 |
| Aspartate aminotransferase (IU/L) | 50 ± 3 | 66 ± 15 | 52 ± 3[c] | 44 ± 3 | 59 ± 6 | 77 ± 14 |
| Sorbitol dehydrogenase (IU/L) | 44 ± 3 | 32 ± 4** | 27 ± 1**[c] | 20 ± 1** | 20 ± 1** | 17 ± 1** |
| Urinalysis | | | | | | |
| n | 10 | 10 | 10 | 10 | 10 | 10 |
| Glucose (mg/hr) | | | | | | |
| Day 46 | 0.008 ± 0.001 | 0.010 ± 0.001 | 0.009 ± 0.001 | 0.011 ± 0.002 | 0.008 ± 0.001 | 0.012 ± 0.001* |
| Week 13 | 0.011 ± 0.002 | 0.007 ± 0.002 | 0.008 ± 0.001 | 0.007 ± 0.001[d] | 0.005 ± 0.000* | 0.008 ± 0.001 |
| Protein (mg/hr) | | | | | | |
| Day 46 | 0.073 ± 0.010 | 0.087 ± 0.011 | 0.090 ± 0.012 | 0.108 ± 0.015 | 0.077 ± 0.012 | 0.131 ± 0.017* |
| Week 13 | 0.071 ± 0.011 | 0.055 ± 0.008 | 0.073 ± 0.013 | 0.065 ± 0.011[d] | 0.061 ± 0.010 | 0.066 ± 0.009 |
| Volume (mL/16 hr) | | | | | | |
| Day 46 | 1.4 ± 0.2 | 1.7 ± 0.5 | 1.2 ± 0.1 | 1.6 ± 0.3 | 1.0 ± 0.2 | 2.7 ± 0.4 |
| Week 13 | 1.5 ± 0.2 | 1.2 ± 0.2 | 1.4 ± 0.3 | 1.3 ± 0.3[d] | 1.0 ± 0.2[d] | 1.5 ± 0.3 |
| Specific gravity | | | | | | |
| Day 46 | 1.021 ± 0.002 | 1.026 ± 0.002 | 1.026 ± 0.002 | 1.027 ± 0.003 | 1.031 ± 0.003 | 1.031 ± 0.004 |
| Week 13 | 1.025 ± 0.002 | 1.023 ± 0.002 | 1.028 ± 0.004 | 1.025 ± 0.003[d] | 1.032 ± 0.005 | 1.037 ± 0.004 |

* Significantly different (P≤0.05) from the control group by Dunn's or Shirley's test
** P≤0.01
[a] Mean ± standard error. Statistical tests were performed on unrounded data.
[b] n=8
[c] n=10
[d] n=9
[e] n=6

# APPENDIX H
# REPRODUCTIVE TISSUE EVALUATIONS AND ESTROUS CYCLE CHARACTERIZATION


| | | |
|---|---|---|
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**Table H1**
**Summary of Reproductive Tissue Evaluations for Male Rats in the 13-Week Dermal Study of Triethanolamine[a]**

| | 0 mg/kg | 500 mg/kg | 1,000 mg/kg | 2,000 mg/kg |
|---|---|---|---|---|
| n | 10 | 10 | 10 | 10 |
| Weights (g) | | | | |
| Necropsy body weight | 299 ± 6 | 287 ± 7 | 295 ± 11 | 248 ± 11** |
| R. cauda epididymis | 0.150 ± 0.003 | 0.154 ± 0.005 | 0.153 ± 0.006 | 0.143 ± 0.006 |
| R. epididymis | 0.421 ± 0.007 | 0.413 ± 0.005 | 0.405 ± 0.008 | 0.388 ± 0.011* |
| R. testis | 1.369 ± 0.026 | 1.345 ± 0.017 | 1.426 ± 0.077 | 1.326 ± 0.041 |
| Epididymal spermatozoal measurements | | | | |
| Motility (%) | 73.50 ± 1.09 | 74.95 ± 1.49 | 74.97 ± 1.65 | 78.26 ± 1.65 |
| Abnormal (%) | 1.220 ± 0.205 | 0.780 ± 0.070 | 1.160 ± 0.299 | 1.200 ± 0.176 |
| Concentration ($10^6$/g cauda epididymal tissue) | 650 ± 35 | 572 ± 48 | 674 ± 36 | 588 ± 29 |

* Significantly different (P≤0.05) from the control group by Dunnett's test
** Significantly different (P≤0.01) from the control group by Williams' test
[a] Data are presented as mean ± standard error. Differences from the control group are not significant by Dunnett's test (right cauda epididymis and testis weights) or Dunn's test (epididymal spermatozoal measurements).

**Table H2**
**Summary of Estrous Cycle Characterization for Female Rats in the 13-Week Dermal Study of Triethanolamine[a]**

| | 0 mg/kg | 500 mg/kg | 1,000 mg/kg | 2,000 mg/kg |
|---|---|---|---|---|
| n | 10 | 10 | 10 | 10 |
| Necropsy body weight (g) | 174 ± 4 | 174 ± 3 | 170 ± 3 | 158 ± 4** |
| Estrous cycle length (days) | 4.70 ± 0.21 | 4.40 ± 0.22 | 4.75 ± 0.25[b] | 4.50 ± 0.27[b] |
| Estrous stages (% of cycle) | | | | |
| Diestrus | 25.7 | 28.6 | 38.6 | 42.9 |
| Proestrus | 17.1 | 7.1 | 11.4 | 12.9 |
| Estrus | 37.1 | 37.1 | 35.7 | 27.1 |
| Metestrus | 18.6 | 25.7 | 11.4 | 17.1 |
| Uncertain diagnoses | 1.4 | 1.4 | 2.9 | 0.0 |

** Significantly different (P≤0.01) from the control group by Williams' test
[a] Necropsy body weight and estrous cycle length data are presented as mean ± standard error. Differences from the control group for estrous cycle length are not significant by Dunn's test. By multivariate analysis of variance, dosed females do not differ significantly from the control females in the relative length of time spent in the estrous stages.
[b] Estrous cycle was longer than 7 days or unclear in 2 of 10 rats.

**TABLE H3**
**Summary of Reproductive Tissue Evaluations for Male Mice in the 13-Week Dermal Study of Triethanolamine[a]**

| | 0 mg/kg | 1,000 mg/kg | 2,000 mg/kg | 4,000 mg/kg |
|---|---|---|---|---|
| n | 10 | 10 | 10 | 10 |
| Weights (g) | | | | |
| Necropsy body weight | 34.2 ± 0.7 | 32.5 ± 0.7 | 32.0 ± 0.8 | 32.0 ± 0.6 |
| R. cauda epididymis | 0.022 ± 0.004 | 0.021 ± 0.002 | 0.016 ± 0.001 | 0.017 ± 0.001 |
| R. epididymis | 0.052 ± 0.003 | 0.052 ± 0.003 | 0.047 ± 0.002 | 0.046 ± 0.002 |
| R. testis | 0.121 ± 0.003 | 0.117 ± 0.003 | 0.115 ± 0.003 | 0.113 ± 0.006 |
| Epididymal spermatozoal measurements | | | | |
| Motility (%) | 71.83 ± 1.84 | 74.35 ± 1.58 | 74.11 ± 1.82 | 71.79 ± 1.84 |
| Abnormal (%) | 1.62 ± 0.12 | 1.52 ± 0.12 | 1.44 ± 0.14 | 1.92 ± 0.43 |
| Concentration ($10^6$/g cauda epididymal tissue) | 628 ± 105 | 603 ± 63 | 617 ± 68 | 676 ± 108 |

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

**TABLE H4**
**Summary of Estrous Cycle Characterization for Female Mice in the 13-Week Dermal Study of Triethanolamine[a]**

| | 0 mg/kg | 1,000 mg/kg | 2,000 mg/kg | 4,000 mg/kg |
|---|---|---|---|---|
| n | 10 | 10 | 10 | 10 |
| Necropsy body weight (g) | 28.2 ± 0.6 | 28.2 ± 0.7 | 27.4 ± 0.5 | 28.2 ± 0.5 |
| Estrous cycle length (days) | 4.00 ± 0.00[b] | 4.00 ± 0.00 | 4.20 ± 0.13 | 4.20 ± 0.25 |
| Estrous stages (% of cycle) | | | | |
| Diestrus | 37.1 | 27.1 | 32.9 | 32.9 |
| Proestrus | 8.6 | 12.9 | 20.0 | 12.9 |
| Estrus | 28.6 | 30.0 | 25.7 | 31.4 |
| Metestrus | 22.9 | 30.0 | 21.4 | 20.0 |
| Uncertain diagnoses | 2.9 | 0.0 | 0.0 | 2.9 |

[a] Necropsy body weight and estrous cycle length data are presented as mean ± standard error. Differences from the control group are not significant by Dunnett's test (necropsy body weight) or Dunn's test (estrous cycle length). By multivariate analysis of variance, dosed females do not differ significantly from the control females in the relative length of time spent in the estrous stages.
[b] Estrous cycle was unclear in 2 of 10 mice.

# APPENDIX I
# CHEMICAL CHARACTERIZATION AND DOSE FORMULATION STUDIES

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# CHEMICAL CHARACTERIZATION AND DOSE FORMULATION STUDIES

## PROCUREMENT AND CHARACTERIZATION OF TRIETHANOLAMINE

Triethanolamine was obtained from Texaco Chemical Company (Division of Texaco, Inc., Bellaire, TX) in two lots (3B-1-84 and 7G-60). Lot 3B-1-84 was used in the 13-week studies and Lot 7G-60 was used during the 2-year studies. Identity, purity, and stability analyses were conducted by the analytical chemistry laboratory, Midwest Research Institute (Kansas City, MO). Reports on analyses performed in support of the triethanolamine studies are on file at the National Institute of Environmental Health Sciences.

The chemical, a clear, colorless, viscous liquid, was identified as triethanolamine by infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopy. All spectra were consistent with the literature spectra (*Sadtler Standard Spectra*, 1970) of triethanolamine (Figures I1 and I2).

The purity of Lot 3B-1-84 was determined by elemental analyses, Karl Fischer water analysis, functional group titration, thin-layer chromatography (TLC), and gas chromatography. For functional group titration, triethanolamine samples were reacted with excess acetic anhydride to identify the presence of monoethanolamine or diethanolamine; the samples were then heated in a steam bath for 10 minutes and cooled. Glacial acetic acid was added, and the samples were titrated with 0.1 N perchloric acid in glacial acetic acid. Additional samples of triethanolamine were prepared by the same method but without the addition of acetic anhydride. All titrations were monitored potentiometrically with a combination pH/mV electrode filled with 0.1 M lithium perchlorate in acetic anhydride. TLC was performed on Silica Gel 60 F-254 plates with two solvent systems: 1) chloroform:methanol:concentrated ammonium hydroxide (55:40:5) and 2) toluene:methanol:concentrated ammonium hydroxide (55:40:5). Diethanolamine was used as a reference standard. The plates were examined with two visualization methods: 1) iodine vapor and 2) a spray of 0.5% ninhydrin in butanol followed by heating. Gas chromatography was performed with a flame ionization detector and a nitrogen carrier gas. Two systems were used:

A) 60/80 mesh Tenax GC column, with an oven temperature program of 50° C for 5 minutes, then 50° to 300° C at 10° C per minute, and a carrier gas flow rate of 15 mL/minute, and

B) 3% SP-2100 DB on 100/120 Supelcoport, with an oven temperature program of 50° C for 5 minutes, then 50° to 250° C at 10° C per minute, and a carrier gas flow rate of 70 mL/minute.

Elemental analyses for hydrogen and nitrogen were in agreement with the theoretical values for triethanolamine; the results for carbon were slightly low. Karl Fischer water analysis indicated 0.45% ± 0.06(s)% water. Functional group titration of triethanolamine samples treated with acetic anhydride indicated 98.4% ± 0.3% total tertiary amines. Titration of samples not pretreated with acetic anhydride indicated 99.0% ± 0.2% total titratable amines; the difference between the two titration values indicated an impurity equivalent to 0.04 mEq/g sample (0.4% w/w, based on diethanolamine being the most likely impurity). TLC by system 1 indicated a major spot and a very slight trace impurity; system 2 indicated a major spot and a trace, a slight trace, and a very slight trace impurity. Gas chromatography with system A indicated one major peak and three impurities with areas totaling 1.43% of the major peak area; system B indicated one major peak and one impurity with an area less than 0.2% relative to the major peak. The overall purity of triethanolamine was determined to be approximately 98%.

Lot 3B-1-84 was further characterized by National Formulary methods (USP XX/NF XV) of testing for trolamine, a mixture of alkanolamines consisting largely of triethanolamine, with some diethanolamine and

monoethanolamine. The bulk chemical produced a deep blue color when reacted with cupric sulfate, followed by the addition of 1 N sodium hydroxide, and produced a carmine red color when reacted with cobaltous chloride. Vapors produced by a heated sample turned moistened red litmus paper blue. A specific gravity of 1.124 ± 0.000 was determined for the bulk chemical. The refractive index was determined to be 1.484 ± 0.000 at 20° C. Karl Fischer water analysis indicated 0.45% ± 0.06% water. After being charred, ignited in a muffle furnace, and then cooled in a desiccator, a 1-gram sample of triethanolamine produced 0.03% ± 0.02% residue. Titration with 1 N hydrochloric acid, with methyl red indicator, indicated 101.2% ± 0.2% alkanolamines. All results were consistent with NF XV requirements for trolamine.

The purity of Lot 7G-60 was also determined by elemental analyses, Karl Fischer water analysis, functional group titration, TLC, and gas chromatography. Functional group titration and TLC methods were the same as those used for Lot 3B-1-84. Two gas chromatographic systems with a flame ionization detector were used:

A) 60/80 mesh Tenax GC column, with an oven temperature program of 50° C for 5 minutes, then 50° to 300° C at 10° C per minute, and a nitrogen carrier gas at a flow rate of 15 mL/minute, and

B) DB-5 Megabore fused silica column, with an oven temperature program of 100° C for 5 minutes, then 100° to 250° C at 10° C per minute, a helium carrier gas at a flow rate of 9 mL/minute, and a nitrogen make-up gas at a flow rate of 23 mL/minute.

