NTP TECHNICAL REPORT

ON THE

TOXICOLOGY AND CARCINOGENESIS

STUDIES OF TRIMETHYLOLPROPANE TRIACRYLATE

(TECHNICAL GRADE)

(CAS NO. 15625-89-5)

IN F344/N RATS AND B6C3F1/N MICE

(DERMAL STUDIES)

Scheduled Peer Review Date: February 8-9, 2012

NTP TR 576

NIH Publication No. 12-5918

National Toxicology Program

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

FOREWORD

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

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

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

NTP Technical Reports are indexed in the NIH/NLM PubMed database and are available free of charge electronically on the NTP website (*http://ntp.niehs.nih.gov*) or in hardcopy upon request from the NTP Central Data Management group at *cdm@niehs.nih.gov* or (919) 541-3419.

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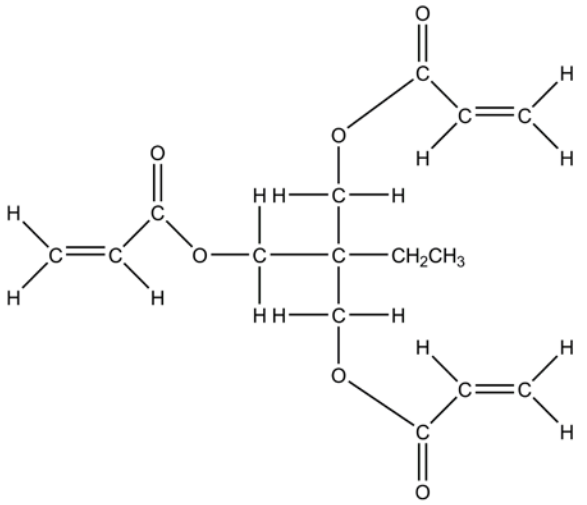
ABSTRACT



TRIMETHYLOLPROPANE TRIACRYLATE

CAS No. 15625-89-5

Chemical Formula: $C_{15}H_{20}O_6$ Molecular Weight: 296.3

Synonyms: Acrylic acid, 2-ethyl-2-(((1-oxo-2-propenyl)oxy)methyl)-1,3-propanediol triester; A-TMPT; 2,2-bis(prop-2-enoyloxymethyl)butyl prop-2-enoate; 2-ethyl-2-(hydroxymethyl)-1,3-propanediol triacrylate; 2-ethyl-2-(((2-oxo-2-propenyl)oxy)methyl)-1,3-propanediyl ester; 2-propenoic acid, 2-ethyl-2-(((1-oxo-2-propenyl)oxy)methyl)-1,3-propanediol ester; TMPTA; 1,1,1-trimethylolpropane triacrylate

Trade names: Aronix M 3090, Monosizer TD 1500A, NK Ester A-TMPT, SARTOMER SR 351, Setalux UV 2241, SR 351, Viscoat

Trimethylolpropane triacrylate is a multifunctional monomer with a wide range of industrial applications. It is used in the production of ultraviolet-curable inks, electron beam irradiation-curable coatings, and polymers and resins; as a component of photopolymer and flexographic printing plates and photoresists; and as an ingredient in acrylic glues, adhesives, and anaerobic sealants. Additionally, trimethylolpropane triacrylate is used in paper and wood impregnates, wire and cable extrusion, polymer-impregnated concrete, and polymer concrete structural composites. Trimethylolpropane triacrylate was nominated by the National Cancer Institute for study due to its high production volume and use, the potential for human exposure, and the lack of adequate chronic toxicity and carcinogenicity data. Male and female F344/N rats and B6C3F1/N mice were administered technical grade trimethylolpropane

triacrylate (greater than 78% pure) in acetone dermally for up to 2 years. Genetic toxicology studies were conducted in *Salmonella typhimurium* and *Escherichia coli*.

2-YEAR STUDY IN RATS

Groups of 65 male and 65 female rats received dermal applications of 0, 0.3, 1.0, or 3.0 mg trimethylolpropane triacrylate/kg of body weight in acetone, 5 days per week for 104 to 105 weeks (core study). At 2 weeks, 13 weeks, and 12 months, five animals per sex per dose group were randomly selected for histological examination of skin tissue. Survival and mean body weights of all dosed groups were similar to those of the vehicle control groups.

In male rats, there was a positive trend in the incidences of malignant mesothelioma; the incidence in 3.0 mg/kg males was significantly greater than the vehicle control incidence.

Nonneoplastic skin lesions at the site of application in core study rats included epidermal hyperplasia and hyperkeratosis. The incidences of these lesions in male rats administered 1.0 or 3.0 mg/kg were significantly increased. In females at the site of application, incidences of epidermal hyperplasia were significantly increased at 1.0 and 3.0 mg/kg and incidences of hyperkeratosis were significantly increased in all dosed groups. At the interim evaluations, increased incidences of epidermal hyperplasia, sebaceous gland hyperplasia, and or hyperkeratosis were observed at the site of application in males and females.

2-YEAR STUDY IN MICE

Groups of 65 male and 65 female mice received dermal applications of 0, 0.3, 1.0, or 3.0 mg trimethylolpropane triacrylate/kg body weight in acetone, 5 days per week for 105 to 106 weeks (core study). At 2 weeks, 13 weeks, and 12 months, five animals per sex per dose group were randomly selected for histological examination of skin tissue. Survival and mean body weights of all dosed groups were similar to those of the vehicle control groups. Liver neoplasms in female mice included hepatoblastoma in the 0.3 and 3.0 mg/kg groups and hepatocholangiocarcinoma in the 1.0 and 3.0 mg/kg groups. Based on the rarity of these neoplasms in female mice,

and their absence in the concurrent vehicle controls, hepatoblastoma and hepatocholangiocarcinoma were considered to be treatment-related lesions.

The incidences of uterine stromal polyp and stromal polyp or stromal sarcoma (combined) in female mice occurred with positive trends, and the incidences were significantly increased in the 3.0 mg/kg group.

Compared to the vehicle control incidences, the incidences of epidermal hyperplasia, melanocyte hyperplasia, and chronic inflammation at the site of application were significantly increased in core study males and females administered 3.0 mg/kg; incidences of epidermal hyperplasia in 1.0 mg/kg females and chronic inflammation in 1.0 mg/kg males were also significantly increased. At the interim evaluations, increased incidences of epidermal hyperplasia and inflammation or chronic active inflammation were observed at the site of application in males and females.

GENETIC TOXICOLOGY

Trimethylolpropane triacrylate (1,500 to 10,000 µg per plate; lot no. 08409HI) did not induce gene mutations in *S. typhimurium* strains TA98 or TA100 or in *E. coli* strain WP2 *uvrA*/pKM101, with or without exogenous metabolic activation.

CONCLUSIONS

Under the conditions of these 2-year dermal studies, there was *some evidence of carcinogenic activity* of trimethylolpropane triacrylate in male F344/N rats based on increased incidences of malignant mesothelioma. There was *no evidence of carcinogenic activity* of trimethylolpropane triacrylate in female F344/N rats administered 0.3, 1.0, or 3.0 mg/kg. There was *no evidence of carcinogenic activity* of trimethylolpropane triacrylate in male B6C3F1/N mice administered 0.3, 1.0, or 3.0 mg/kg. There was *some evidence of carcinogenic activity* of trimethylolpropane triacrylate in female B6C3F1/N mice based on increased incidences of uncommon malignant hepatic neoplasms (hepatoblastoma and hepatocholangiocarcinoma) and stromal polyp or stromal sarcoma of the uterus.

Dermal application of trimethylolpropane triacrylate for 2-years resulted in increased incidences of nonneoplastic lesions in the skin of male and female rats and mice.

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* Explanation of Levels of Evidence of Carcinogenic Activity is on page 10.