Elemental analyses for carbon, hydrogen, and nitrogen were in agreement with the theoretical values for triethanolamine. Karl Fischer water analysis indicated 0.09% ± 0.01% water. Functional group titration indicated 99.3% ± 0.6% total tertiary amines and 100.2% ± 0.4% total titratable amines; the difference between the two titration values indicated an impurity equivalent to 0.04 mEq/g sample (0.4% w/w based on diethanolamine being the most likely impurity). TLC by system 1 indicated a major spot and two trace impurities; system 2 indicated a major spot, a trace impurity, and three slight trace impurities. Gas chromatography by system A indicated one major peak and one impurity, with an area of 0.16% relative to the major peak; system B indicated one major peak and no impurities with areas of 0.1% or greater relative to the major peak. The overall purity of Lot 7G-60 was determined to be approximately 99%.

The concentrations of nonpolar nitrosamines (*N*-nitrosodimethylamine, *N*-nitrosomethylethylamine, *N*-nitrosodiethylamine, *N*-nitrosodi-n-propylamine, *N*-nitrosodi-n-butylamine, *N*-nitrosopiperidine, *N*-nitrosopyrrolidine, and *N*-nitrosomorpholine) and the polar nitrosamine *N*-nitrosodiethanolamine in lot 7G-60 were determined by Covance Laboratories, Inc. (Madison, WI). To measure nonpolar nitrosamines, samples were diluted with high-performance liquid chromatography (HPLC)-grade water and then partitioned three times with dichloromethane:pentane (35:65); samples were vortexed and centrifuged between each partitioning. The pentane fractions were transferred to a Kuderna-Danish concentrator tube with an attached concentrator flask, and dichloromethane, isooctane, and an ebullator were added. A three-ball Snyder column prewet with dichloromethane was attached to the concentrator tube, and the entire apparatus was placed in a hot water bath until the volume of the solvent was reduced to 4 to 8 mL. The sample was allowed to cool, and the concentrated extract was collected with dichloromethane. The sample was then heated under a stream of nitrogen until the concentration was less than 1 mL; the volume was adjusted to 1.0 mL with isooctane. The samples were then analyzed for nonpolar nitrosamines by gas chromatography with a thermal energy detector, a 10% Carbowax 1540 100/120 WHP in 5% KOH column, and an argon carrier gas at a flow rate of 25 mL/minute. The oven temperature program was 120° C for 4 minutes, then 120° to 180° C at 4° C per minute, with a final hold of 8 minutes at 180° C. No nonpolar nitrosamines were present at concentrations greater than the limit of detection (0.1 ppm).

To measure the polar nitrosamine *N*-nitrosodiethanolamine, samples were diluted with distilled water, and 1 N hydrogen chloride was added. The samples were mixed and shaken, then further diluted with distilled water and remixed. Two cation exchange columns were prepared; first the solvent, then 0.05 N hydrogen chloride, then distilled water was drained in the column to the top of the resin bed. The columns were connected in a series with a ChemElut-extraction column. The sample, followed by distilled water, was allowed to drip through the three columns and allowed to be absorbed onto the dry column for 10 minutes. The columns were then rinsed with 10% acetone in ethyl acetate; *N*-nitrosodiethanolamine was eluted with additional acetone in ethyl acetate, and the samples were concentrated to complete dryness on a rotary evaporator with a hot water bath. The dry column was rinsed with methanol three times, and the collected samples were dried under a stream of nitrogen; 1 mL of methanol was added, and the samples were then analyzed for N-nitrosodiethanolamine by HPLC with a thermal energy detector, an Alltech platinum 5$\mu$ CN column, and an isocratic solvent system of isooctane:dichloromethane:methanol (71:18:11). The flow rate was 0.4 mL/minute. No *N*-nitrosodiethanolamine was present at a concentration greater than the limit of detection (1.0 ppm).

Stability studies of the bulk chemical were performed on Lot 3B-1-84 with gas chromatography by the analytical chemistry laboratory. System A, as described for the purity analyses for this lot, was used, but with an isothermal oven temperature of 240° C, and with triethylene glycol added as an internal standard. These studies indicated that triethanolamine was stable as a bulk chemical for 2 weeks when stored under a nitrogen headspace, protected from light, at temperatures up to 60° C. To ensure stability, the bulk chemical was stored at room temperature in amber glass containers under a nitrogen headspace during the 2-year studies. Stability was monitored by the study laboratory during the 13-week studies with gas chromatography and nonaqueous amine titration and during the 2-year studies with gas chromatography. No degradation of the bulk chemical was detected.

## PREPARATION AND ANALYSIS OF DOSE FORMULATIONS

During the 13-week studies, the highest exposure concentrations were applied neat. The lower concentrations in the 13-week studies and all dose formulations in the 2-year studies were prepared by mixing triethanolamine and acetone to give the required concentration (Table I1). The dose formulations were prepared once every 2 weeks and were stored at 5° C in amber glass bottles under a nitrogen headspace, protected from light, for up to 3 weeks.

Stability studies of the 70 mg/mL (125 mg/kg - rats; 250 mg/kg - mice) dose formulation were performed with gas chromatography. System A as described for the purity analyses of Lot 3B-1-84 was used, but with an isothermal oven temperature of 220° C. The stability of the dose formulations was confirmed for at least 3 weeks when stored at room temperature in sealed glass vials, under a nitrogen headspace, in the dark and for at least 3 hours under animal room conditions (open to air and light). The stability of 10 mg/mL triethanolamine in acetone was also confirmed under these conditions by gas chromatography with flame ionization detection, a DB-1 column, and an oven temperature program of 80° C for 5 minutes, then 80° to 190° C at 15° C per minute, with a 3-minute hold. A helium carrier gas at a flow rate of 26 mL/minute was used.

Periodic analyses of the dose formulations of triethanolamine were conducted at the study laboratory and analytical chemistry laboratory with gas chromatography. For the 13-week studies, the formulations were analyzed at the beginning, midpoint, and end of the studies; animal-room samples of the same dose formulations were also analyzed (Table I2). All dose formulations and animal-room samples were within 10% of the target concentrations. For the 2-year studies, the dose formulations were analyzed at the beginning of the studies and every 6 to 10 weeks thereafter; additionally, animal-room samples were analyzed every 22 to 26 weeks (Table I3). Of the dose formulations analyzed, 95% (59/62) for rats and all formulations for mice were within 10% of the target concentration. All animal-room samples for rats and

97% (29/30) for mice were within 10% of the target concentrations. Results of periodic referee analyses performed by the analytical chemistry laboratory agreed with the results obtained by the study laboratory (Table I4).

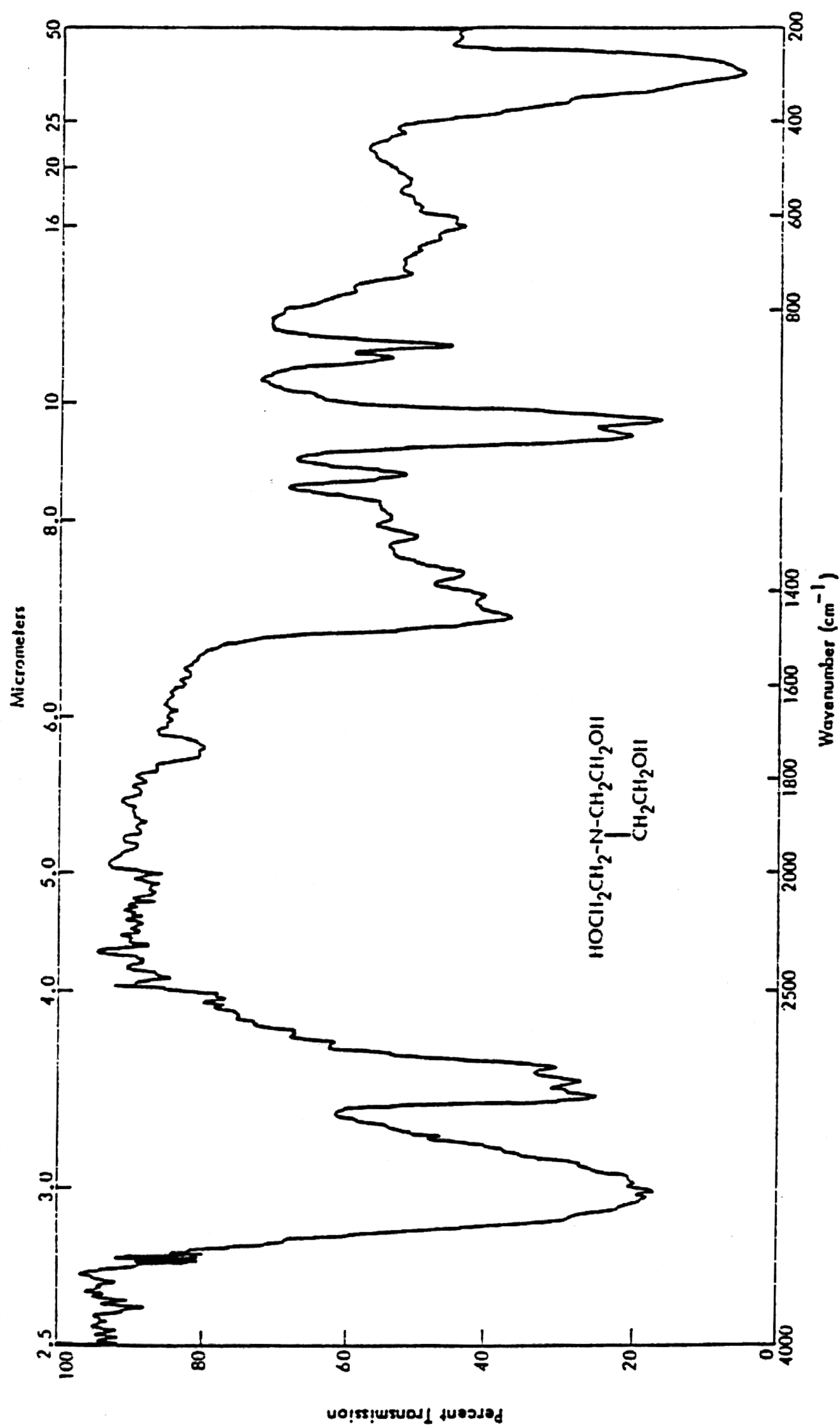


**FIGURE I1**
**Infrared Absorption Spectrum of Triethanolamine**

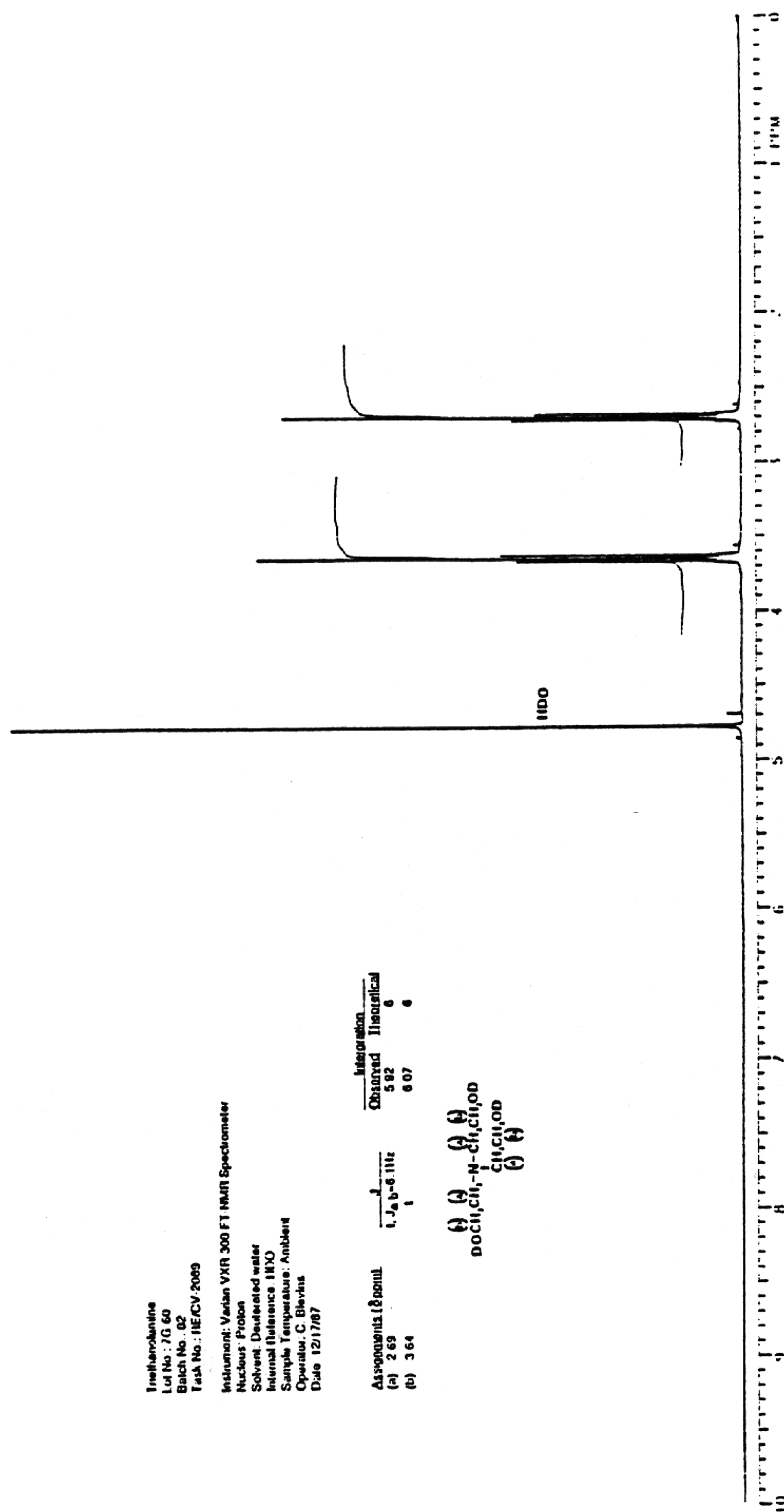

**FIGURE I2**
**Nuclear Magnetic Resonance Spectrum of Triethanolamine**

**Table I1**
**Preparation and Storage of Dose Formulations in the Dermal Studies of Triethanolamine**

| 13-Week Studies | 2-Year Studies |
|---|---|
| **Preparation** | |
| The highest doses (rats, 2,000 mg/kg; mice, 4,000 mg/kg) were applied neat; other doses were prepared by mixing triethanolamine with acetone and inverting repeatedly. Doses were prepared every 2 weeks. | Same as 13-week studies |
| **Chemical Lot Number** | |
| 3B-1-84 | 7G-60 |
| **Maximum Storage Time** | |
| 3 weeks | 3 weeks |
| **Storage Conditions** | |
| Neat chemical stored at room temperature; triethanolamine:acetone mixtures stored at 5° C, protected from light | Same as 13-week studies |
| **Study Laboratory** | |
| Battelle Columbus Laboratories (Columbus, OH) | Battelle Columbus Laboratories (Columbus, OH) |
| **Referee Laboratory** | |
| Midwest Research Institute (Kansas City, MO) | Midwest Research Institute (Kansas City, MO) |

**TABLE I2**
**Results of Analysis of Dose Formulations Administered to Rats and Mice in the 13-Week Dermal Studies of Triethanolamine**

| Date Prepared | Date Analyzed | Target Concentration (mg/mL) | Determined Concentration[a] (mg/mL) | Difference from Target (%) |
|---|---|---|---|---|
| **Rats** | | | | |
| 23 June 1986 | 26 June 1986 | 70 | 70.8 | +1 |
| | | 140 | 141 | +1 |
| | | 280 | 279 | 0 |
| | | 560 | 560 | 0 |
| | 16 July 1986[b] | 70 | 72.3 | +3 |
| | | 140 | 145 | +4 |
| | | 280 | 284 | +1 |
| | | 560 | 571 | +2 |
| 4 August 1986 | 7 August 1986 | 70 | 67.2 | −4 |
| | | 140 | 143 | +2 |
| | | 280 | 283 | +1 |
| | | 560 | 561 | 0 |
| | 2 September 1986[b] | 70 | 73.1 | +4 |
| | | 140 | 143 | +2 |
| | | 280 | 283 | +1 |
| | | 560 | 567 | +1 |
| 15 September 1986 | 16 September 1986 | 70 | 71.1 | +2 |
| | | 140 | 136 | −3 |
| | | 280 | 271 | −3 |
| | | 560 | 559 | 0 |
| | 7 October 1986[b] | 70 | 67.8 | −3 |
| | | 140 | 144 | +3 |
| | | 280 | 297 | +6 |
| | | 560 | 568 | +1 |
| **Mice** | | | | |
| 4 August 1986 | 7 August 1986 | 70 | 67.9 | −3 |
| | | 140 | 144 | +3 |
| | | 280 | 279 | 0 |
| | | 560 | 561 | 0 |
| | 2 September 1986[b] | 70 | 75.1 | +7 |
| | | 140 | 143 | +2 |
| | | 280 | 285 | +2 |
| | | 560 | 551 | −2 |
| 15 September 1986 | 16 September 1986 | 70 | 69.6 | −1 |
| | | 140 | 134 | −4 |
| | | 280 | 258 | −8 |
| | | 560 | 535 | −5 |
| | 7 October 1986[b] | 70 | 67.3 | −4 |
| | | 140 | 144 | +3 |
| | | 280 | 284 | +1 |
| | | 560 | 562 | 0 |

**TABLE I2**
**Results of Analysis of Dose Formulations Administered to Rats and Mice in the 13-Week Dermal Studies of Triethanolamine** (continued)

| Date Prepared | Date Analyzed | Target Concentration (mg/mL) | Determined Concentration (mg/mL) | Difference from Target (%) |
|---|---|---|---|---|
| **Mice** (continued) | | | | |
| 27 October 1986 | 28 October 1986 | 70 | 68.6 | −2 |
| | | 140 | 138 | −1 |
| | | 280 | 277 | −1 |
| | | 560 | 544 | −3 |
| | 19 November 1986[b] | 70 | 66.9 | −4 |
| | | 140 | 140 | 0 |
| | | 280 | 284 | +1 |
| | | 560 | 563 | +1 |

[a] Results of duplicate analyses. For rats, 70 mg/mL=125 mg/kg; 140 mg/mL=250 mg/kg; 280 mg/mL=500 mg/kg; 560 mg/mL=1,000 mg/kg. For mice, 70 mg/mL=250 mg/kg; 140 mg/mL=500 mg/kg; 280 mg/mL=1,000 mg/kg; 560 mg/mL=2,000 mg/kg.
[b] Animal room samples

**TABLE I3**
**Results of Analysis of Dose Formulations Administered to Rats and Mice in the 2-Year Dermal Studies of Triethanolamine**

| Date Prepared | Date Analyzed | Target Concentration (mg/mL) | Determined Concentration[a] (mg/mL) | Difference from Target (%) |
|---|---|---|---|---|
| **Rats** | | | | |
| 7 November 1988 | 9 November 1988 | 50 | 48.9 | −2 |
| | | 100[b] | 98.1 | −2 |
| | | 100[c] | 98.0 | −2 |
| | | 200[b] | 195 | −2 |
| | | 200[c] | 195 | −2 |
| | | 400 | 393 | −2 |
| | 1-2 December 1988[d] | 50 | 53.0 | +6 |
| | | 100[b] | 108 | +8 |
| | | 100[c] | 106 | +6 |
| | | 200[b] | 197 | −1 |
| | | 200[c] | 198 | −1 |
| | | 400 | 395 | −1 |
| 20 December 1988 | 23-24 December 1988 | 50 | 50.3 | +1 |
| | | 100[b] | 103 | +3 |
| | | 100[c] | 101 | +1 |
| | | 200[b] | 203 | +2 |
| | | 200[c] | 197 | −1 |
| | | 400 | 396 | −1 |
| 14 February 1989 | 16-18 February 1989 | 50 | 47.8 | −4 |
| | | 100[b] | 97.4 | −3 |
| | | 100[c] | 100 | 0 |
| | | 200[b] | 201 | +1 |
| | | 200[c] | 203 | +2 |
| | | 400 | 391 | −2 |
| 11 April 1989 | 14-15 April 1989 | 50 | 48.8 | −2 |
| | | 100 | 103 | +3 |
| | | 200 | 193 | −3 |
| | | 400 | 386 | −3 |
| | 25-26 April 1989[d] | 50 | 50.4 | +1 |
| | | 100[b] | 103 | +3 |
| | | 100[c] | 99.0 | −1 |
| | | 200[b] | 203 | +2 |
| | | 200[c] | 207 | +4 |
| | | 400 | 397 | −1 |
| 6 June 1989 | 7-8 June 1989 | 50 | 50.0 | 0 |
| | | 100 | 104 | +4 |
| | | 200 | 213 | +7 |
| | | 400 | 408 | +2 |
| 1 August 1989 | 3 August 1989 | 50 | 55.2 | +10 |
| | | 100 | 109 | +9 |
| | | 200 | 203 | +2 |
| | | 400 | 403 | +1 |
| | 4 August 1989[e] | 50 | 50.8 | +2 |

**TABLE I3**
**Results of Analysis of Dose Formulations Administered to Rats and Mice in the 2-Year Dermal Studies of Triethanolamine** (continued)

| Date Prepared | Date Analyzed | Target Concentration (mg/mL) | Determined Concentration (mg/mL) | Difference from Target (%) |
|---|---|---|---|---|
| **Rats** (continued) | | | | |
| 26 September 1989 | 29 September 1989 | 50 | 55.5 | +11 |
| | | 100 | 123 | +23 |
| | | 200 | 210 | +5 |
| | | 400 | 400 | 0 |
| | 30 September - 1 October 1989[e] | 50 | 48.1 | −4 |
| | | 100 | 98.0 | −2 |
| | 19 October 1989[d] | 50 | 48.7 | −3 |
| | | 100[b] | 103 | +3 |
| | | 100[c] | 102 | +2 |
| | | 200[b] | 211 | +6 |
| | | 200[c] | 209 | +5 |
| | | 400 | 414 | +4 |
| 20 November 1989 | 22 November 1989 | 50 | 53.1 | +6 |
| | | 100 | 107 | +7 |
| | | 200 | 212 | +6 |
| | | 400 | 405 | +1 |
| 16 January 1990 | 18 January 1990 | 50 | 51.1 | +2 |
| | | 100 | 102 | +2 |
| | | 200 | 206 | +3 |
| | | 400 | 402 | +1 |
| 13 March 1990 | 16 March 1990 | 50 | 48.8 | −2 |
| | | 100 | 98.0 | −2 |
| | | 200 | 199 | 0 |
| | | 400 | 402 | +1 |
| 23 April 1990 | 26 April 1990 | 50 | 49.6 | −1 |
| | | 100 | 96.2 | −4 |
| | | 200 | 192 | −4 |
| | | 400 | 382 | −4 |
| | 9 May 1990[d] | 50 | 50.9 | +2 |
| | | 100[b] | 103 | +3 |
| | | 100[c] | 104 | +4 |
| | | 200[b] | 206 | +3 |
| | | 200[c] | 208 | +4 |
| | | 400 | 408 | +2 |
| 18 June 1990 | 19 June 1990 | 50 | 50.9 | +2 |
| | | 100 | 103 | +3 |
| | | 200 | 202 | +1 |
| | | 400 | 415 | +4 |

**TABLE I3**
**Results of Analysis of Dose Formulations Administered to Rats and Mice in the 2-Year Dermal Studies of Triethanolamine** (continued)

| Date Prepared | Date Analyzed | Target Concentration (mg/mL) | Determined Concentration (mg/mL) | Difference from Target (%) |
|---|---|---|---|---|
| **Rats** (continued) | | | | |
| 13 August 1990 | 15 August 1990 | 50 | 50.2 | 0 |
| | | 100 | 101 | +1 |
| | | 200 | 209 | +5 |
| | | 400 | 434 | +9 |
| 8 October 1990 | 10 October 1990 | 50 | 52.9 | +6 |
| | | 100 | 108 | +8 |
| | | 200 | 405 | +103 |
| | | 400 | 420 | +5 |
| 12 October 1990[f] | 12 October 1990 | 200 | 199 | 0 |
| 8 and 12 October 1990 | 31 October 1990[d] | 50 | 53.0 | +6 |
| | | 100[b] | 109 | +9 |
| | | 100[c] | 109 | +9 |
| | | 200[b] | 211 | +6 |
| | | 200[c] | 214 | +7 |
| | | 400 | 436 | +9 |
| **Mice** | | | | |
| 25 October 1988 | 27-28 October 1988 | 50 | 49.4 | −1 |
| | | 100 | 99.9 | 0 |
| | | 150 | 147 | −2 |
| | | 300 | 294 | −2 |
| | | 500 | 486 | −3 |
| | | 1,000 | 1,030 | +3 |
| | 11 November 1988[d] | 50 | 52.2 | +4 |
| | | 100 | 103 | +3 |
| | | 150 | 154 | +3 |
| | | 300 | 306 | +2 |
| | | 500 | 511 | +2 |
| | | 1,000 | 999 | 0 |
| 20 December 1988 | 23-24 December 1988 | 50 | 50.4 | +1 |
| | | 100 | 102 | +2 |
| | | 150 | 154 | +3 |
| | | 300 | 305 | +2 |
| | | 500 | 492 | −2 |
| | | 1,000 | 1,060 | +6 |
| 14 February 1989 | 16-18 February 1989 | 50 | 48.6 | −3 |
| | | 100 | 97.5 | −2 |
| | | 150 | 146 | −3 |
| | | 300 | 298 | −1 |
| | | 500 | 503 | +1 |
| | | 1,000 | 977 | −2 |

**TABLE I3**
**Results of Analysis of Dose Formulations Administered to Rats and Mice in the 2-Year Dermal Studies of Triethanolamine** (continued)

| Date Prepared | Date Analyzed | Target Concentration (mg/mL) | Determined Concentration (mg/mL) | Difference from Target (%) |
|---|---|---|---|---|
| **Mice** (continued) | | | | |
| 11 April 1989 | 14-15 April 1989 | 50 | 50.0 | 0 |
| | | 100 | 98.9 | –1 |
| | | 150 | 146 | –3 |
| | | 300 | 294 | –2 |
| | | 500 | 510 | +2 |
| | | 1,000 | 956[g] | –4 |
| 15 April 1989[f] | 16 April 1989 | 1,000 | 1,030 | +3 |
| 11 and 15 April 1989 | 25-26 April 1989[d] | 50 | 52.0 | +4 |
| | | 100 | 107 | +7 |
| | | 150 | 157 | +5 |
| | | 300 | 311 | +4 |
| | | 500 | 515 | +3 |
| | | 1,000 | 1,060 | +6 |
| 6 June 1989 | 7-8 June 1989 | 50 | 49.3 | –1 |
| | | 100 | 101 | +1 |
| | | 150 | 153 | +2 |
| | | 300 | 308 | +3 |
| | | 500 | 513 | +3 |
| | | 1,000 | 1,030 | +3 |
| 1 August 1989 | 3 August 1989 | 50 | 54.4 | +9 |
| | | 100 | 108 | +8 |
| | | 150 | 161 | +7 |
| | | 300 | 316 | +5 |
| | | 500 | 530 | +6 |
| | | 1,000 | 1,100 | +10 |
| | 4 August 1989[e] | 50 | 53.9 | +8 |
| | | 100 | 107 | +7 |
| | | 1,000 | 1,050 | +5 |
| 26 September 1989 | 29 September 1989 | 50 | 52.9 | +6 |
| | | 100 | 107 | +7 |
| | | 150 | 165 | +10 |
| | | 300 | 337 | +12 |
| | | 500 | 537 | +7 |
| | | 1,000 | 1,060 | +6 |
| | 30 September - 1 October 1989[e] | 150 | 153 | +2 |
| | | 300 | 304 | +1 |
| | 19 October 1989[d] | 50 | 49.4 | –1 |
| | | 100 | 101 | +1 |
| | | 150 | 158 | +5 |
| | | 300 | 304 | +1 |
| | | 500 | 538 | +8 |
| | | 1,000 | 1,050 | +5 |