Summary of the 2-Year Carcinogenesis and Genetic Toxicology Studies of Trimethylolpropane Triacrylate

	Male F344/N Rats	Female F344/N Rats	Male B6C3F1/N Mice	Female B6C3F1/N Mice
Concentrations in acetone by dermal application	0, 0.3, 1.0, or 3.0 mg/kg	0, 0.3, 1.0, or 3.0 mg/kg	0, 0.3, 1.0, or 3.0 mg/kg	0, 0.3, 1.0, or 3.0 mg/kg
Body weights	Dosed groups within 10% of the vehicle control group	Dosed groups within 10% of the vehicle control group	Dosed groups within 10% of the vehicle control group	Dosed groups within 10% of the vehicle control group
Survival rates	23/50, 18/50, 28/50, 23/50	27/50, 31/50, 24/50, 32/50	30/50, 35/50, 29/50, 38/50	39/50, 31/50, 30/50, 30/50
Nonneoplastic effects	Skin (site of application): epidermis, hyperplasia (1/50, 0/50, 12/50, 28/50); hyperkeratosis (2/50, 4/50, 33/50, 49/50)	Skin (site of application): epidermis, hyperplasia (0/50, 4/50, 11/50, 25/50); hyperkeratosis (0/50, 11/50, 42/50, 50/50)	Skin (site of application): epidermis, hyperplasia (10/50, 7/50, 15/50, 44/50); hyperplasia, melanocyte (0/50, 0/50, 0/50, 19/50); inflammation, chronic (13/50, 17/50, 26/50, 43/50)	Skin (site of application): epidermis, hyperplasia (7/50, 7/50, 15/50, 34/50); hyperplasia, melanocyte (1/50, 1/50, 3/50, 33/50); inflammation, chronic (37/50, 36/50, 43/50, 48/50)
Neoplastic effects	Malignant mesothelioma: (0/50, 2/50, 2/50, 5/50)	None	None	Liver: hepatoblastoma (0/50, 4/50, 0/50, 3/50); hepatocholangiocarcinoma (0/50, 0/50, 1/50, 2/50) Uterus: stromal polyp or stromal sarcoma (0/50, 1/50, 2/50, 6/50)
Level of evidence of carcinogenic activity	Some evidence	No evidence	No evidence	Some evidence
Genetic toxicology Bacterial gene mutations:	Negative in S*almonella typhimurium* strains TA98 and TA100 and *Escherichia coli* strain WP2 *uvrA*/pKM101, with or without S9			

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 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 on March 1986 for use in the Technical Report series to incorporate more specifically the concept of actual weight of evidence of carcinogenic activity. For each separate experiment (male rats, female rats, male mice, female mice), one of the following five categories is selected to describe the findings. These categories refer to the strength of the experimental evidence and not to potency or mechanism.

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

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

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

- adequacy of the experimental design and conduct;
- occurrence of common versus uncommon neoplasia;
- progression (or lack thereof) from benign to malignant neoplasia as well as from preneoplastic to neoplastic lesions;
- some benign neoplasms have the capacity to regress but others (of the same morphologic type) progress. At present, it is impossible to identify the difference. Therefore, where progression is known to be a possibility, the most prudent course is to assume that benign neoplasms of those types have the potential to become malignant;
- combining benign and malignant tumor incidence known or thought to represent stages of progression in the same organ or tissue;
- latency in tumor induction;
- multiplicity in site-specific neoplasia;
- metastases;
- supporting information from proliferative lesions (hyperplasia) in the same site of neoplasia or 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 TECHNICAL REPORTS
PEER REVIEW PANEL

The members of the Peer Review Panel who evaluated the draft NTP Technical Report on trimethylolpropane triacrylate on February 8-9, 2012, are listed below. Panel members serve as independent scientists, not as representatives of any institution, company, or governmental agency. In this capacity, panel members have five major responsibilities in reviewing the NTP studies:

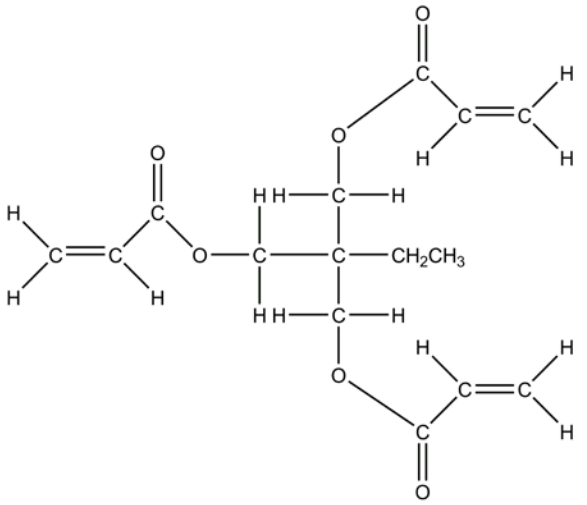
- to ascertain that all relevant literature data have been adequately cited and interpreted,
- to determine if the design and conditions of the NTP studies were appropriate,
- to ensure that the Technical Report presents the experimental results and conclusions fully and clearly,
- to judge the significance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

NOTE: The list of Peer Review Panel members will appear in a future draft of this report.

SUMMARY OF PEER REVIEW PANEL COMMENTS

NOTE: A summary of the Peer Review Panel's remarks will appear in a future draft of this report.

INTRODUCTION



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CHEMICAL AND PHYSICAL PROPERTIES

Trimethylolpropane triacrylate is a viscous, colorless to tan liquid with an acrylic or pungent odor and a boiling point greater than 200° C at 1 mm Hg (AIHA, 1981; Lenga, 1988; Alfa, 1990). At 25° C, it has a specific gravity of 1.1084 and a vapor pressure of less than 1.0 mm Hg (AIHA, 1981; ARCO, 1989); the refractive index is 1.4736 at 20° C (Lenga, 1988). It is insoluble in water and is hygroscopic, light sensitive, and incompatible with strong oxidizing agents, acids, and bases. Trimethylolpropane triacrylate may undergo spontaneous polymerization when exposed to direct sunlight and heat but may be stabilized with the monomethyl ester of hydroquinone (AIHA, 1981; Lenga, 1988). Trimethylolpropane triacrylate is combustible, with a flashpoint of greater than 110° C (Lenga,

1988). Decomposition produces toxic fumes of carbon monoxide and carbon dioxide (Lenga, 1988). The chemical is reactive and is, therefore, available only as technical grade.

PRODUCTION, USE, AND HUMAN EXPOSURE

Trimethylolpropane triacrylate is manufactured by esterification of trimethylolpropane (*Kirk-Othmer*, 1978); acrylic acid is a known impurity in the technical-grade compound (Celanese, 1982). Based on 2006 Inventory Update Reporting, a national production volume of 10 to 50 million pounds of trimethylolpropane triacrylate was reported at more than 1,000 sites (USEPA, 2006).

Trimethylolpropane triacrylate is a multifunctional monomer with a wide range of industrial applications as a cross-linking agent, reactive diluent, and chemical intermediate. It is used in the production of ultraviolet-curable inks, electron beam irradiation-curable coatings, thermal paper, plastic hardener, optical fibers, UV-cured acrylate varnishes in the furniture industry, and polymers and resins; as a component of photopolymer and flexographic printing plates and photoresists; and as an ingredient in acrylic glues, adhesives, and anaerobic sealants. It is incorporated in colloidal dispersions for industrial baked coatings, waterborne and solvent based alkyds, and vinyl/acrylic nonwoven binders. Additionally, trimethylolpropane triacrylate is used in paper and wood impregnates, wire and cable extrusion, polymer-impregnated concrete, polymer concrete structural composites, and production of superabsorbent polymers for baby diapers (Celanese, 1982; Dahlquist *et al*., 1983; Björkner, 1984; Maurice and Rycroft, 1986; Dearfield *et al.*, 1989; Radak, 1990; Voog and Jansson, 1992; Goon *et al*., 2002; Sánchez-Garcia *et al*., 2009).

Workers involved in the manufacturing, processing, product handling, and application of trimethylolpropane triacrylate are at risk of exposure (AIHA, 1981). Surveys by the National Institute for Occupational Safety and Health (1990) indicated that approximately 4,180 workers were exposed to trimethylolpropane triacrylate between 1981 and 1983. Furthermore, a potential exists for widespread exposure of consumers through the use of trimethylolpropane triacrylate in products such as latex paints and furniture and floor polishes (Dearfield *et al*., 1989; Voog and Jansson, 1992).

REGULATORY STATUS

Trimethylolpropane triacrylate is included on the Toxic Substances Control Act (TSCA) inventory (USEPA, 2011). It is also listed on the Canadian Domestic Substances List (CEPA, 2011). The American Industrial Hygiene Association (1981) established a workplace environmental exposure level (8-hour time-weighted average) of 1 mg/m^3 trimethylolpropane triacrylate; no other exposure regulations or recommendations have been established.

ABSORPTION, DISTRIBUTION, METABOLISM, AND EXCRETION

Experimental Animals

Metabolism and disposition of [^{14}C]-trimethylolpropane triacrylate was investigated in male F344/N rats and B6C3F_1 mice following single intravenous administration and dermal application (protected from oral grooming) (NTP, 2005a). In male rats, the percent dose absorbed was 55.7%, 32.7%, or 18.7% at 72 hours following dermal application of 1.7, 15.2, or 130 mg/kg. In mass terms, approximately five times more trimethylolpropane triacrylate was absorbed as the dose concentration increased by one order of magnitude. About 9% of the dose was recovered from the dose site regardless of the applied dose. About 45%, 19%, or 5% of the applied dose was recovered in the excreta 72 hours after dermal application of 1.7, 15.2, or 130 mg/kg, respectively. The radioactivity associated with tissues at 72 hours was less than 1%. The kidney had elevated tissue:blood ratios at each dose. Following intravenous administration of 9.4 mg/kg [^{14}C]-trimethylolpropane triacrylate in male rats, a total of 77.4% of the applied dose was excreted in urine, feces, and exhaled carbon dioxide 72 hours after administration. Among the tissues collected, the highest radiolabeled concentration was associated with blood.

In male B6C3F_1 mice, 75% of the dose was absorbed 72 hours after a single application of 1.2 mg/kg. The percent dose remaining at the dose site was higher in mice (31%) than in rats (9%) (NTP, 2005a). Approximately 42% of the applied dose was recovered in urine, feces, and exhaled carbon dioxide 72 hours after application, an amount similar to that excreted by rats (45%) following dermal application of 1.7 mg/kg. The radioactivity associated with tissues at 72 hours was less than 1%. The nonapplication site skin had an elevated tissue:blood ratio.

After a single 124 mg/kg dermal application of [^{14}C]-trimethylolpropane triacrylate in male rats followed by tape stripping the application site at 72 hours, most of the radioactivity associated with the dose site was trimethylolpropane triacrylate thereby confirming that the test article was stable on the skin (NTP, 2005a).

In order to evaluate whether the high tissue:blood ratio in the kidney is due to covalent binding, total binding found in kidney samples from dermal application and intravenous administration was determined (NTP, 2005a). Following dermal application, binding to kidney was low indicating that the high radioactivity is likely associated with urine. In contrast, following intravenous administration, high radioactivity in kidney was associated with covalent binding.

Humans

Data on metabolism and disposition of trimethylolpropane triacrylate in humans are not available.

TOXICITY

Experimental Animals

Acute oral LD_{50} values reported for trimethylolpropane triacrylate in rats were 3.84 to 7.01 mL trimethylolpropane triacrylate/kg body weight (Carpenter *et al*., 1974) or 5,000 mg/kg (Andrews and Clary, 1986). Dermal LD_{50} values for rabbits were 200 to 2,000 mg/kg (Andrews and Clary, 1986), 3.89 to 10.04 mL/kg (Carpenter *et al*., 1974), or 5,170 mg/kg for a 24-hour exposure period (AIHA, 1981).

In a series of studies conducted by Celanese Corporation, Inc. (Andrews and Clary, 1986), trimethylolpropane triacrylate was administered undiluted or in acetone or mineral oil to the interscapular region of male C3H/HeJ mice. All five mice administered 50 mg undiluted trimethylolpropane triacrylate died 1 day after treatment; clinical findings included lethargy, inactivity, and salivation shortly after application. A group of three mice administered 50 mg of a 10% solution in acetone twice per week for 2 weeks developed epilated, crusty, severely burned skin. Very slight crusting of the skin was observed in mice treated with 50 mg of a 5% solution in mineral oil twice per week for 5 weeks.

Immunized, outbred, male and female Hartley guinea pigs (number per group not reported) received daily applications of 0.2 mL of a solution of 0.1%, 0.25%, or 0.5% trimethylolpropane triacrylate in acetone:olive oil (4:1) for 7 days (Parker and Turk, 1983). Based on skin reactions graded on a scale of 0 (no reaction) to 3 (severe reaction), the guinea pigs developed mild to moderate skin sensitization.

In a sensitization study by Nethercott *et al.* (1983), groups of 10 female albino Hartley/Dalkin guinea pigs were induced and then challenged with trimethylolpropane triacrylate. Three intradermal injections were administered to each shoulder: 0.1 mL of a 0.5% or 10% solution of trimethylolpropane triacrylate in propylene glycol; 0.05 mL Freund's Complete Adjuvant (FCA) and 0.05 mL of a 0.5% or 10% solution of trimethylolpropane triacrylate in propylene glycol; and 0.1 mL FCA. After 1 week, 0.5% or 10% trimethylolpropane triacrylate in petrolatum was applied to the animals' shaved shoulders, which were then wrapped for 48 hours. The animals were challenged 2 weeks after the topical exposure with skin patches of nonirritant concentrations of trimethylolpropane triacrylate for 24 hours. Four guinea pigs that were administered 0.5% trimethylolpropane triacrylate and 10 of 20 guinea pigs administered the 10% solution became sensitized; the intradermal sensitivity concentration for 50% of the animals was determined to be 5.4%.

In a maximization test to determine skin sensitivity and cross-sensitivity reactions, groups of 15 female albino Dunkin/Hartley guinea pigs were sensitized topically with 25% solutions of commercial-grade pentaerythritol tri- or tetraacrylate in petrolatum and then challenged with two applications on the flank, 1 week apart, of 0.015 g pentaerythritol tri- or tetraacrylate (commercial grade and purified) or trimethylolpropane triacrylate in petrolatum (Björkner, 1984). A booster of the sensitizing chemical was administered intradermally on the neck 48 hours after the first challenge. Of the 10 animals that became sensitized to commercial-grade pentaerythritol triacrylate, seven also reacted to trimethylolpropane triacrylate. Only one guinea pig became sensitized to commercial grade pentaerythritol tetraacrylate; this animal also reacted to trimethylolpropane triacrylate. These results indicated that pentaerythritol triacrylate was the more potent sensitizer and that guinea pigs sensitized to pentaerythritol triacrylate may cross-react to trimethylolpropane triacrylate.

In a maximization test of acrylates and methacrylate esters, outbred female SSc:AL guinea pigs were induced with three 2 × 50 μL intradermal injections, including one of FCA in sterile water and one each of a test compound (methyl methacrylate, ethyleneglycol dimethacrylate, triethyleneglycol dimethacrylate, or trimethylolpropane trimethylacrylate) in soybean oil and in a mixture of emulsified FCA and water (Clemmensen, 1984). On day 7, approximately 250 mg of 10% sodium lauryl sulfate in petrolatum was applied to the neck and left uncovered for 24 hours. On day 8, the test compound or petrolatum (400 μL) was applied to a filter paper patch that was applied to the flank and left in place for 48 hours. On day 21, the guinea pigs were challenged with up to six patches containing 25 μL of the sensitizing compound: 2-hydroxy-methacrylate, 1,6-hexane diolodiacrylate, pentaerythritol triacrylate, or trimethylolpropane triacrylate. Sensitization determinations were made at 48 and 72 hours. The treatment was repeated on the opposite flank of each animal after 35 days. Positive skin sensitization reactions occurred in 14 of 19 guinea pigs induced with trimethylolpropane trimethylacrylate and challenged with 2% trimethylolpropane triacrylate; animals induced with the other test chemicals did not have cross reactions with trimethylolpropane triacrylate.

Parker *et al.* (1985) immunized outbred male and female Hartley guinea pigs (number not specified) with subcutaneous injection into the footpad and the nape of the neck with 0.1 mL of an emulsion containing trimethylolpropane triacrylate in ethanol:saline (1:4) in FCA. The total trimethylolpropane triacrylate dose was 11.5 μmol. Skin tests of 0.02 mL of 0.25% or 0.5% trimethylolpropane triacrylate in acetone:olive oil (4:1) were then applied to the shaved flank of the guinea pig, and reactions were recorded at 24, 48, 72, and 96 hours. Skin reactions were graded on a scale of 0 (no reaction) to 3 (severe reaction). On day 7, the reactions for both concentrations were mild at 24 hours and moderate at 48 hours; the 24- and 48-hour reactions on day 14 were moderate. Parker *et al.* (1985) also conducted cross sensitivity tests with trimethylolpropane triacrylate on groups of five guinea pigs immunized with methyl acrylate, methyl vinyl ketone, 4-vinyl pyridine, pentaerythritol triacrylate, and trimethylolpropane triacrylate in FCA. Cross sensitivity to trimethylolpropane triacrylate occurred in guinea pigs immunized with methyl acrylate, methyl vinyl ketone, and pentaerythritol triacrylate; the reactions were 20% to 60%, 60% to 80%, and greater than 80%, respectively, relative to the sensitizer response.

The NTP conducted a contact hypersensitivity study in conjunction with a subchronic study of technical grade trimethylolpropane triacrylate. It was not shown to be a skin sensitizer in female BALB/c mice (NTP, 2005a). Although there was a significant trend toward increased responses at doses of 0.05%, 0.1%, and 0.25% in the murine local lymph node assay (LLNA), no individual dose was significantly different from the vehicle control and the highest response did not reach the threefold stimulation index suggested for a positive in the LLNA (Kimber *et al.*, 1994). Trimethylolpropane triacrylate was negative in a mouse ear swelling test (NTP, 2005a). In the same study, trimethylolpropane triacrylate was positive in the murine irritancy assay at concentrations of 0.05%, 0.25%, and 0.5% when applied directly to the skin.