**TABLE I3**
**Results of Analysis of Dose Formulations Administered to Rats and Mice in the 2-Year Dermal Studies of Triethanolamine** (continued)

| Date Prepared | Date Analyzed | Target Concentration (mg/mL) | Determined Concentration (mg/mL) | Difference from Target (%) |
|---|---|---|---|---|
| **Mice** (continued) | | | | |
| 20 November 1989 | 22 November 1989 | 50 | 52.5 | +5 |
| | | 100 | 109 | +9 |
| | | 150 | 159 | +6 |
| | | 300 | 315 | +5 |
| | | 500 | 522 | +4 |
| | | 1,000 | 1,090 | +9 |
| 16 January 1990 | 18 January 1990 | 50 | 51.7 | +3 |
| | | 100 | 103 | +3 |
| | | 150 | 154 | +3 |
| | | 300 | 303 | +1 |
| | | 500 | 505 | +1 |
| | | 1,000 | 1,030 | +3 |
| 13 March 1990 | 16 March 1990 | 50 | 49.4 | −1 |
| | | 100 | 98.5 | −1 |
| | | 150 | 150 | 0 |
| | | 300 | 302 | +1 |
| | | 500 | 505 | +1 |
| | | 1,000 | 945 | −5 |
| 23 April 1990 | 26 April 1990 | 50 | 45.8 | −8 |
| | | 100 | 103 | +3 |
| | | 150 | 139 | −7 |
| | | 300 | 275 | −8 |
| | | 500 | 466 | −7 |
| | | 1,000 | 939 | −6 |
| | 9 May 1990[d] | 50 | 52.0 | +4 |
| | | 100 | 100 | 0 |
| | | 150 | 151 | +1 |
| | | 300 | 291 | −3 |
| | | 500 | 498 | 0 |
| | | 1,000 | 975 | −2 |
| 18 June 1990 | 19 June 1990 | 50 | 49.9 | 0 |
| | | 100 | 99.1 | −1 |
| | | 150 | 149 | −1 |
| | | 300 | 299 | 0 |
| | | 500 | 499 | 0 |
| | | 1,000 | 1,030 | +3 |
| 13 August 1990 | 15 August 1990 | 50 | 50.3 | +1 |
| | | 100 | 107 | +7 |
| | | 150 | 162 | +8 |
| | | 300 | 324 | +8 |
| | | 500 | 530 | +6 |
| | | 1,000 | 1,050 | +5 |

**TABLE I3**
**Results of Analysis of Dose Formulations Administered to Rats and Mice in the 2-Year Dermal Studies of Triethanolamine** (continued)

| Date Prepared | Date Analyzed | Target Concentration (mg/mL) | Determined Concentration (mg/mL) | Difference from Target (%) |
|---|---|---|---|---|
| **Mice** (continued) | | | | |
| 8 October 1990 | 11 October 1990 | 50 | 52.6 | +5 |
| | | 100 | 107 | +7 |
| | | 150 | 156 | +4 |
| | | 300 | 311 | +4 |
| | | 500 | 514 | +3 |
| | | 1,000 | 1,100 | +10 |
| | 31 October 1990[d] | 50 | 51.5 | +3 |
| | | 100 | 111 | +11 |
| | | 150 | 160 | +7 |
| | | 300 | 324 | +8 |
| | | 500 | 519 | +4 |
| | | 1,000 | 1,030 | +3 |

[a] Results of duplicate analyses. For rats, 50 mg/mL=32 mg/kg; 100 mg/mL=63 mg/kg; 200 mg/mL=125 mg/kg; 400 mg/mL=250 mg/kg. For mice, 50 mg/mL=100 mg/kg; 100 mg/mL=200 mg/kg; 150 mg/mL=300 mg/kg; 300 mg/mL=630 mg/kg; 500 mg/mL=1,000 mg/kg; 1,000 mg/mL=2,000 mg/kg.
[b] Dose formulations for males
[c] Dose formulations for females
[d] Animal-room samples
[e] Dose formulations were reanalyzed due to problems associated with a changing baseline (3 August 1989 formulations) or integration problems resulting from solvent peak tailing.
[f] Results of remix of dosing solutions prepared on 8 October 1990 (rats) and 11 April 1989 (mice)
[g] Duplicate and triplicate analyses indicated E/O (expected/observed) was less than 0.90; dose formulation was remixed.

**TABLE I4**
**Results of Referee Analysis of Dose Formulations Administered to Rats and Mice in the 13-Week and 2-Year Dermal Studies of Triethanolamine**

| Date Prepared | Target Concentration (mg/mL)[a] | Determined Concentration (mg/mL) Study Laboratory[b] | Referee Laboratory[c] |
|---|---|---|---|
| **13-Week Study** | | | |
| Rats | | | |
| 23 June 1986 | 280 | 279 | 288 ± 2 |
| 15 September 1986 | 70 | 71.1 | 69.8 ± 0.3 |
| **2-Year Studies** | | | |
| Rats | | | |
| 7 November 1988 | 400 | 393 | 401 ± 3 |
| 11 April 1989 | 50 | 48.8 | 52.6 ± 2.0 |
| 26 September 1989 | 200 | 210 | 207 ± 1 |
| Mice | | | |
| 25 October 1988 | 150 | 147 | 154 ± 1 |

[a] For 13-week study rats, 70 mg/mL=125 mg/kg; 280 mg/mL=500 mg/kg. For 2-year study rats, 50 mg/mL=32 mg/kg; 200 mg/mL=125 mg/kg; 400 mg/mL=250 mg/kg. For mice, 150 mg/mL=300 mg/kg.
[b] Results of duplicate analyses
[c] Results of triplicate analyses (mean ± standard error)

# APPENDIX J
# INGREDIENTS, NUTRIENT COMPOSITION, AND CONTAMINANT LEVELS IN NIH-07 RAT AND MOUSE RATION


| | | |
|---|---|---|
| TABLE J1 | Ingredients of NIH-07 Rat and Mouse Ration . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . | 268 |
| TABLE J2 | Vitamins and Minerals in NIH-07 Rat and Mouse Ration . . . . . . . . . . . . . . . . . . . . . . . . | 268 |
| TABLE J3 | Nutrient Composition of NIH-07 Rat and Mouse Ration . . . . . . . . . . . . . . . . . . . . . . . | 269 |
| TABLE J4 | Contaminant Levels in NIH-07 Rat and Mouse Ration . . . . . . . . . . . . . . . . . . . . . . . . . | 270 |

**TABLE J1**
**Ingredients of NIH-07 Rat and Mouse Ration[a]**

| Ingredients[b] | Percent by Weight |
|---|---|
| Ground #2 yellow shelled corn | 24.50 |
| Ground hard winter wheat | 23.00 |
| Soybean meal (49% protein) | 12.00 |
| Fish meal (60% protein) | 10.00 |
| Wheat middlings | 10.00 |
| Dried skim milk | 5.00 |
| Alfalfa meal (dehydrated, 17% protein) | 4.00 |
| Corn gluten meal (60% protein) | 3.00 |
| Soy oil | 2.50 |
| Dried brewer's yeast | 2.00 |
| Dry molasses | 1.50 |
| Dicalcium phosphate | 1.25 |
| Ground limestone | 0.50 |
| Salt | 0.50 |
| Premixes (vitamin and mineral) | 0.25 |

[a] NCI, 1976; NIH, 1978
[b] Ingredients were ground to pass through a U.S. Standard Screen No. 16 before being mixed.

**TABLE J2**
**Vitamins and Minerals in NIH-07 Rat and Mouse Ration[a]**

| | Amount | Source |
|---|---|---|
| **Vitamins** | | |
| A | 5,500,000 IU | Stabilized vitamin A palmitate or acetate |
| $D_3$ | 4,600,000 IU | D-activated animal sterol |
| $K_3$ | 2.8 g | Menadione |
| *d*-α-Tocopheryl acetate | 20,000 IU | |
| Choline | 560.0 g | Choline chloride |
| Folic acid | 2.2 g | |
| Niacin | 30.0 g | |
| *d*-Pantothenic acid | 18.0 g | *d*-Calcium pantothenate |
| Riboflavin | 3.4 g | |
| Thiamine | 10.0 g | Thiamine mononitrate |
| $B_{12}$ | 4,000 μg | |
| Pyridoxine | 1.7 g | Pyridoxine hydrochloride |
| Biotin | 140.0 mg | *d*-Biotin |
| **Minerals** | | |
| Iron | 120.0 g | Iron sulfate |
| Manganese | 60.0 g | Manganous oxide |
| Zinc | 16.0 g | Zinc oxide |
| Copper | 4.0 g | Copper sulfate |
| Iodine | 1.4 g | Calcium iodate |
| Cobalt | 0.4 g | Cobalt carbonate |

[a] Per ton (2,000 lb) of finished product

**Table J3**
**Nutrient Composition of NIH-07 Rat and Mouse Ration**

| Nutrient | Mean ± Standard Deviation | Range | Number of Samples |
|---|---|---|---|
| Protein (% by weight) | 23.16 ± 0.68 | 21.80 - 24.20 | 24 |
| Crude fat (% by weight) | 5.30 ± 0.22 | 4.60 - 5.60 | 24 |
| Crude fiber (% by weight) | 3.63 ± 0.41 | 2.80 - 4.30 | 24 |
| Ash (% by weight) | 6.50 ± 0.21 | 6.11 - 7.00 | 24 |
| **Amino Acids (% of total diet)** | | | |
| Arginine | 1.287 ± 0.084 | 1.100 - 1.390 | 10 |
| Cystine | 0.306 ± 0.075 | 0.181 - 0.400 | 10 |
| Glycine | 1.160 ± 0.050 | 1.060 - 1.220 | 10 |
| Histidine | 0.580 ± 0.024 | 0.531 - 0.608 | 10 |
| Isoleucine | 0.917 ± 0.034 | 0.867 - 0.965 | 10 |
| Leucine | 1.972 ± 0.052 | 1.850 - 2.040 | 10 |
| Lysine | 1.273 ± 0.051 | 1.200 - 1.370 | 10 |
| Methionine | 0.437 ± 0.115 | 0.306 - 0.699 | 10 |
| Phenylalanine | 0.994 ± 0.125 | 0.665 - 1.110 | 10 |
| Threonine | 0.896 ± 0.055 | 0.824 - 0.985 | 10 |
| Tryptophan | 0.223 ± 0.160 | 0.107 - 0.671 | 10 |
| Tyrosine | 0.677 ± 0.105 | 0.564 - 0.794 | 10 |
| Valine | 1.089 ± 0.057 | 0.962 - 1.170 | 10 |
| **Essential Fatty Acids (% of total diet)** | | | |
| Linoleic | 2.389 ± 0.233 | 1.830 - 2.570 | 9 |
| Linolenic | 0.277 ± 0.036 | 0.210 - 0.320 | 9 |
| **Vitamins** | | | |
| Vitamin A (IU/kg) | 6,690 ± 2,011 | 4,180 - 12,140 | 24 |
| Vitamin D (IU/kg) | 4,450 ± 1,382 | 3,000 - 6,300 | 4 |
| α-Tocopherol (ppm) | 36.92 ± 9.32 | 22.5 - 48.9 | 9 |
| Thiamine (ppm) | 19.20 ± 2.30 | 16.0 - 28.0 | 24 |
| Riboflavin (ppm) | 7.92 ± 0.93 | 6.10 - 9.00 | 10 |
| Niacin (ppm) | 100.95 ± 25.92 | 65.0 - 150.0 | 9 |
| Pantothenic acid (ppm) | 30.30 ± 3.60 | 23.0 - 34.6 | 10 |
| Pyridoxine (ppm) | 9.25 ± 2.62 | 5.60 - 14.0 | 10 |
| Folic acid (ppm) | 2.51 ± 0.64 | 1.80 - 3.70 | 10 |
| Biotin (ppm) | 0.267 ± 0.049 | 0.19 - 0.35 | 10 |
| Vitamin $B_{12}$ (ppb) | 40.14 ± 20.04 | 10.6 - 65.0 | 10 |
| Choline (ppm) | 3,068 ± 314 | 2,400 - 3,430 | 9 |
| **Minerals** | | | |
| Calcium (%) | 1.22 ± 0.11 | 1.00 - 1.54 | 24 |
| Phosphorus (%) | 0.95 ± 0.03 | 0.90 - 1.00 | 24 |
| Potassium (%) | 0.887 ± 0.067 | 0.772 - 0.971 | 8 |
| Chloride (%) | 0.526 ± 0.092 | 0.380 - 0.635 | 8 |
| Sodium (%) | 0.315 ± 0.344 | 0.258 - 0.370 | 10 |
| Magnesium (%) | 0.168 ± 0.008 | 0.151 - 0.180 | 10 |
| Sulfur (%) | 0.274 ± 0.063 | 0.208 - 0.420 | 10 |
| Iron (ppm) | 356.2 ± 90.0 | 255.0 - 523.0 | 10 |
| Manganese (ppm) | 92.24 ± 5.35 | 81.70 - 99.40 | 10 |
| Zinc (ppm) | 58.14 ± 9.91 | 46.10 - 81.60 | 10 |
| Copper (ppm) | 11.50 ± 2.40 | 8.090 - 15.39 | 10 |
| Iodine (ppm) | 3.70 ± 1.14 | 1.52 - 5.83 | 10 |
| Chromium (ppm) | 1.71 ± 0.45 | 0.85 - 2.09 | 9 |
| Cobalt (ppm) | 0.80 ± 0.23 | 0.490 - 1.150 | 6 |