Additionally, eye irritation in rabbits was reported. Eye irritation was scored 9 on a 10-grade scale 24 hours after application of trimethylolpropane triacrylate (Mortensen, 1992). By a Draize test, instillation of trimethylolpropane triacrylate into rabbit eyes induced irritation and reversible corneal opacity for 7 days (Andrews and Clary, 1986).

The NTP conducted a subchronic toxicity study of trimethylolpropane triacrylate in rodents and identified skin as a target organ (NTP, 2005a). F344/N rats were treated topically with up to 12 mg/kg trimethylolpropane triacrylate in acetone 5 days per week for 14 weeks. All rats survived to the end of the study with no effect on body weight. Irritation at the site of application was observed in half of males and all females receiving 12 mg/kg trimethylolpropane triacrylate. At the site of application, nonneoplastic skin lesions including epidermal hyperplasia and chronic inflammation were observed in males and females (Table 1). B6C3F_1 mice were administered up to 12 mg/kg trimethylolpropane triacrylate in acetone topically, 5 days per week for 14 weeks (NTP, 2005a). All mice survived to the end of the study without an effect on body weight. In males and females administered 12 mg/kg trimethylolpropane triacrylate, irritation at the site of application was observed. Nonneoplastic skin lesions including epidermal hyperplasia, hyperkeratosis, necrosis, and chronic inflammation were observed at the site of application in males and females (Table 2).

TABLE 1
Incidences of Selected Nonneoplastic Lesions of the Skin (Site of Application) in F344/N Rats in the 3-Month Dermal Study of Trimethylolpropane Triacrylate[a]

	Vehicle Control	0.75 mg/kg	1.5 mg/kg	3 mg/kg	6 mg/kg	12 mg/kg
Male						
Number Examined						
Microscopically	10	10	10	10	10	10
Epidermis, Hyperplasia[b]	0	4* (1.0)[c]	7** (1.0)	10** (1.2)	10** (1.1)	10** (1.6)
Epidermis, Degeneration	0	0	4* (1.0)	7** (1.0)	9** (1.0)	8** (1.9)
Dermis, Inflammation, Chronic Active	0	1 (1.0)	3 (1.0)	6** (1.0)	10** (1.0)	10** (2.1)
Hyperkeratosis	0	0	5* (1.0)	10** (1.2)	10** (1.3)	10** (1.6)
Epidermis, Inflammation, Suppurative	0	0	0	0	0	4* (1.5)
Sebaceous Gland, Hyperplasia	0	0	5* (1.0)	10** (1.2)	10** (1.5)	10** (2.6)
Female						
Number Examined						
Microscopically	10	10	10	10	10	10
Epidermis, Hyperplasia	0	0	0	7** (1.0)	10** (1.1)	10** (1.4)
Epidermis, Degeneration	0	0	0	4* (1.0)	7** (1.0)	10** (2.0)
Epidermis, Necrosis	0	0	0	0	0	5* (2.0)
Dermis, Inflammation, Chronic Active	1 (1.0)	2 (1.0)	1 (1.0)	9** (1.0)	8** (1.0)	10** (1.8)
Hyperkeratosis	0	0	3 (1.0)	9** (1.0)	10** (1.1)	10** (2.0)
Epidermis, Inflammation, Suppurative	0	0	0	0	0	6** (1.3)
Sebaceous Gland, Hyperplasia	0	1 (1.0)	6** (1.0)	9** (1.1)	10** (1.3)	10** (2.1)

* Significantly different ($P \leq 0.05$) from the vehicle control group by the Fisher exact test
** $P \leq 0.01$
[a] NTP, 2005a
[b] Number of animals with lesion
[c] Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked

TABLE 2
Incidences of Selected Nonneoplastic Lesions of the Skin (Site of Application) in B6C3F$_1$ Mice in the 3-Month Dermal Study of Trimethylolpropane Triacrylate[a]

	Vehicle Control	0.75 mg/kg	1.5 mg/kg	3 mg/kg	6 mg/kg	12 mg/kg
Male						
Number Examined Microscopically	10	10	10	10	10	10
Epidermis, Hyperplasia[b]	0	0	3 (1.0)[c]	10** (1.0)	10** (1.4)	10** (2.2)
Epidermis, Degeneration	0	0	0	4* (1.0)	8** (1.0)	9** (1.8)
Epidermis, Necrosis	0	0	1 (1.0)	1 (1.0)	2 (1.5)	7** (2.1)
Dermis, Inflammation, Chronic Active	1 (1.0)	0	2 (1.0)	10** (1.1)	9** (1.4)	10** (1.8)
Hyperkeratosis	0	0	3 (1.0)	8** (1.0)	8** (1.0)	10** (1.4)
Epidermis, Inflammation, Suppurative	0	0	1 (1.0)	0	1 (1.0)	8** (1.6)
Dermis, Fibrosis	0	0	0	0	0	7** (1.1)
Sebaceous Gland, Hyperplasia	0	0	0	9** (1.0)	10** (1.7)	10** (2.3)
Female						
Number Examined Microscopically	10	10	10	10	10	10
Epidermis, Hyperplasia	0	0	3 (1.0)	10** (1.0)	9** (1.1)	10** (1.3)
Epidermis, Degeneration	0	0	0	0	5* (1.0)	9** (1.6)
Epidermis, Necrosis	0	0	0	1 (1.0)	2 (2.0)	8** (2.0)
Dermis, Inflammation, Chronic Active	0	0	7** (1.0)	10** (1.1)	10** (2.0)	10** (1.8)
Hyperkeratosis	0	0	3 (1.0)	10** (1.0)	9** (1.0)	8** (1.1)
Epidermis, Inflammation, Suppurative	0	0	1 (1.0)	1 (1.0)	2 (1.5)	5* (1.4)
Dermis, Fibrosis	0	0	0	0	1 (1.0)	7** (1.6)
Sebaceous Gland, Hyperplasia	0	0	1 (1.0)	10** (1.0)	10** (2.0)	10** (2.3)

* Significantly different ($P \leq 0.05$) from the vehicle control group by the Fisher exact test
** $P \leq 0.01$
[a] NTP, 2005a
[b] Number of animals with lesion
[c] Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked

Tg.AC hemizygous mice were treated topically with up to 12 mg/kg trimethylolpropane triacrylate in acetone 5 days per week for 28 weeks (NTP, 2005a). Survival and mean body weights of dosed groups were similar to those of the vehicle controls throughout the study. Nonneoplastic effects at the site of application were epidermal hyperplasia, hyperkeratosis, and chronic active inflammation (Table 3). Papillomas were formed at the site of application in males and females receiving 3 mg/kg or greater of trimethylolpropane triacrylate. Squamous cell carcinomas were also formed in one female in each group receiving 1.5, 6, or 12 mg/kg trimethylolpropane triacrylate. In females receiving 12 mg/kg, the incidence of squamous cell papilloma in the forestomach was significantly higher compared to the vehicle control incidence.

TABLE 3
Incidences of Neoplasms and Nonneoplastic Lesions of the Skin (Site of Application) in Tg.AC Hemizygous Mice in the 6-Month Dermal Study of Trimethylolpropane Triacrylate[a]

	Vehicle Control	0.75 mg/kg	1.5 mg/kg	3 mg/kg	6 mg/kg	12 mg/kg
Male						
Number Examined						
Microscopically	15	15	15	15	15	15
Epidermis, Hyperplasia[b]	0	0	0	6** (1.0)[c]	14** (1.7)	15** (1.9)
Hyperkeratosis	0	0	1 (2.0)	15** (1.0)	14** (1.1)	12** (1.7)
Inflammation, Chronic Active	0	0	1 (1.0)	1 (1.0)	9** (1.1)	12** (1.3)
Squamous Cell Papilloma, Multiple	0	0	0	0	12**	13**
Squamous Cell Papilloma (includes multiple)						
Overall rate[d]	0/15 (0%)	0/15 (0%)	0/15 (0%)	2/15 (13%)	12/15 (80%)	13/15 (87%)
Adjusted rate[e]	0.0%	0.0%	0.0%	14.0%	85.1%	86.7%
Terminal rate[f]	0/14 (0%)	0/15 (0%)	0/12 (0%)	2/14 (14%)	11/13 (85%)	9/14 (82%)
First incidence (days)	—[h]	—	—	192 (T)	180	161
Poly-3 test[g]	P<0.001	—[i]	—	P=0.234	P<0.001	P<0.001
Female						
Number Examined						
Microscopically	15	15	15	15	15	15
Epidermis, Hyperplasia	0	0	1 (2.0)	4* (1.0)	15** (1.2)	15** (2.0)
Hyperkeratosis	0	0	1 (1.0)	7** (1.0)	14** (1.1)	13** (1.6)
Inflammation, Chronic Active	0	0	0	3 (1.0)	14** (1.0)	12** (1.3)
Squamous Cell Papilloma, Multiple	0	0	0	0	5*	15**
Squamous Cell Papilloma (includes multiple)						
Overall rate	0/15 (0%)	0/15 (0%)	0/15 (0%)	1/15 (7%)	11/15 (73%)	15/15 (100%)
Adjusted rate	0.0%	0.0%	0.0%	7.0%	73.3%	100%
Terminal rate	0/15 (0%)	0/14 (0%)	0/12 (0%)	1/14	10/14 (71%)	12/12 (82%)
First incidence (days)	—	—	—	193 (T)	162	161
Poly-3 test	P<0.001	—	—	P=0.234	P<0.001	P<0.001
Squamous Cell Carcinoma	0	0	1	0	1	1

(T) Terminal kill
* Significantly different (P≤0.05) from the vehicle control group by the Poly-3 test
** P≤0.01
[a] NTP, 2005a
[b] Number of animals with lesion
[c] Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked ted
[d] Number of neoplasm-bearing animals/number of animals with skin examined microscopically
[e] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[f] Observed incidence at terminal kill
[g] Beneath the vehicle control incidence is the P value associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the vehicle controls and that dosed group. The Poly-3 test accounts for the differential mortality in animals that do not reach terminal kill.
[h] Not applicable; no neoplasms in animal group
[i] Value of statistic cannot be computed.

Humans

A number of studies have reported the development of dermatitis, characterized by itching of the exposed skin followed by erythema and scaling upon prolonged exposure, after workplace exposure to compounds containing trimethylolpropane triacrylate. In many cases of exposure to industrial mixtures of acrylates, individuals displayed positive reactions to two or more acrylates, making it difficult to establish the potency of trimethylolpropane triacrylate alone (Anonymous, 1985). Irritant or allergic contact dermatitis and irritant contact conjunctivitis occurred in 15 of 19 workers who cured multifunctional acrylic monomers in ultraviolet-curable inks (Nethercott, 1978). Three workers did not have direct contact with the acrylic monomers and were apparently exposed to airborne vapors. Two workers with allergic contact dermatitis had positive vesicular skin reactions to a 48-hour skin patch test with 0.1% trimethylolpropane triacrylate.

After trimethylolpropane triacrylate and pentaerythritol triacrylate were introduced as components of radiation drying ink in an ink formulating facility, five of 26 workers developed eczematous dermatitis (Emmett, 1977). Four of the five affected workers had positive reactions to patch tests using 0.2% trimethylolpropane triacrylate in a varnish formulation or in solution in petrolatum; the fifth worker developed irritant dermatitis to undiluted polyfunctional acrylates. Björkner *et al.* (1980) reported the development of allergic dermatitis in six people who worked with ultraviolet-curable inks containing trimethylolpropane triacrylate for 3 to 32 weeks. All six had positive reactions to skin patch tests with 0.1% or 0.5% trimethylolpropane triacrylate in acetone. Seven of 10 workers exposed to ultraviolet-curable printing inks at a plastic food container manufacturing plant developed contact dermatitis; one person had a positive reaction for sensitization to 0.1% trimethylolpropane triacrylate in petrolatum (Nethercott *et al.*, 1983).

Four workers in a plastic floor manufacturing facility developed hand and face dermatitis a year after the introduction of a varnish with an aziridine-based hardener containing 3% to 5% trimethylolpropane triacrylate (Dahlquist *et al.*, 1983). The workers had positive reactions to skin patch tests with trimethylolpropane triacrylate in acetone at 0.0001% (1/4), 0.03% (3/4), and 0.1% (4/4), with the most severe reactions occurring in the worker who reacted to the 0.0001% formulation. Contact dermatitis occurred in 13 of 51 workers at a wallpaper printing company following the introduction of a water-based ink containing a polyfunctional aziridine hardening agent, of

which trimethylolpropane triacrylate was a component (Garabrant, 1985). A worker in optical fiber manufacturing developed dermatitis of the hands, face, and eyelids after 2 years of exposure to ultraviolet-curing acrylate resin coatings containing trimethylolpropane triacrylate and urethane acrylate; the dermatitis cleared within a week after the exposure ended (Maurice and Rycroft, 1986). This worker had positive reactions to 2- and 4-day skin patch tests with 0.01% (2-day test only) and 0.1% trimethylolpropane triacrylate in petrolatum.

Cofield *et al.* (1985) reported that five of 44 patients administered a skin patch test with 0.5% trimethylolpropane triacrylate in petrolatum demonstrated irritant reactions that diminished after 1 week; concentrations of 0.001% to 0.19% induced no reactions. A group of 50 patients had no reaction to a skin patch test of a crosslinking agent (containing trimethylolpropane triacrylate and aziridine) at a concentration of 0.1% in petrolatum.

Skin sensitivity and photo patch testing of 0.2% trimethylolpropane triacrylate in petrolatum was performed on 47 employees of a citrus juice bottling plant who were exposed to ultraviolet-cured printing inks (NIOSH, 1987). All 47 workers had positive reactions to one or both tests. Because few workers showed skin sensitization to trimethylolpropane triacrylate, the past skin reactions were considered to be irritant, not allergic, reactions to the inks and their components.

A small number of case reports of allergic conjunctivitis (Kanerva *et al*., 1998; Mancuso and Berdondini, 2008), and asthma (Sánchez-Garcia *et al*., 2009) due to occupational exposure to trimethylolpropane triacrylate have been noted for individuals exposed while working with UV-cured paints and inks. A 28-year-old man developed conjunctivitis starting 1 month after using UV-cured paint (Mancuso and Berdondini, 2008). He had a positive patch test result with 0.001% trimethylolpropane triacrylate. A 51-year-old woman monitoring a laminating machine that used photosensitive resist containing 0.08% trimethylolpropane triacrylate in a small room developed conjunctivitis (Kanerva *et al*., 1998). She had a positive patch test against 0.1% trimethylolpropane triacrylate. A 62-year-old woman who worked in a small, confined space while using a thermal printer developed asthma (Sánchez-Garcia *et al.,* 2009). All of these individuals became asymptomatic when exposure to the compounds containing trimethylolpropane triacrylate ceased.

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

No data on the reproductive or teratogenic effects of trimethylolpropane triacrylate in experimental animals or humans were found in the literature.

CARCINOGENICITY

Experimental Animals

No neoplasms occurred in 50 male C3H/HeJ mice dermally administered 100 mg/kg of a solution of 5% trimethylolpropane triacrylate in mineral oil to the interscapular region twice per week for up to 80 weeks (Andrews and Clary, 1986). Ten percent of the group was examined histologically. Slight epilation of the skin was noted at the site of application; in addition, acanthosis of the epidermis occurred in 46 mice and fibrosis of the dermis in 38 mice. No lesions were noted in control mice.

Humans

No epidemiology studies or case reports associating trimethylolpropane triacrylate exposure with cancer risk in humans were found in the literature.

RELATED COMPOUNDS

In a series of studies of eight multifunctional alkyl acrylates performed by Celanese Corporation, Inc., groups of 50 male C3H/HeJ mice were given dermal applications twice weekly for up to 80 weeks (Andrews and Clary 1986). No increases in the incidences of skin or visceral tumors were induced by trimethylolpropane trimethacrylate, 1,6-hexanediol diacrylate, tripropyleneglycol diacrylate; or triethyleneglycol dimethacrylate. However, pentaerythritol triacrylate, triethyleneglycol diacrylate, and tetraethyleneglycol diacrylate showed some potential for carcinogenicity when administered at doses of 100 mg/kg in mineral oil. Pentaerythritol triacrylate induced lymphoma with spleen or lymph node involvement in six mice. However, these lesions were not verified in subsequent examinations. Triethyleneglycol diacrylate induced skin tumors in six mice and lymphomas in four mice; tetraethyleneglycol diacrylate induced skin tumors in six mice. However, in 78-week dermal carcinogenicity

studies, neither triethyleneglycol diacrylate (0.05%, 0.1%, or 0.5% in acetone) nor triethyleneglycol dimethacrylate (5%, 25%, or 50% in acetone) were carcinogenic in male C3H/HeNHsd mice (Van Miller *et al.*, 2003).

In another study, groups of 40 male C3H/HeJ mice were given dermal applications of 5 mg (approximately 200 mg/kg) neopentylglycol diacrylate or 3 mg (approximately 120 mg/kg) pentaerythritol triacrylate in acetone three times weekly for the lifetime of the animals (DePass *et al.*, 1995). Among mice administered neopentylglycol diacrylate, five had skin papilloma and three had skin carcinoma. No skin neoplasms were observed in pentaerythritol triacrylate-treated mice.