**TABLE J4**
**Contaminant Levels in NIH-07 Rat and Mouse Ration[a]**

| | Mean ± Standard Deviation[b] | Range | Number of Samples |
|---|---|---|---|
| **Contaminants** | | | |
| Arsenic (ppm) | 0.27 ± 0.18 | 0.06 - 0.06 | 24 |
| Cadmium (ppm) | 0.08 ± 0.02 | 0.05 - 0.10 | 24 |
| Lead (ppm) | 0.23 ± 0.09 | 0.10 - 0.40 | 24 |
| Mercury (ppm) | 0.04 ± 0.02 | 0.02 - 0.11 | 24 |
| Selenium (ppm)[c] | 0.42 ± 0.25 | 0.20 - 1.21 | 24 |
| Aflatoxins (ppb)[d] | <5.0 | | 24 |
| Nitrate nitrogen (ppm)[e] | 16.70 ± 4.10 | 8.60 - 24.0 | 24 |
| Nitrite nitrogen (ppm)[e] | 0.25 ± 0.20 | <0.10 - 0.70 | 24 |
| BHA (ppm)[f] | 1.42 ± 0.58 | <1.00 - 3.00 | 24 |
| BHT (ppm)[f] | 1.38 ± 0.58 | <1.00 - 3.00 | 24 |
| Aerobic plate count (CFU/g) | 41,892 ± 25,056 | 6,700 - 120,000 | 24 |
| Coliform (MPN/g) | 4.60 ± 5.40 | 3.00 - 23.00 | 24 |
| *Escherichia coli* (MPN/g) | <3.00 | | 24 |
| *Salmonella* (MPN/g) | Negative | | 13 |
| Total nitrosoamines (ppb)[g] | 7.70 ± 2.90 | 3.60 - 16.5 | 24 |
| *N*-Nitrosodimethylamine (ppb)[g] | 5.90 ± 2.60 | 2.60 - 13.0 | 24 |
| *N*-Nitrosopyrrolidine (ppb)[g] | 1.81 ± 0.90 | 1.00 - 3.9 | 24 |
| **Pesticides (ppm)** | | | |
| α-BHC | <0.01 | | 25 |
| β-BHC | <0.02 | | 25 |
| γ-BHC | <0.01 | | 25 |
| δ-BHC | <0.01 | | 25 |
| Heptachlor | <0.01 | | 25 |
| Aldrin | <0.01 | | 25 |
| Heptachlor epoxide | <0.01 | | 25 |
| DDE | <0.01 | | 25 |
| DDD | <0.01 | | 25 |
| DDT | <0.01 | | 25 |
| HCB | <0.01 | | 25 |
| Mirex | <0.01 | | 25 |
| Methoxychlor | <0.05 | | 25 |
| Dieldrin | <0.01 | | 25 |
| Endrin | <0.01 | | 25 |
| Telodrin | <0.01 | | 25 |
| Chlordane | <0.05 | | 25 |
| Toxaphene | <0.1 | | 25 |
| Estimated PCBs | <0.2 | | 25 |
| Ronnel | <0.01 | | 25 |
| Ethion | <0.02 | | 25 |
| Trithion | <0.05 | | 25 |
| Diazinon | <0.1 | | 25 |
| Methyl parathion | <0.02 | | 25 |
| Ethyl parathion | <0.02 | | 25 |
| Malathion[h] | 0.23 ± 0.20 | <0.05 - 1.00 | 24 |
| Endosulfan I | <0.01 | | 25 |
| Endosulfan II | <0.01 | | 25 |
| Endosulfan sulfate | <0.03 | | 25 |

[a] CFU=colony-forming units; MPN=most probable number; BHC=hexachlorocyclohexane or benzene hexachloride
[b] For values less than the limit of detection, the detection limit is given as the mean.
[c] One lot milled 2 March 1989 and one lot milled 2 June 1989 contained more than 0.6 ppm.
[d] No aflatoxin measurement was recorded for the lot milled 2 October 1989.
[e] Sources of contamination: alfalfa, grains, and fish meal
[f] Sources of contamination: soy oil and fish meal
[g] All values were corrected for percent recovery.
[h] One lot milled 1 September 1989 contained more than 0.51 ppm.

# APPENDIX K
# SENTINEL ANIMAL PROGRAM

METHODS . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . 272
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# SENTINEL ANIMAL PROGRAM

## METHODS

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

Serum samples were collected from randomly selected rats and mice during the 13-week and 2-year studies. During the 2-year mouse study, the evaluations usually performed at 6 months were performed at 5½ months, and an extra mouse hepatitis virus screening was performed at 6 months. Blood from each animal was collected, allowed to clot, and the serum separated. The samples were processed appropriately and sent to Microbiological Associates, Inc. (Bethesda, MD), for determination of antibody titers. The laboratory serology methods and viral agents for which testing was performed are tabulated below; the times at which blood was collected during the studies are also listed.

| Method and Test | Time of Analysis |
|---|---|
| **RATS** | |
| **13-Week Study** | |
| ELISA | |
| *Mycoplasma arthritidis* | Quarantine and study initiation |
| *Mycoplasma pulmonis* | Quarantine and study initiation |
| PVM (pneumonia virus of mice) | Quarantine, study initiation, and study termination |
| RCV (rat coronavirus) | Study initiation and study termination |
| RCV/SDA (rat coronavirus/sialodacryoadenitis virus) | Quarantine |
| Sendai | Quarantine, study initiation, and study termination |
| Hemagglutination Inhibition | |
| H-1 (Toolan's H-1 virus) | Quarantine, study initiation, and study termination |
| KRV (Kilham rat virus) | Quarantine, study initiation, and study termination |
| **2-Year Study** | |
| ELISA | |
| *M. arthritidis* | 24 months |
| *M. pulmonis* | 24 months |
| PVM | Quarantine, 6, 12, 18, and 24 months |
| RCV/SDA | Quarantine, 6, 12, 18, and 24 months |
| Sendai | Quarantine, 6, 12, 18, and 24 months |
| Immunofluorescence Assay | |
| RCV/SDA | 12, 18, and 24 months |
| Hemagglutination Inhibition | |
| H-1 | Quarantine, 6, 12, 18, and 24 months |
| KRV | Quarantine, 6, 12, 18, and 24 months |

## MICE

**13-Week Study**

Complement Fixation

| | |
|---|---|
| LCM (lymphocytic choriomeningitis virus) | Quarantine and study initiation |

ELISA

| | |
|---|---|
| CARB (cilia-associated respiratory bacillus) | Quarantine and study initiation |
| Ectromelia virus | Quarantine, study initiation, and study termination |
| GDVII (mouse encephalomyelitis virus) | Quarantine, study initiation, and study termination |
| *M. arthritidis* | Quarantine and study initiation |
| *M. pulmonis* | Quarantine and study initiation |
| Mouse adenoma virus | Quarantine, study initiation, and study termination |
| MHV (mouse hepatitis virus) | Quarantine, study initiation, and study termination |
| PVM | Quarantine, study initiation, and study termination |
| Reovirus 3 | Quarantine, study initiation, and study termination |
| Sendai | Quarantine, study initiation, and study termination |

Immunofluorescence Assay

| | |
|---|---|
| EDIM (epizootic diarrhea of infant mice) | Quarantine, study initiation, and study termination |
| LCM | Study termination |

Hemagglutination Inhibition

| | |
|---|---|
| K (papovavirus) | Quarantine, study initiation, and study termination |
| MVM (minute virus of mice) | Quarantine, study initiation, and study termination |
| Polyoma virus | Quarantine, study initiation, and study termination |

**2-Year Study**

ELISA

| | |
|---|---|
| Ectromelia virus | Quarantine, 5½, 12, 18, and 24 months |
| EDIM | 18 and 24 months |
| GDVII | Quarantine, 5½, 12, 18, and 24 months |
| LCM | 12, 18, and 24 months |
| *M. arthritidis* | 24 months |
| *M. pulmonis* | 24 months |
| MVM | Quarantine and 5½ months |
| Mouse adenoma virus | Quarantine, 5½, 12, and 18 months |
| Mouse adenoma virus-FL | 24 months |
| MHV | Quarantine, 5½, 6, 12, 18, and 24 months |
| PVM | Quarantine, 5½, 12, 18, and 24 months |
| Reovirus 3 | Quarantine, 5½, 12, 18, and 24 months |
| Sendai | Quarantine, 5½, 12, 18, and 24 months |

Immunofluorescence Assay

| | |
|---|---|
| EDIM | Quarantine, 5½, 12, and 18 months |
| GDVII | 24 months |
| LCM | Quarantine and 5½ months |
| Mouse adenoma virus-FL | 12 and 24 months |
| MVM | 12 and 18 months |
| MHV | 5½ months |
| Reovirus 3 | 24 months |

## MICE (continued)

**2-Year Study** (continued)

Hemagglutination Inhibition

| | |
|---|---|
| K | Quarantine, 5½, 12, 18, and 24 months |
| MVM | 24 months |
| Polyoma virus | Quarantine, 5½, 12, 18, and 24 months |

## RESULTS

One rat had positive titers to *M. arthritidis* at the beginning of the 13-week study; one rat and one mouse also had positive titers to *M. arthritidis* at the end of the 2-year studies. Further evaluation of serum positive for *M. arthritidis* by immunoblot and Western blot procedures indicated that the positive titers may have been due to cross reaction with antibodies of nonpathogenic *Mycoplasma* or other agents. Only sporadic samples were positive, and there were no clinical findings or histopathologic changes of *M. arthritidis* infection in animals with positive titers. Accordingly, *M. arthritidis*-positive titers were considered to be false positives.

# APPENDIX L
# IMPACT OF *HELICOBACTER HEPATICUS* INFECTION IN B6C3F$_1$ MICE FROM 12 NTP 2-YEAR CARCINOGENESIS STUDIES

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# IMPACT OF *HELICOBACTER HEPATICUS* INFECTION IN B6C3F$_1$ MICE FROM 12 NTP 2-YEAR CARCINOGENESIS STUDIES

## ABSTRACT

Male and female B6C3F$_1$ mice from 12 NTP 2-year carcinogenesis studies were found to be infected with *Helicobacter hepaticus*. Many of the male mice from nine of these studies ("affected" studies) had an associated hepatitis. The current evaluations were performed in an attempt to determine if the data from the *H. hepaticus*-affected NTP B6C3F$_1$ mouse studies were compromised and unsuitable for cancer hazard identification. The incidences of neoplasms of the liver (both hepatocellular neoplasms and hemangiosarcoma), but not of other organs in control male B6C3F$_1$ mice, were found to be increased in affected studies compared to control males from unaffected studies. The increased incidence of hepatocellular neoplasms was observed in those males exhibiting *H. hepaticus*-associated hepatitis. Other observations further differentiated control male mice from affected and unaffected studies. H-*ras* codon 61 CAA-to-AAA mutations were less common in liver neoplasms in males from affected studies compared to historical and unaffected study controls. In addition, increases in cell proliferation rates and apoptosis were observed in the livers of male mice with *H. hepaticus*-associated hepatitis. These data support the hypothesis that the increased incidence of liver neoplasms is associated with *H. hepaticus* and that hepatitis may be important in the pathogenesis. Therefore, interpretation of carcinogenic effects in the liver of B6C3F$_1$ mice may be confounded if there is *H. hepaticus*-associated hepatitis.

## INTRODUCTION

### *Helicobacter*-Induced Diseases

Since the bacterium *H. pylori* was isolated from humans in 1983, numerous *Helicobacter* species have been identified in several laboratory and domestic animal species. Their pathogenicity varies, with some species inducing significant disease while others appear merely to colonize the gastrointestinal tract. *H. pylori* is known to cause chronic gastritis and peptic ulcers in humans (Marshall and Warren, 1984; Graham, 1989; Lee *et al.*, 1993) and, more recently, has been linked to adenocarcinoma and mucosa-associated lymphoma of the stomach (Fox *et al.*, 1989; Nomura *et al.*, 1991; Parsonnet *et al.*, 1991; Wotherspoon *et al.*, 1993). Based on epidemiological and pathology findings, the International Agency for Research on Cancer (1994) has classified *H. pylori* as a group 1 carcinogen in humans. *H. hepaticus* is associated with an increase in liver neoplasm incidences in A/JCr mice (Ward *et al.*, 1994a; Fox *et al.*, 1996).

*H. hepaticus* commonly colonizes the gastrointestinal tract of many strains of mice from many sources (Fox *et al.*, 1994; Ward *et al.*, 1994b; Shames *et al.*, 1995). It has been shown to be pathogenic, with hepatitis highly prevalent in some strains of mice (A/JCr, BALB/cAnNCr, C3H/HeNCr, SJL/NCr, and SCID/NCr) (Ward *et al.*, 1994b). Intestinal colonization does not necessarily result in subsequent hepatitis, and the conditions that lead to migration of the organism from the intestine to the liver have not been determined. *H. hepaticus* appears to reside primarily within the bile canaliculi. Male mice were reported to have a greater incidence and severity of hepatitis than female mice, and this finding occurred in NTP studies as well. The recently identified *H. bilis*, like *H. hepaticus*, colonizes the biliary tract, liver, and intestine of mice. While *H. bilis* has been identified in animals with chronic hepatitis, whether it caused the hepatitis is not known (Fox *et al.*, 1995).

The pathogenesis of *H. hepaticus*-induced disease has not been fully characterized. In susceptible strains of mice, *H. hepaticus* can cause acute, focal, nonsuppurative, necrotizing hepatitis, which progresses to chronic, active hepatitis characterized by minimal necrosis, hepatocytomegaly, oval cell hyperplasia, and

cholangitis. *H. hepaticus* has been found to possess high levels of urease (Fox *et al.*, 1994). *H. hepaticus* is often isolated from the cecum and colon but is not necessarily isolated from the liver of A/JCr mice, even though these animals develop severe hepatitis. Culture supernatants from several strains of *H. hepaticus* and several other *Helicobacter* species were shown to cause cytopathic effects in a rodent hepatocyte cell line (Taylor *et al.*, 1995). Ward *et al.* (1996) suggested that autoimmunity may play a role in the progressive hepatitis and carcinogenesis in livers infected with *H. hepaticus*.

## NTP Infectious Disease Surveillance

In 1993, during the histological evaluation of an NTP 2-year study, pathologists identified a constellation of liver lesions (hepatitis) in control and treated male mice that was consistent with what would later be described in mice infected with *H. hepaticus* (Ward *et al.*, 1993, 1994a; Fox *et al.*, 1994). Subsequently, pathology results from all mouse studies begun since 1984 (67 two-year studies) were reviewed for diagnoses of the characteristic hepatitis; the lesions were identified in nine studies (NTP, 1998a,b,c,d, 1999a,b). Silver stains revealed helical bacteria consistent with *Helicobacter* present in the liver of male mice in the nine studies.

Every reasonable measure is taken to prevent the occurrence of infectious diseases during NTP 2-year carcinogenicity studies. When infections occasionally occur, care is taken to identify the causal agent and its source, measures are taken to ensure that animals in later studies will not be infected, and the potential impact on biological parameters (primarily neoplastic endpoints) important in interpretation of the study is determined. To date, animals (control and treated) from a few studies have had a mild pulmonary inflammatory response presumed to be caused by an infectious agent. In other studies, there have been utero-ovarian infections with *Klebsiella* sp. (Rao *et al.*, 1987) and fungal infections of the nasal cavity. For scientifically valid reasons, interpretation of chemical-related effects was not considered significantly compromised in any of these studies. Unlike the previous infections, *H. hepaticus* involves the liver, the major metabolic organ, and has been associated with an increase in incidences of liver neoplasms in the A/JCr mouse (Ward *et al.*, 1994a). Therefore, when the contemporary epizootic of *H. hepaticus* infection in the United States affected several NTP studies, use of the data for hazard identification was questioned. The first step was to determine the extent of the infection within NTP studies and then evaluate the impact the infection had on biological parameters important in interpretation of the carcinogenic potential of test chemicals.

# MATERIALS AND METHODS

## Histologic Examination

Studies in which mice were potentially infected with *H. hepaticus* were identified by reviewing the summary pathology tables for characteristic diagnoses: oval and/or biliary epithelial hyperplasia, hepatocyte enlargement (often diagnosed as karyomegaly), chronic inflammation, and regenerative hyperplasia. All 13-week and 2-year studies begun by the NTP since 1984 and for which complete pathology data were available (67 two-year studies) were examined. Eight contemporary studies in which the characteristic lesions were not identified from pathology tables were randomly selected for histologic reevaluation. Slides containing sections of hematoxylin- and eosin-stained livers from 20 to 25 control and 20 to 25 high-dose male mice from each of seven 2-year studies and one 13-week study (10 animals from each group) were reexamined microscopically for the presence of hepatitis potentially related to *H. hepaticus* infection. Hepatitis consistent with that observed with *H. hepaticus* infection was not observed in any of these studies.

Liver sections from five or more animals from each of nine 2-year studies in which hepatitis was observed were prepared using the Warthin-Starry silver stain or Steiner's modification to identify silver-positive helical bacteria.

## PCR-RFLP Detection of *Helicobacter* DNA

Assays based on polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) were conducted at the NIEHS (Malarkey *et al.*, 1997) and the University of Missouri Research Animal Diagnostic and Investigative Laboratory (MU-RADIL) (Riley *et al.*, 1996) on liver tissue from approximately 20 animals from each of 32 NTP 2-year studies (including the nine affected studies) and three NTP 13-week studies. The majority of these studies were selected because they were begun at approximately the same time (1988-1990) as the nine affected studies. Also, two earlier studies (1984-1985; mouse life-span and *p*-nitroaniline studies) and one later study (1993; methyleugenol) were selected. The mouse life-span study was designed to evaluate the incidences of spontaneous changes associated with age; therefore, there is no NTP Technical Report. Frozen tissue was available from 22 of these studies, while only formalin-fixed tissue was available for the remaining ten 2-year studies and the three 13-week studies. Most of the assays were conducted by MU-RADIL, which used *Helicobacter* genus-specific primers; MU-RADIL used restriction endonucleases on a subset of positives to determine if the species was *H. hepaticus*. DNA was isolated from frozen liver samples with a QIAamp Tissue Kit (Qiagen Inc., Chatsworth, CA) according to the manufacturer's recommendations or routine phenol/chloroform extraction (Malarkey *et al.*, 1997). DNA content and purity were determined spectrophotometrically by measuring the $A_{260}/A_{280}$ optical density ratio. To isolate DNA from paraffin-embedded samples, five 10-µm sections were washed twice with 1 mL xylene and twice with 500 µL ethanol. Tissues were then dried within a vacuum centrifuge prior to DNA isolation as described above. Routine measures were taken to avoid contamination at every step from tissue collection to PCR amplification, and concurrently run controls without DNA were consistently negative.

## Statistical Analyses

Multiple regression procedures were used to compare control neoplasm rates in the nine affected studies with the 26 unaffected contemporary studies which had no histologic evidence of *H. hepaticus*-associated liver disease. While frozen liver tissue was unavailable from 13 of these 26 studies, none showed the hepatitis indicative of *H. hepaticus* and thus were assumed to be unaffected. Potential confounding factors such as body weight, date study was begun, route of administration, and animal supplier were included as covariables in the statistical analysis.

## Analysis for H-*ras* Codon 61 CAA-to-AAA Mutations

For analyses of formalin-fixed tissue, three to five unstained serial sections (10 µm thick) were cut from paraffin blocks containing hepatocellular adenomas or carcinomas. Paraffin-embedded tissues were deparaffinized and rehydrated prior to being digested with proteinase k overnight at 55° C to isolate DNA. Frozen tissues were digested with 10 mg/mL pronase in 1% sodium dodecyl sulfate in TNE buffer (10 mM TRIS, 150 mM NaCl, and 2 mM EDTA; pH 7.5) overnight at 37° C; DNA was isolated by phenol chloroform extraction and precipitated with ethanol (Marmur, 1961; Sills *et al.*, 1995).

Nested primers were used for amplification of exon 2 of H-*ras* by PCR. The outer primers were 5'-CCA CTA AGC CTG TTG TGT TTT GCA G-3' (forward primer) and 5'-CTG TAC TGA TGG ATG TCC TCG AAG GA-3' (reverse primer). The inner primers (second round of amplification) were 5'-GAC ATC TTA GAC ACA GCA GTT-3' (forward primer) and 5'-GGT GTT GTT GAT GGC AAA TAC-3' (reverse primer). Although the normal sequence of codon 60 is GCT, the forward PCR primer is made with a T at the penultimate 3' base to create the restriction site for Mse1.

A nonradioactive RFLP method was employed to identify CAA-to-AAA mutations in the H-*ras* gene at codon 61 in liver neoplasms (Lee and Drinkwater, 1995). This was based on Mse1 enzyme restriction cutting only the sequence 5'-TTAA-3'. Thus, Mse1 will detect C→A conversion mutation at the first position of codon 61.

## Analysis of PCNA and Apoptosis

Detailed methods are included in a report by Nyska *et al.* (1997). Cell proliferation was assessed in nonneoplastic areas of the liver, kidney, and lung by determining a PCNA S-phase labeling index (the percentage of cells in S phase). The identification of apoptotic cells was based on morphologic criteria (Garewal *et al.*, 1996; Goldsworthy *et al.*, 1996) and confirmed immunohistochemically by the terminal deoxynucleotidyl transferase-mediated dUTP-biotin nick end labeling (TUNEL) procedure (Gavrieli *et al.*, 1992).

# RESULTS AND DISCUSSION

## Identification of *H. hepaticus* Infection in NTP Studies

Determining the extent of *H. hepaticus* infection involved a three-pronged approach of histologic evaluation, silver stains, and PCR-RFLP based assays; all were necessary because of the limitations identified for each. In NTP studies, and as reported in other studies (Ward *et al.*, 1994b), there were no obvious clinical signs of infection, and the only significant histologic lesion (hepatitis) was observed in the liver, primarily in males. Therefore, summary pathology tables were reviewed to identify studies that may have been affected by *H. hepaticus*-associated hepatitis. Male mice from nine studies were identified (Table L1) as having the hepatitis. Eight of the nine studies were begun during a time span of about 6 months (July 1990 to January 1991), while the other study was begun much earlier (October 1988). The hepatitis was not observed in any 13-week studies. Use of histologic evaluation for identification of infected animals has limitations, however. It is somewhat insensitive, as *H. hepaticus* has been cultured and identified by PCR-RFLP methods within livers of animals with no histological evidence of infection (Fox *et al.*, 1999). This may be explained in part by the limited sampling (two liver sections) and the sometimes focal nature of *H. hepaticus*-associated hepatitis. Also, while in the more severely affected animals the hepatitis appears somewhat characteristic, component lesions of the hepatitis are not pathognomonic, and, when the hepatitis is subtle in 2-year old animals, it is more difficult to recognize or attribute to *H. hepaticus*.

Within affected studies, the incidences of the hepatitis in male mice varied from 16% to 78% (Table L1). While generally mild to moderate, the hepatitis varied in severity from barely detectable in some animals to extensive liver involvement and regeneration in others. Only a few females were identified as having the characteristic hepatitis (Table L1). In general, the incidences and severities of *H. hepaticus*-associated hepatitis were similar between control and treated groups. This constellation of nonneoplastic liver lesions, while not pathognomonic, was certainly suggestive of an *H. hepaticus* infection, particularly when observed in control animals. Characteristic lesions included proliferation of oval and/or biliary epithelial cells, hepatocyte enlargement (diagnosed as karyomegaly), and chronic inflammation. In many instances, areas of regenerative hyperplasia were identified within diseased liver.

*Helicobacter* spp. are not usually observed on routine histologic examination of hematoxylin and eosin-stained sections of liver. The methods for confirmation of infection with *Helicobacter* include Warthin-Starry silver stain or Steiner's modification (Garvey *et al.*, 1985) of this stain for direct microscopic observation of the organisms in tissue; however, this can be a relatively insensitive technique when few organisms are present. In most instances, histologic differentiation between *Helicobacter* species is not possible. Speciation can usually be accomplished with electron microscopy, but this technique is both time consuming and labor intensive. Microbiologic culture of feces, cecal smears, and fresh or frozen liver is also possible. Currently, assays involving amplification of the DNA of the organism using PCR are the most rapid and perhaps the most sensitive methods of detection, and the use of restriction endonucleases has allowed a determination of the species present. PCR-based methods also can be used on feces, cecal contents, or liver homogenates and are most sensitive when using fresh or frozen tissue (Riley *et al.*, 1996; Malarkey *et al.*, 1997).

Using Warthin-Starry silver stains or Steiner's modification on the livers of five or more animals per study, helical bacteria (*Helicobacter*) were identified in animals from the nine affected studies. In some animals, helical bacteria were numerous, suggesting a heavy bacterial burden in these infected animals. However, even in these animals with abundant organisms, few to none were observed in proliferative hepatic lesions such as foci and neoplasms. Helical bacteria were not identified in approximately 25% of males with moderate hepatitis and were rarely identified in males without hepatitis or in females. The absence of identification of helical organisms by silver stains does not preclude infection, nor does the presence of organisms confirm *H. hepaticus*. Based upon current knowledge, however, the characteristic liver lesions in B6C3F$_1$ mice, coupled with the presence of silver-positive helical organisms, are highly suggestive of *H. hepaticus* infection.

As the NTP evaluation evolved, PCR-based assays were developed that appeared more sensitive than histologic evaluation and silver stains for identification and speciation of *Helicobacter*. Therefore, PCR-RFLP-based assays were used to confirm the presence of pathogenic *Helicobacter* (primarily *H. hepaticus*) within the nine affected studies and to determine whether there was *H. hepaticus* infection in other NTP studies. Unfortunately, none of the PCR-based assays had been specifically developed for, or proven reliable for use with, formalin-fixed tissue. Frozen tissue was available from a limited number of animals from a limited number of NTP studies, including only three of the nine affected studies. Furthermore, available frozen liver was almost always limited to tissue from a neoplasm, and, based upon results obtained with silver stains, organisms are generally not readily observed within proliferative hepatic lesions, even when organisms are abundant in adjacent liver tissue. Because the availability of frozen tissue was limited, a PCR-RFLP-based assay was developed and evaluated (Malarkey *et al.*, 1997) for use with frozen or formalin-fixed tissue.

The NIEHS and MU-RADIL laboratories conducted PCR-RFLP-based assays on 32 NTP 2-year studies and three NTP 13-week studies (data not shown); frozen tissues from 22 of the 2-year studies were available. All three bioassays in which hepatitis was identified and for which frozen tissue was available were positive for *H. hepaticus* by the PCR-RFLP-based assays (Table L2). At a third laboratory, *H. hepaticus* was also cultured from the liver tissue of animals in one of these studies (Fox *et al.*, 1999). Formalin-fixed tissues from two of the three studies were evaluated and were also positive; these tissues had been fixed in formalin for less than 48 hours. In the other six affected studies, for which only formalin-fixed tissue was available, *H. hepaticus* was identified in only 1 of 120 animals (Table L2). This decreased sensitivity was considered to be related to the prolonged formalin fixation (Malarkey *et al.*, 1997) rather than proof of an absence of *H. hepaticus*. The presence or absence of *H. hepaticus* apparently cannot be confirmed with current PCR-RFLP-based assays in liver that has been fixed in formalin for long periods (weeks or months). In the three 13-week studies with formalin-fixed tissue, only 1 of 30 animals was positive for *H. hepaticus*.

Within the three affected, PCR-RFLP-positive 2-year studies, *H. hepaticus* was often identified by PCR in frozen livers of mice that had no overt hepatitis. In fact, based upon the combined data from two studies (including PCR results from three laboratories), of 57 animals without characteristic liver lesions, 13 of 24 male mice (54%) and 17 of 33 female mice (52%) were positive for *H. hepaticus*. Furthermore, *H. hepaticus* was identified by PCR in frozen liver of several animals from three "unaffected" studies in which hepatitis typical of that associated with *H. hepaticus* was not observed (Table L2). Apparent variability occurs between various strains of mice and between individual mice from affected studies in developing hepatitis in response to *H. hepaticus* infection. One would assume that, within affected studies, most or all animals have been exposed to the organism, and even animals resistant to developing hepatitis may have organisms within the liver. This assumption is supported by the fact that animals without hepatitis are often positive with PCR-RFLP-based assays. Therefore, although alternative explanations are possible, the three PCR-RFLP-positive studies in which liver lesions are absent are assumed to be true positives. In fact, helical organisms were identified with a silver stain in one animal from one of these studies (Malarkey *et al.*, 1997). Therefore, in addition to assessing the affect of *H. hepaticus* in the nine affected 2-year

studies, the significance of a positive PCR-RFLP assay for *H. hepaticus* in the absence of liver lesions is also an important question.