Tg.AC hemizygous mice were treated topically with doses of 0, 0.75, 1.3, 6, or 12 mg/kg pentaerythritol triacrylate in acetone 5 days per week for 27 weeks (NTP, 2005b). Survival of all dosed groups of mice was similar to that of the vehicle controls. With the exception of the 3 mg/kg group, body weights of male mice were less than those of the vehicle controls during the last 3 to 6 weeks of the study. Females administered 3 mg/kg had generally reduced body weights during the last month of the study. At 6 months, all 3 and 6 mg/kg males had squamous cell papilloma at the site of application, and the incidences of this neoplasm were significantly increased in males and females receiving 3 mg/kg or more. Squamous cell carcinomas at the site of application occurred in two 3 mg/kg males, three 12 mg/kg males, and one 12 mg/kg female.

GENETIC TOXICITY

The results from genotoxicity assays with trimethylolpropane triacrylate are mixed. Gene mutation studies generally yielded negative results while results from *in vitro* tests for induction of chromosomal damage were positive. In contrast with the *in vitro* test results, no evidence of chromosomal damage induced by trimethylolpropane triacrylate in rodent models *in vivo* has been reported.

Trimethylolpropane triacrylate monomer (79% pure) demonstrated weak mutagenic activity in *Salmonella typhimurium* strain TA1535 when testing occurred in the presence of hamster liver S9 activation enzymes (Cameron *et al*., 1991); negative results were obtained with other strains, with and without induced rat or hamster

liver S9 enzymes. Tests conducted with the cross-linked polymer (molecular weights that ranged up to 1,000,000), using concentrations up to 6,666 µg/plate, showed no mutagenic activity in any of several strains of *S. typhimurium*, with or without exogenous metabolic activation derived from induced rat liver (Thompson *et al*., 1991).

Trimethylolpropane triacrylate monomer, at doses of 0.6, 0.65, and 0.7 µg/mL, was tested in mouse lymphoma L5178Y $tk^{+/-}$ cells, in the absence of exogenous metabolic activation, for induction of forward mutations at the tk locus, and induction of chromosomal aberrations and micronuclei (Dearfield *et al*., 1989). Significant dose-related increases were observed for all three endpoints; mutant tk colonies were almost exclusively small in size, indicative of the induction of large deletions or other chromosomal alterations rather than point mutations. Further supporting a clastogenic mechanism for the mutagenicity of trimethylolpropane triacrylate are the results reported by Moore *et al*. (1989), who conducted comparative studies with the $tk^{+/-}$ locus in L5178Y cells and the hemizygous HGPRT locus in Chinese hamster ovary (CHO) cells as targets. Although significant increases in mutant tk small colonies were observed in the L5178Y cells, no increase in the frequency of HGPRT mutant CHO cells was seen. The authors suggested that the hemizygous nature of the HGPRT locus renders it insensitive to the action of clastogens. Results reported by Cameron *et al*. (1991) confirmed the positive results with the trimethylolpropane triacrylate monomer in mutagenicity tests using L5178Y mouse lymphoma cells without S9 activation. The trimethylolpropane triacrylate cross-linked polymer was also tested in mouse lymphoma L5178Y cells for induction of mutations in the presence and the absence of exogenous metabolic activation, and results were negative over a range of concentrations up to 1,392 µg/mL (Thompson *et al*., 1991). Additional tests with the trimethylolpropane triacrylate cross-linked polymer that were part of the comprehensive investigation of Thompson *et al.* (1991) showed no induction of unscheduled DNA synthesis in rat primary hepatocyte cultures and no increase in the incidence of chromosomal aberrations in bone marrow of male or female rats administered the trimethylolpropane triacrylate cross-linked polymer as slurries by oral gavage in amounts up to 16 mL/kg. The trimethylolpropane triacrylate monomer was positive in tests for chromosomal aberration induction in CHO cells and in mouse lymphoma L5178Y $tk^{+/-}$ cells, producing dose-related increases in aberrations in both systems over dose ranges that reached 0.7 µg/mL (Moore *et al*., 1989).

No increase in the frequency of micronucleated normochromatic erythrocytes (NCEs) was observed in peripheral blood samples from male or female mice administered dermal applications of 0.75 to 12 mg trimethylolpropane triacrylate/kg body weight for 3 or 6 months (NTP, 2005a). In the 3-month study, ratios of micronucleated polychromatic erythrocytes (PCEs) to NCEs in peripheral blood were unaltered by chemical treatment, indicating an absence of induced bone marrow toxicity. However, in the 6-month study, increases in the percentage of PCEs were noted in 12 mg/kg male and female mice, indicating a stimulation of erythropoiesis and the presence of increased numbers of immature erythrocytes in circulating blood.

STUDY RATIONALE

Trimethylolpropane triacrylate was nominated by the National Cancer Institute for study due to its high production volume and use, the potential for human exposure, and the lack of adequate chronic toxicity and carcinogenicity data. It was also chosen as a representative of the multifunctional acrylate class. Trimethylolpropane triacrylate is a suspected carcinogen as a member of this class of compounds; some members of this class have been shown to be carcinogenic to mice in dermal studies. Trimethylolpropane triacrylate was studied in the Tg.AC hemizygous mouse model by the NTP and was found to be positive for carcinogenic activity, but the Tg.AC hemizygous mouse model was not accepted by the NTP Board of Scientific Counselors as an alternative test system for evaluation of potential carcinogenic activity (NTP, 2005a). Therefore, the NTP decided to perform the 2-year carcinogenicity studies in rats and mice that are reported here.

MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION

Trimethylolpropane Triacrylate

Trimethylolpropane triacrylate was obtained from Aldrich Chemical Company (Milwaukee, WI) in one lot (08409HI) which was used for the 2-year studies. Identity and purity analyses were conducted by the analytical chemistry laboratory at Battelle Columbus Laboratories (Columbus, OH) and by the study laboratory at Southern Research Institute (Birmingham, AL); Karl Fischer titration and elemental analysis were performed by Prevalere Life Sciences, Inc. (Whitesboro, NY) (Appendix F). Reports on analyses performed in support of the trimethylolpropane triacrylate studies are on file at the National Institute of Environmental Health Sciences.

The chemical, a colorless to yellow viscous liquid, was identified as trimethylolpropane triacrylate by the analytical chemistry laboratory using infrared, and proton and carbon-13 nuclear magnetic resonance spectroscopy, and was confirmed by the study laboratory using infrared spectroscopy. The purity was determined by the analytical chemistry laboratory using gas chromatography (GC) with flame ionization detection (FID) and high-performance liquid chromatography (HPLC) with ultraviolet detection. Karl Fischer titration indicated an average water content of 0.10%; elemental analyses for carbon and hydrogen were in agreement with the theoretical values for trimethylolpropane triacrylate. GC analysis indicated one major peak consisting of 87.4% of the total peak area and five impurities, each 0.1% or greater of the total peak area (0.1%, 0.1%, 9.9%, 0.2%, and 2.3%). HPLC/UV analysis indicated one major peak (78.2%) and four impurities, each greater than 0.1% of the total peak area. Three of the four impurities were tentatively identified as structurally related compounds (trimethylolpropane diacrylate, trimethylolpropane triacrylate-trimethylolpropane monocrylate adduct, and trimethylolpropane triacrylate-trimethylolpropane diacrylate adduct); the fourth impurity was not identified. HPLC/MS analysis indicated that all impurities appear to be consistent with trimethylolpropane triacrylate adducts and that neither hydroquinone nor methyl hydroquinone was detected above 0.1% of the total peak area in the bulk chemical. HPLC/MS analysis of

impurities indicated that they were chiefly acrylic acid esters and adducts. The overall purity of lot 08409HI was determined to be greater than 78%.

To ensure stability, the bulk chemical was stored at room temperature protected from light in amber glass containers sealed with Teflon®-lined lids. Periodic reanalyses of the bulk chemical were performed at least every 6 months by the study laboratory using GC/FID, and no degradation of the bulk chemical was detected.

Acetone

Acetone was obtained from Sigma-Aldrich, Inc. (Milwaukee, WI), in two lots (00557CC and 01039LD) for use during the 2-year studies. The chemical, a clear liquid, was identified as acetone by the study laboratory using infrared spectroscopy. The purity of each lot was determined using GC/FID; no impurities were detected that exceeded a relative concentration of 0.1% of the total peak area in either lot.

PREPARATION AND ANALYSIS OF DOSE FORMULATIONS

The dose formulations were prepared approximately every 4 weeks by mixing trimethylolpropane triacrylate with acetone (Table F3). Stability studies of 50 and 400 µg/mL formulations were performed by the analytical chemistry laboratory using GC/FID. Stability was confirmed for up to 35 days for formulations stored in amber glass containers sealed with Teflon®-lined lids at temperatures up to room temperature and for up to 3 hours under simulated animal room conditions, with the condition that animal room samples be covered with a watch glass between dosing to prevent evaporation of the acetone. During the study, fresh bottles of dose formulations were provided each day for each concentration for both rats and mice.