## Inconsistent Results with PCR-Based Methods

As with any technique, the PCR-RFLP-based assays have limitations even when used to assay fresh and frozen tissue. One assessment of the variability in results of PCR and serologic analyses for *Helicobacter* among three commercial laboratories revealed significant inconsistencies (Dew *et al.*, 1997). Others (J.M. Ward and J. Thigpen, personal communications) have obtained similarly inconsistent results when sending replicate samples to different laboratories. Though the number of samples evaluated by both the NIEHS and MU-RADIL laboratories was limited, there was good, but not complete, correlation of PCR-RFLP results. Also, within the affected studies, the PCR assays were not positive in some animals with liver disease. This result may be explained, in part, by the fact that the only frozen tissues available were neoplasms; as described above, neoplasms are expected to have fewer organisms.

## Analysis of *H. hepaticus*-Affected and Unaffected Studies for Incidence of Common Neoplasms

To determine whether the incidences of various neoplasms were different between control groups from affected and unaffected studies, the nine affected studies were compared to 26 unaffected studies begun at relatively similar times (Table L3). There were no statistically significant differences in body weight or survival among the affected and unaffected studies. The neoplasms evaluated represent those that occurred at high enough incidences in various organs for statistically significant differences to be detected. Using multiple regression procedures, male mice in the nine affected studies were demonstrated to have a significantly ($P<0.05$) increased incidence of only two neoplasm types, both of which were in the liver (hepatocellular neoplasms and hemangiosarcoma), when compared to the unaffected studies. Because of these differences, there was also a corresponding significant difference in the overall incidence of malignant neoplasms (all sites) as well as in the overall proportion of neoplasm-bearing animals. No other tissue site showed a significant difference in the incidence of neoplasms. For female mice, the slightly increased incidence of hepatocellular neoplasms observed in the affected studies was not statistically significant.

This seemingly simple analysis is complicated by several potential confounding variables. There have been coordinate, time-related increases in body weight and in the incidence of liver neoplasms in mice in NTP studies (Haseman, 1992). Table L4 presents the liver neoplasm incidences in relation to the dates the studies began and clearly shows the increases in liver neoplasm incidences and body weights (Seilkop, 1995). In assessing differences in neoplasm incidences between *H. hepaticus*-affected and unaffected studies, the most relevant comparison would be between studies begun at approximately the same time. The starts of 20 of the 26 unaffected studies were clustered near the early part of the time frame (April 1988 to June 1990), while the starts of the affected studies were clustered toward the later end, with eight of the nine studies begun between July 1990 and January 1991; incidences of liver neoplasms in these later studies are expected to be higher based on trends in body weight alone. While the slightly increased incidences of liver neoplasms observed in female control mice in the nine affected studies is likely due to clustering in time, clearly, this alone cannot account for the increased liver neoplasm incidences observed in control male mice in the affected studies (Table L3).

Ideally, unaffected studies used in the above comparison should not only be free of histologic evidence of infection with *H. hepaticus* but should be confirmed as negative by PCR assays. Thirteen of these 26 studies could not be confirmed as negative by PCR because frozen tissue was not available; however, *H. hepaticus*-associated hepatitis was not present in any of the 26 studies. Because these and other data reported to date suggest that hepatitis is associated with neoplasm development in the liver, it seems reasonable to include those 13 studies, unconfirmed by PCR, in this analysis. The majority of the 13 studies confirmed as negative by PCR were begun much earlier than the clearly affected studies, and, therefore, comparing them alone to the nine affected studies is not reasonable. Although not presented

here, a number of comparisons were made with various groupings of studies based on the degree of confidence in their infection status. Although the outcomes of the various comparisons varied somewhat, incidences of hepatocellular neoplasms and hemangiosarcomas of the liver were consistently increased in control male mice from affected studies compared to control males from unaffected studies. Significantly increased liver neoplasm incidences generally were not observed in females. Importantly, the following data corroborate the findings and association with *H. hepaticus* identified in these analyses.

## Analysis of Hepatitis-Positive and Hepatitis-Negative Mice for Liver Neoplasm Incidence

Several infectious agents known to be associated with increased incidences of neoplasms cause chronic inflammation in the target tissue or organ. It is commonly hypothesized that this inflammatory process may cause or contribute to the development of neoplasms. One approach to address this was to stratify the mice from the affected studies according to the severity of hepatitis and examine liver neoplasm incidences in relation to these groupings. Thus, animals within the nine affected studies were placed into three groups: 1) animals with mild to moderate hepatitis considered related to *H. hepaticus* infection (+), 2) animals with minimal to mild hepatitis that may have been associated with *H. hepaticus* (±), and 3) animals with no hepatitis that was considered to be associated with *H. hepaticus* (**S**). Within these groupings, the incidence of liver neoplasms was significantly increased ($P<0.05$) in males with mild to moderate *H. hepaticus*-associated hepatitis (+) when compared to animals without such hepatitis (Table L5). The neoplasm incidence in animals with minimal lesions (±) was also increased. The liver neoplasm incidence in males without hepatitis (58%) was similar to the incidence (54.8%) in males from the 26 unaffected studies (Table L3). This analysis clearly suggests an association of *H. hepaticus*-associated hepatitis with increased liver neoplasm incidences. Females showed a similar trend, albeit not significant; however, these comparisons are weak because of the low numbers of females with hepatitis.

## Analysis of H-*ras* Oncogene Mutations in Liver Neoplasms in Mice from Affected and Unaffected Studies

Liver neoplasms commonly occur in control $B6C3F_1$ mice in 2-year studies. In the historical database of 333 male and female mice with liver neoplasms, 106 (32%) had H-*ras* codon 61 CAA-to-AAA mutations (Maronpot *et al.*, 1995). This historical control database is composed primarily of male data; however, adequate numbers of females have been assayed, and there was no significant difference in the incidences of CAA-to-AAA mutations between males and females.

In an attempt to examine further whether *H. hepaticus* infection had an effect on the development of hepatocellular neoplasms, neoplasms from control male mice from selected affected (NTP, 1998a,b, 1999a) and unaffected (NTP, 1993, 1999c) studies were evaluated for H-*ras* codon 61 CAA-to-AAA mutations (Table L6). Only 6% (2/33) of the hepatocellular neoplasms from control males with hepatitis from three affected studies had this mutation. This percentage is significantly ($P<0.01$) less than the 32% (11/34) observed in males from the two unaffected studies and less than the 32% (106/333) that occurred in historical control animals. In addition, neoplasms from males without hepatitis from the affected, PCR-positive triethanolamine study (NTP, 1999a) and the unaffected, PCR-positive methyleugenol study (NTP, 1999d) were evaluated; the incidences of mutations in those groups were 3/14 (21%) and 2/17 (12%), respectively.

Neoplasms from control female mice (none had hepatitis) from affected and unaffected studies were evaluated for the CAA-to-AAA mutation (Table L6). The mutation rate was low in both the affected studies (1/25; 4%) and the unaffected study (1/11; 9%) when compared to the 32% observed in the historical control groups.

The finding of a different H-*ras* mutation profile in neoplasms of male mice from affected studies tends to support the association of increased neoplasm incidences with *H. hepaticus,* although there is no mechanistic

understanding behind this observation. In a study of *H. hepaticus*-infected A/JCr mice, *ras* mutations were not detected in the 25 hepatocellular neoplasms analyzed using a PCR/single-strand conformation polymorphism assay (Sipowicz *et al.*, 1997). Because of the low spontaneous rate of liver neoplasms in the A/JCr mouse, there are few or no conclusive data on *ras* mutations in uninfected animals, however. Point mutations at codons 12, 13, and 61 of the Ki-, Ha- and N-*ras* genes were not identified in 45 early gastric carcinomas in humans, whether or not *H. pylori* was present (Craanen *et al.*, 1995). If the increased incidence of hepatocellular neoplasms is associated with hepatitis, as many suspect, then one would expect the neoplasms from animals without hepatitis to have a similar mutational profile as that of the historical controls. The data do not provide a clear answer, because the hepatitis-free males from the affected triethanolamine study (NTP, 1999a) and the males from the methyleugenol study (NTP, 1999d), which were positive by PCR but lacked hepatitis, had mutation frequencies between those of the unaffected controls and the hepatitis-positive mice. Furthermore, mutations in neoplasms from females, none of which had hepatitis, from two affected and one unaffected study were very low compared to the historical controls. These findings were unexpected, and their significance is not understood.

## *H. hepaticus*-Associated Alterations in Cell Kinetics

Studies evaluating cell kinetics were completed to explore further the link between hepatitis and the increased incidence of liver neoplasms (Table L7; Nyska *et al.*, 1997). One of the major objectives was to determine whether there were differences between PCNA labeling indices in the livers of animals with hepatitis from three affected studies, cobalt sulfate heptahydrate, chloroprene, and triethanolamine (NTP, 1998a,b, 1999a), compared to animals without hepatitis, whether from the same three affected studies or from an unaffected study, 1-trans-delta$^9$-tetrahydrocannabinol (NTP, 1996). Male mice with hepatitis from the three affected studies had a significantly increased ($P<0.001$) labeling index, with a 24-fold increase over males from the unaffected study and a sixfold increase over males without hepatitis from the same three affected studies (Table L7). The labeling index increase in these mice was substantial and was considered biologically significant. Male mice without hepatitis from the three affected studies had a significantly greater labeling index (increased fourfold) than male mice from the unaffected study (Table L7). The significance of this finding is uncertain, as differences of a similar magnitude were observed in other comparisons. For example, the labeling index of females from the unaffected 1-trans-delta$^9$-tetrahydrocannabinol study (Table L7; NTP, 1996) was increased fivefold over females from the PCR-positive, hepatitis-negative scopolamine hydrobromide trihydrate study (NTP, 1997). Such differences may be within the limits of normal variability for 2-year-old animals.

A second objective of the cell proliferation studies of the liver was to determine if labeling indices were increased in animals from the PCR-positive, hepatitis-negative methyleugenol (NTP, 1999d), scopolamine hydrobromide trihydrate (NTP, 1997), and mouse life-span studies compared to an unaffected PCR-negative and hepatitis-negative 1-trans-delta$^9$-tetrahydrocannabinol study (NTP, 1996). The scopolamine hydrobromide trihydrate study was evaluated and included in the study by Nyska *et al.* (1997), while the methyleugenol and mouse life-span studies were completed later and are included in Table L7. The labeling indices of males from two of these three studies were almost identical to those of males from the unaffected study. However, the labeling index of males from the mouse life-span study is increased approximately fivefold over that of males from the unaffected study as well as fivefold over the labeling indices of males from the two like studies of scopolamine hydrobromide trihydrate and methyleugenol. This finding suggests that the increase observed in the mouse life-span study is not attributable to the presence of *H. hepaticus,* as two other studies also positive for *H. hepaticus* did not show a similar increase.

The cell proliferation data for the liver from NTP studies are consistent with data from a study by Fox *et al.* (1996) in which cell proliferation indices were evaluated at 8, 10, and 13 months in the A/JCr mouse, which is generally believed to be more susceptible to *H. hepaticus*-associated hepatitis than the $B6C3F_1$ mouse. In the study by Fox *et al.* (1996), cell proliferation rates were significantly increased at all time points in males. Some increases were observed in females in that study but did not reach statistical

significance. An increased incidence of hepatocellular neoplasms was observed only in the males. Though liver lesions were observed in females in that study, they were less severe than those in males.

In addition to the liver, cell proliferation indices (PCNA) were evaluated in the kidneys and lungs of male and female mice in affected studies versus those in unaffected studies (Nyska *et al.*, 1997). No apparent effect of *H. hepaticus* infection or the presence of hepatitis on PCNA indices was observed for the kidneys or lungs.

Apoptosis (programmed cell death) is another important parameter in evaluations of cell kinetics. The apoptotic index in the liver of male mice with hepatitis from an affected study, cobalt sulfate heptahydrate (NTP, 1998a), was significantly ($P < 0.01$) greater than that observed in males from the unaffected 1-trans-delta$^9$-tetrahydrocannabinol study and the PCR-positive, hepatitis-negative scopolamine hydrobromide trihydrate study (Nyska *et al.*, 1997). For females, there were no significant differences among the three studies.

Two 13-week studies which were begun during the same time as the nine affected studies were randomly selected for evaluation of PCNA indices. *H. hepaticus* was not identified in either of the studies by PCR-RFLP; however, as with all NTP 13-week studies, only tissue fixed in formalin for an unspecified period was available. Because of this, no true negative control group was available; therefore, the labeling index of these 19- to 20-week-old animals was compared to values cited in the literature (Eldridge and Goldsworthy, 1996) for 20-week-old B6C3F$_1$ mice. The labeling index in the NTP studies clearly was not increased (data not shown).

## The Impact of *H. hepaticus* on the Interpretation of 2-Year Carcinogenesis Studies

Increases in the incidences of neoplasms are associated with a number of infectious agents. The chronic inflammation caused by these agents has been hypothesized to be important in the pathogenesis of the increased neoplasm incidences (e.g., gastric cancer associated with *H. pylori*). The increased incidences of liver neoplasms in male mice from the nine affected NTP studies were observed in the animals with *H. hepaticus*-associated hepatitis. Neoplasms from males with hepatitis tended to have an H-*ras* mutation profile different from that of animals from unaffected studies. Further, cell replication rates at 2 years were significantly higher in males with hepatitis compared to those in males without hepatitis. The data suggest that *H. hepaticus*-associated hepatitis is associated with the increased incidences of liver neoplasms in the male B6C3F$_1$ mouse. Therefore, the most important consideration in evaluating the impact of *H. hepaticus* infection on the interpretation of study results appears to be the presence or absence of significant hepatitis.

For any carcinogenicity study, data within and specific to the individual study provide the greatest basis for an accurate interpretation. However, it is prudent to consider and evaluate all data or information which may affect the interpretation. Based upon the data presented in this and other reports, general guidelines emerge that may be useful in interpreting potential chemical-associated carcinogenic effects in *H. hepaticus*-infected B6C3F$_1$ mice. In a study with sufficient evidence of *H. hepaticus*-associated hepatitis ($>10\%$ of the animals having the characteristic hepatitis may be a reasonable guideline), interpretation of increased incidences of liver neoplasms (hepatocellular neoplasms and hemangiosarcoma) of male mice is considered to be potentially confounded.