Periodic analyses of the dose formulations of trimethylolpropane triacrylate were conducted by the study laboratory using GC/FID. Dose formulations were analyzed approximately every 3 months during the 2-year studies; animal room samples were also analyzed. Of the dose formulations analyzed and used for rats, all 35 were within 10% of the target concentrations; two of 12 animal room samples were within 10% of the target concentrations (Table F4). Of the dose formulations analyzed and used for mice, all 37 were within 10% of the target concentrations; eight of

15 animal room samples were within 10% of the target concentrations (Table F4). The animal room sample concentrations were generally high due to the evaporation of acetone during dosing.

2-YEAR STUDIES

Study Design

In the 2-week and 3-month dermal toxicity studies (NTP, 2005a), the skin was the only target organ identified for trimethylolpropane triacrylate. Therefore, the dose levels for the trimethylolpropane triacrylate 2-year studies were selected based on the severity of the skin lesions. Doses were selected, as is routine for NTP dermal studies, to avoid significant skin irritation, and to preclude adverse effects on survival and growth of animals. Based upon the histologic data from the 3-month studies, 3 mg/kg was considered the likely maximum tolerated dose and an acceptable high dose for the 2-year toxicity and carcinogenicity studies. Thus, the doses selected for both rats and mice were 0, 0.3, 1.0, and 3.0 mg trimethylolpropane triacrylate/kg body weight in acetone.

Groups of 65 male and 65 female rats and mice received dermal applications of 0, 0.3, 1.0, or 3.0 mg/kg, 5 days per week for up to 104 to 105 (rats) or 105 to 106 (mice) weeks. All doses were administered in acetone at volumes of 0.5 mL/kg for rats and 2.0 mL/kg for mice. The single daily doses were applied to a clipped area in the interscapular region of the back, using a positive displacement micropipetter. At 2 weeks, 13 weeks, and 12 months, five rats and mice per sex per dose group were randomly selected for histologic examination of skin tissue.

Source and Specification of Animals

Male and female F344/N rats and B6C3F1/N mice were obtained from Taconic Farms, Inc. (Germantown, NY), for use in the 2-year studies. Rats were quarantined for 13 days and mice were quarantined for 12 days before the beginning of the studies. Two male rats, five female rats, and five male and five female mice were randomly selected for parasite evaluation and gross observation of disease. Rats were approximately 6 weeks old and mice approximately 5 to 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 H).

Animal Maintenance

All animal studies were conducted in an animal facility accredited by the association for the Assessment and Accreditation of Laboratory Animal Care International. Studies were approved by the Southern Research Institute Animal Care and Use Committee and conducted in accordance with all relevant NTP animal care and use policies and applicable federal, state, and local regulations and guidelines. Rats and mice were housed individually. Feed and water were available *ad libitum*. Cages and racks were changed weekly and rotated every 2 weeks. Further details of animal maintenance are given in Table 4. Information on feed composition and contaminants is provided in Appendix G.

Clinical Examinations and Pathology

All animals were observed twice daily. Body weights were recorded initially, approximately weekly for the first 13 weeks, at 4-week intervals thereafter, and at study termination. Clinical findings were recorded on day 4 for male mice and day 5 for female mice and at 4-week intervals beginning week 5 for all animals.

At 2 weeks, 13 weeks, and 12 months, skin from the site of application was collected from interim evaluation animals, fixed in formalin, and examined microscopically. Complete necropsies and microscopic examinations were performed on all core study animals. At necropsy, all organs and tissues were examined for grossly visible lesions, and all major tissues were fixed and preserved in 10% neutral buffered formalin, processed and trimmed, embedded in paraffin, sectioned to a thickness of 4 to 6 µm, and stained with hematoxylin and eosin for microscopic examination. For all paired organs (e.g., adrenal gland, kidney, ovary), samples from each organ were examined. Tissues examined microscopically are listed in Table 4.

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

assessment pathologist evaluated slides from all tumors and all potential target organs, which included the skin of all animals; the mesentery, pituitary gland, and nose of male rats; the liver of mice; the heart and adrenal gland of male mice; and the uterus of female mice.

The quality assessment report and the reviewed slides were submitted to the NTP Pathology Working Group (PWG) coordinator, 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 coordinator 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. 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 4
Experimental Design and Materials and Methods in the 2-Year Dermal Studies of Trimethylolpropane Triacrylate

Study Laboratory
Southern Research Institute (Birmingham, AL)

Strain and Species
F344/N rats
B6C3F1/N mice

Animal Source
Taconic Farms, Inc. (Germantown, NY)

Time Held Before Studies
Rats: 13 days
Mice: 12 days

Average Age When Studies Began
Rats: 6 weeks
Mice: 5 to 6 weeks

Date of First Dose
Rats: January 18, 2005
Mice: December 13, 2004

Duration of Dosing
Rats: 5 days per week for 2 weeks, 13 weeks, or 12 months (interim evaluations) or 104 to 105 weeks
Mice: 5 days per week for 2 weeks, 13 weeks, or 12 months (interim evaluations) or 105 to 106 weeks

Date of Last Dose
Rats: January 15 to 21, 2007
Mice: December 10 to 18, 2006

Necropsy Dates
Rats: January 16 to 22, 2007
Mice: December 11 to 19, 2006

Average Age at Necropsy
Rats: 110-111 weeks
Mice: 109-111 weeks

Size of Study Groups
65 males and 65 females

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

Animals per Cage
1

Method of Animal Identification
Tail tattoo

Diet
Irradiated NTP-2000 open formula wafers (Zeigler Brothers, Inc., Gardners, PA), available *ad libitum*

Water
Tap water (Birmingham, AL, municipal supply) via automatic watering system (Edstrom Industries, Inc., Waterford, WI), available *ad libitum*

Cages
Solid-bottom polycarbonate (Lab Products, Inc. Maywood, NJ), changed weekly

TABLE 4
Experimental Design and Materials and Methods in the 2-Year Dermal Studies of Trimethylolpropane Triacrylate

Bedding
Heat-treated, irradiated hardwood chips (P.J. Murphy Forest Products, Inc., Montville, NJ), changed once weekly

Cage Filters
Remay® spun-bonded polyester (Andico, Birmingham, AL), changed weekly

Racks
Stainless steel (Lab Products, Maywood, NJ), cleaned weekly and rotated every 2 weeks

Animal Room Environment
Temperature: 72° ± 3° F
Relative humidity: 50% ± 15%
Room fluorescent light: 12 hours/day
Room air changes: 10/hour

Doses
0, 0.3, 1.0, or 3.0 mg/kg in acetone (dosing volume 0.5 mL/kg for rats and 2.0 mL/kg for mice)

Type and Frequency of Observation
Observed twice daily. Animals were weighed initially, approximately weekly for 13 weeks, monthly thereafter, and at the end of the studies. Clinical findings were recorded on day 4 (male mice), day 5 (female mice), and at 4-week intervals beginning week 5.

Method of Kill
Carbon dioxide asphyxiation

Necropsy
Necropsies were performed on all core study animals.

Histopathology
Complete histopathology was performed on all core study rats and mice. In addition to gross lesions and tissue masses, the following tissues were examined: adrenal gland, bone, brain, clitoral gland, esophagus, eyes, gallbladder (mice), Harderian gland, heart and aorta, large intestine (cecum, colon, rectum), small intestine (duodenum, jejunum, ileum), kidney, liver, lung and mainstem bronchi, lymph nodes (mandibular and mesenteric), mammary gland, nose, ovary, pancreas, parathyroid gland, pituitary gland, preputial gland, prostate gland, salivary gland, skin (site of application and control site), spleen, stomach (forestomach and glandular), testis with epididymis and seminal vesicle, thymus, thyroid gland, trachea, urinary bladder, and uterus. At 2 weeks, 13 weeks, and 12 months, groups of 5 male and 5 female rats and mice per dose group were evaluated for histological changes of the skin from the site of application.

STATISTICAL METHODS

Survival Analyses

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

Calculation of Incidence

The incidences of neoplasms or nonneoplastic lesions are presented in Tables A1, A4, B1, B3, C1, C3, D1, and D4 as the numbers of animals bearing such lesions at a specific anatomic site and the numbers of animals with that site examined microscopically. For calculation of statistical significance, the incidences of most neoplasms (Tables A2, B2, C2, and D2) 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., mesentery, pleura, peripheral nerve, skeletal muscle, tongue, tooth, and Zymbal's gland) before microscopic evaluation, the denominators consist of the number of animals that had a gross abnormality. 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 A2, B2, C2, and D2 also give the survival-adjusted neoplasm rate for each group and each site-specific neoplasm. This survival-adjusted rate (based on the Poly-3 method described below) accounts for differential mortality by assigning a reduced risk of neoplasm, proportional to the third power of the fraction of time on study, only to site-specific, lesion-free animals that do not reach terminal kill.