Altered chemical uptake and metabolism, due to the intestinal load of *H. hepaticus* and to *H. hepaticus*-associated liver disease, respectively, are possible reasons for considering that the male mouse response to chemical administration at sites other than the liver should also be considered confounded. Data do not currently exist that definitively answer this question. In this group of nine studies, however, there is no evidence to suggest that affected mice responded to chemical treatment in organs other than the liver in a manner different from mice in nonaffected studies. Within each study, there was excellent concordance in chemical-associated neoplasms between the male mice and the females, which had little or no hepatitis

(Table L8). Furthermore, analyses indicate that *H. hepaticus* is not associated with neoplastic responses outside the liver; incidences of neoplasms at sites other than the liver were not different between control groups from affected and unaffected studies (Table L3). Cell replication rates in two major organs (lung and kidney) also were not increased in control groups from affected studies compared to those from unaffected studies.

One of the more difficult issues to address is whether interpretation of a treatment-related increase in liver neoplasm incidences in the female mouse is confounded when *H. hepaticus*-associated hepatitis is present within the male mice in the study. Most evidence to date links hepatitis with the increased liver neoplasm incidences observed in males, and female $B6C3F_1$ mice in affected studies do not have significant hepatitis at 2 years. The lack of hepatitis in females, however, is based on an analysis in which only late time points were evaluated histologically. Therefore, it is conceivable that hepatitis along with increased cell proliferation could have occurred earlier and resolved by 18 months to 2 years. Data collected to date, however, suggest that *H. hepaticus*-associated hepatitis is a late-developing and persistent disease in the $B6C3F_1$ mouse. *H. hepaticus*-associated hepatitis has never been observed in any NTP 13-week studies, including five begun during the same 6-month time span as eight of the nine affected 2-year studies. Also, within affected 2-year studies, more males (51%) that were 18 to 24 months of age had hepatitis than those (34%) that were 12 to 18 months of age. This is consistent with a report by Ward *et al.* (1994b) that *H. hepaticus*-associated liver lesions are not observed at early time points in the $B6C3F_1$ mouse.

Nonetheless, within affected studies, female control mice did have a slightly elevated incidence of liver neoplasms when compared to control mice from unaffected studies, and the data derived from the H-*ras* mutation frequency analysis were inconclusive. The possibility that *H. hepaticus*-infected female mice from affected studies may respond differently to a liver carcinogen than mice from unaffected studies cannot be eliminated at this time. However, because within an affected study hepatitis is observed only rarely in females, until definitive data suggest otherwise, it is concluded that the interpretation of an apparent chemical-induced neoplastic effect in the liver of female mice is not confounded. To censor the few females with *H. hepaticus*-associated hepatitis from any statistical analyses of hepatocellular neoplasms would be prudent. Studies in the ostensibly more sensitive A/JCr mouse (Fox *et al.*, 1996) also showed significant increases in neoplasm incidences and cell proliferation rates in the liver of *H. hepaticus*-infected males, but not females.

Another concern is how to interpret possible chemical-related effects in a study in which the status of *H. hepaticus* infection cannot be determined by PCR-RFLP because only tissues fixed in formalin for more than 48 hours are available. While histologic evaluation is inadequate to identify infection, it appears adequate for identifying hepatitis severe enough to alter the outcome of the study. Therefore, in the absence of significant histologic evidence of *H. hepaticus*-associated hepatitis, the outcome of a 2-year study should not be considered potentially compromised.

The causality between *H. hepaticus* infection and neoplasia has not been proven in the $B6C3F_1$ mouse in these studies, nor has the mechanism of this association been determined; further studies are needed. However, sufficient information exists to make reasonable scientific judgments relative to the interpretation of data from the nine 2-year carcinogenicity studies in the $B6C3F_1$ mouse. Refinements to the above interpretive positions may occur if warranted by future information.

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**TABLE L1**
**Incidence of *Helicobacter hepaticus*-Associated Hepatitis in Control B6C3F$_1$ Mice from Nine NTP 2-Year Studies[a]**

| Study | Incidence of Hepatitis (%) Males | Females |
|---|---|---|
| Sodium xylenesulfonate | 78 | 4 |
| AZT/5,000 U α-interferon A/D | 76 | 4 |
| Cobalt sulfate heptahydrate | 72 | 8 |
| AZT/500 U α-interferon A/D | 66 | 0 |
| Chloroprene | 54 | 0 |
| Theophylline | 32 | 0 |
| α-Interferon A/D | 22 | 4 |
| Triethanolamine | 20 | 0 |
| AZT | 16 | 2 |
| Average | 48 | 2 |

[a] Includes regeneration and mild to marked (excludes minimal) chronic inflammation, karyomegaly, oval cell hyperplasia, and bile duct hyperplasia. AZT=3′-azido-3′-deoxythymidine

**TABLE L2**
**Identification of *Helicobacter hepaticus* with PCR-RFLP-Based Assays in Control B6C3F$_1$ Mice from 32 NTP 2-Year Studies and Three NTP 13-Week Studies[a]**

| Type of Sample | Total Studies | *H. hepaticus*-Positive Studies[b] Affected Studies | Unaffected Studies |
|---|---|---|---|
| **13-Week Studies** | | | |
| Formalin-fixed liver | 3 | — | 1/3[c] |
| **2-Year Studies** | | | |
| Frozen liver | 22 | 3/3 | 3/19 |
| Formalin-fixed liver | 10 | 1/6[c] | 0/4 |

[a] PCR-RFLP=polymerase chain reaction-restriction fragment length polymorphism
[b] Number of *H. hepaticus*-positive studies/number of affected or unaffected studies. Affected studies are those in which hepatitis typical of that associated with *H. hepaticus* infection occurred in many male mice.
[c] Only one animal in the positive study was positive for *H. hepaticus*.

**TABLE L3**
**Comparison of Neoplasm Incidences in Control $B6C3F_1$ Mice from *Helicobacter hepaticus*-Affected and Unaffected NTP 2-Year Studies**

| | Males | | Females | |
|---|---|---|---|---|
| | Affected Studies[a] | Unaffected Studies | Affected Studies | Unaffected Studies |
| Number of studies | 9 | 26 | 9 | 26 |
| Survival (%) | 64 | 71 | 68 | 68 |
| 12-Month body wt (g) | 48.0 | 48.3 | 48.1 | 47.0 |
| Neoplasm incidence (%) | | | | |
| Liver | 71.3* | 54.8 | 50.3 | 40.5 |
| Lung | 26.6 | 23.2 | 7.6 | 10.3 |
| Pituitary gland | 0.4 | 0.8 | 14.7 | 14.3 |
| Harderian gland | 5.6 | 6.1 | 6.0 | 4.9 |
| Lymphoma | 6.9 | 6.3 | 16.2 | 15.5 |
| Circulatory system | 9.8 | 6.0 | 5.3 | 4.7 |
| liver only | 7.1* | 2.5 | — | — |
| All benign | 61.8 | 57.2 | 59.1 | 54.6 |
| All malignant | 61.3* | 40.9 | 50.0 | 44.2 |
| All neoplasms | 88.0* | 77.4 | 82.7 | 75.4 |

* Significantly different ($P \leq 0.05$) from the unaffected studies
[a] Affected studies are those in which hepatitis typical of that associated with *H. hepaticus* infection occurred in many male mice.

**TABLE L4**
**Liver Neoplasm Incidences and Body Weights of Control $B6C3F_1$ Mice in Relation to Study Start Dates of *Helicobacter hepaticus*-Affected and Unaffected NTP 2-Year Studies**[a]

| Study Start Date | Liver Neoplasm Incidence (%) | | Mean Body Weight (g) | |
|---|---|---|---|---|
| | Affected Studies[a] | Unaffected Studies | Affected Studies | Unaffected Studies |
| **Male** | | | | |
| April to September 1988 | — | 43.8 (8)[b] | — | 46.2 (8) |
| October 1988 | 62.0 (1) | — | 48.3 (1) | — |
| November 1988 to September 1989 | — | 52.6 (7) | — | 48.7 (7) |
| October 1989 to June 1990 | — | 61.2 (5) | — | 48.9 (5) |
| July 1990 to January 1991 | 72.5 (8) | 66.2 (4) | 48.0 (8) | 49.0 (4) |
| February 1991 to April 1992 | — | 68.0 (2) | — | 52.8 (2) |
| Average | 71.3 | 54.8 | 48.0 | 48.3 |
| **Female** | | | | |
| April to September 1988 | — | 31.1 (8) | — | 44.8 (8) |
| October 1988 | 46.0 (1) | — | 46.4 (1) | — |
| November 1988 to September 1989 | — | 39.9 (7) | — | 47.2 (7) |
| October 1989 to June 1990 | — | 38.6 (5) | — | 45.9 (5) |
| July 1990 to January 1991 | 50.9 (8) | 54.2 (4) | 48.3 (8) | 48.0 (4) |
| February 1991 to April 1992 | — | 58.0 (2) | — | 55.6 (2) |
| Average | 50.3 | 40.5 | 48.1 | 47.0 |

[a] Includes nine affected studies (those in which hepatitis typical of that associated with *H. hepaticus* infection occurred in many male mice) and 26 unaffected studies
[b] Number of studies is given in parentheses.

**TABLE L5**
**Association of Liver Neoplasm Incidence and Severity of *Helicobacter hepaticus*-Associated Hepatitis in Control B6C3F$_1$ Mice from Nine Affected NTP 2-Year Studies[a]**

| Severity of Hepatitis | Liver Neoplasm Incidence Males | Liver Neoplasm Incidence Females |
|---|---|---|
| Absent | 101/175 (58%) | 196/396 (49%) |
| Minimal | 44/57 (77%) | 23/42 (55%) |
| Mild/moderate | 176/218 (81%) | 7/11 (64%) |
| Significance of association | $P < 0.05$ | NS[b] |

[a] Affected studies are those in which hepatitis typical of that associated with *H. hepaticus* infection occurred in many male mice.
[b] NS=not significant

**TABLE L6**
**H-*ras* Codon 61 AAA Mutations in Spontaneous Liver Neoplasms in Control B6C3F$_1$ Mice from *Helicobacter hepaticus*-Affected and Unaffected NTP 2-Year Studies**

| Study | Affected[a] | H-*ras* AAA Mutations |
|---|---|---|
| **Male** | | |
| Cobalt sulfate heptahydrate | + | 0/10 (0%) |
| Chloroprene | + | 1/13 (8%) |
| Triethanolamine | + | 1/10 (10%) |
| Oxazepam | — | 7/18 (39%) |
| Diethanolamine | — | 4/16 (25%) |
| Historical control database | | 106/333 (32%) |
| **Female** | | |
| Chloroprene | + | 0/10 (0%) |
| Triethanolamine | + | 1/15 (7%) |
| Diethanolamine | — | 1/11 (9%) |
| Historical control database | | 106/333 (32%) |

[a] +=affected; —=not affected. Affected studies are those in which hepatitis typical of that associated with *H. hepaticus* infection occurred in many male mice.

**TABLE L7**
**Proliferating Cell Nuclear Antigen Labeling Indices in the Liver of Control $B6C3F_1$ Mice[a]**

| | Hepatitis | No. of Animals | PCNA Labeling Index[b] | Average PCNA Labeling Index[c] |
|---|---|---|---|---|
| **Male** | | | | |
| Cobalt sulfate heptahydrate[d] | + | 15 | 0.535 ± 0.129 | |
| Chloroprene[d] | + | 12 | 1.452 ± 0.386 | |
| Triethanolamine[d] | + | 9 | 1.215 ± 0.374 | 1.011 |
| Cobalt sulfate heptahydrate | — | 7 | 0.175 ± 0.117 | |
| Chloroprene | — | 10 | 0.296 ± 0.124 | |
| Triethanolamine | — | 12 | 0.100 ± 0.042 | 0.186 |
| 1-Trans-delta$^9$-tetrahydrocannabinol[e] | — | 15 | 0.042 ± 0.011 | |
| Scopolamine hydrobromide trihydrate[f] | — | 14 | 0.043 ± 0.012 | |
| Methyleugenol[f] | — | 14 | 0.077 ± 0.020 | |
| Mouse life-span study[f] | — | 15 | 0.217 ± 0.880 | |
| **Female** | | | | |
| Cobalt sulfate heptahydrate | + | 5 | 0.161 ± 0.062 | |
| Cobalt sulfate heptahydrate | — | 17 | 0.055 ± 0.015 | |
| Chloroprene | — | 12 | 0.154 ± 0.050 | |
| Triethanolamine | — | 12 | 0.138 ± 0.053 | 0.108 |
| 1-Trans-delta$^9$-tetrahydrocannabinol | — | 13 | 0.156 ± 0.047 | |
| Scopolamine hydrobromide trihydrate | — | 15 | 0.032 ± 0.009 | |

[a] A portion of these data are presented in Nyska *et al.* (1997). + = hepatitis present; — = no hepatitis present
[b] Mean ± standard error; PCNA = proliferating cell nuclear antigen
[c] Average of the mean labeling indices for animals from all three studies
[d] Affected study (one in which hepatitis typical of that associated with *H. hepaticus* occurred in many male mice)
[e] Unaffected study (one in which the typical hepatitis did not occur in mice)
[f] Unaffected study with no typical hepatitis, but positive for *H. hepaticus* by polymerase chain reaction-restriction fragment length polymorphism-based assay

**TABLE L8**
**Summary of Target Sites of Carcinogenicity in B6C3F$_1$ Mice from NTP 2-Year Studies with *Helicobacter hepaticus*-Associated Hepatitis**

| | Males | Females |
|---|---|---|
| Chloroprene | Lung<br>Circulatory system[a]<br>Harderian gland<br>Forestomach<br>Kidney | Lung<br>Circulatory system<br>Harderian gland<br>Forestomach<br>Liver<br>Skin<br>Mesentery<br>Zymbal's gland<br>Mammary gland |
| Cobalt sulfate heptahydrate[b] | Lung | Lung |
| Triethanolamine | Liver | Liver |
| AZT[c] | None | Vagina |
| Sodium xylenesulfonate | None | None |
| Theophylline | None | None |

[a] Hemangioma and hemangiosarcoma of the liver were excluded from the analysis in males.
[b] An apparent treatment-related increase in the incidence of hemangiosarcoma of the liver was discounted in male mice because of the presence of *H. hepaticus*.
[c] AZT=3′-azido-3′-deoxythymidine. Includes four studies: AZT; α-interferon A/D; AZT/500 U α-interferon A/D; and AZT/5,000 U α-interferon A/D