Analysis of Neoplasm and Nonneoplastic Lesion Incidences

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

This method yields a lesion prevalence rate that depends only upon the choice of a shape parameter for a Weibull hazard function describing cumulative lesion incidence over time (Bailer and Portier, 1988). Unless otherwise specified, a value of k=3 was used in the analysis of site-specific lesions. This value was recommended by Bailer and Portier (1988) following an evaluation of neoplasm onset time distributions for a variety of site-specific

neoplasms in control F344 rats and B6C3F1 mice (Portier *et al.*, 1986). Bailer and Portier (1988) showed that the Poly-3 test gave valid results if the true value of k was anywhere in the range from 1 to 5. A further advantage of the Poly-3 method is that it does not require lesion lethality assumptions. Variation introduced by the use of risk weights, which reflect differential mortality, was accommodated by adjusting the variance of the Poly-3 statistic as recommended by Bieler and Williams (1993).

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

Historical Control Data

The concurrent control group represents the most valid comparison to the treated groups and is the only control group analyzed statistically in NTP bioassays. However, historical control data are often helpful in interpreting potential treatment-related effects, particularly for uncommon or rare neoplasm types. For meaningful comparisons, the conditions for studies in the historical database must be generally similar. One significant factor affecting the background incidence of neoplasms at a variety of sites is diet. In 1995, the NTP incorporated a new diet (NTP-2000) that contains less protein and more fiber and fat than the NIH-07 diet previously used in toxicity and carcinogenicity studies (Rao, 1996, 1997). The NTP historical database contains all studies that use the NTP-2000 diet with histopathology findings completed within the most recent 5-year period. A second potential source of variability is route of administration. In general, the historical database for a given study will include studies using the same route of administration, and the overall incidences of neoplasms for all routes of administration are included for comparison. For the current study, the incidences for dermal studies with all vehicles were combined because the historical database does not include any other dermal studies with acetone as the vehicle; these incidences and the overall incidences for all routes of administration were used for comparison.

QUALITY ASSURANCE METHODS

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

GENETIC TOXICOLOGY

The genetic toxicity of trimethylolpropane triacrylate was assessed by testing the ability of the chemical to induce mutations in various strains of *Salmonella typhimurium* and *Escherichia coli* strain WP2 *uvrA*/pKM101. The protocol for these studies and the results are given in Appendix E.

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

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

tests can provide useful information on the types of DNA and chromosomal damage induced by the chemical under investigation.

RESULTS

2-YEAR RAT STUDY

Survival

Estimates of 2-year survival probabilities for male and female rats are shown in Table 5 and in the Kaplan-Meier survival curves (Figure 1). Survival of all dosed groups was similar to that of the vehicle control groups.

TABLE 5
Survival of Rats in the 2-Year Dermal Study of Trimethylolpropane Triacrylate

	Vehicle Control	0.3 mg/kg	1.0 mg/kg	3.0 mg/kg
Male				
Animals initially in study	65	65	65	65
2-Week interim evaluation[a]	5	5	5	5
13-Week interim evaluation[a]	5	5	5	5
12-Month interim evaluation[a]	5	5	5	5
Accidental death[a]	0	1	0	0
Moribund	19	24	19	16
Natural deaths	8	7	3	11
Animals surviving to study termination	23	18	28	23
Percent probability of survival at end of study[b]	46	37	56	46
Mean survival (days)[c]	560	512	552	550
Survival analysis[d]	P=0.626N	P=0.161	P=0.581N	P=1.000
Female				
Animals initially in study	65	65	65	65
2-Week interim evaluation[a]	5	5	5	5
13-Week interim evaluation[a]	5	5	5	5
12-Month interim evaluation[a]	5	5	5	5
Moribund	10	12	17	10
Natural deaths	13	7	9	8
Animals surviving to study termination	27	31	24[e]	32
Percent probability of survival at end of study	54	62	48	64
Mean survival (days)	565	576	546	556
Survival analysis	P=0.603N	P=0.394N	P=0.559	P=0.485N

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

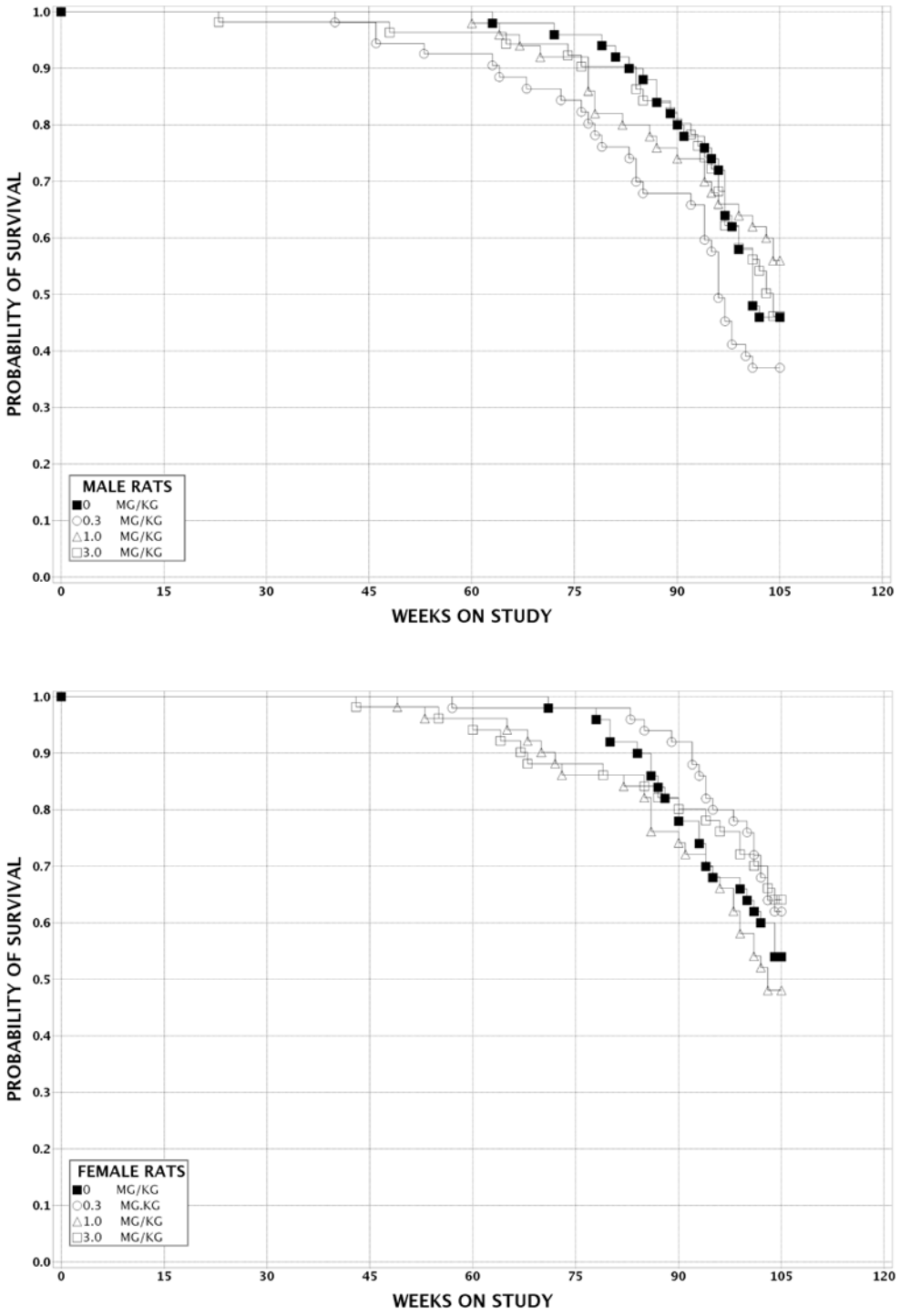


FIGURE 1
Kaplan-Meier Survival Curves for Rats
Administered Trimethylolpropane Triacrylate Dermally for 2 Years

Body Weights and Clinical Findings

Mean body weights of all dosed groups of male and female rats were within 10% of those of the vehicle control groups throughout the study (Tables 6 and 7; Figure 2). No chemical-related clinical findings were observed.

TABLE 6
Mean Body Weights and Survival of Male Rats in the 2-Year Dermal Study of Trimethylolpropane Triacrylate

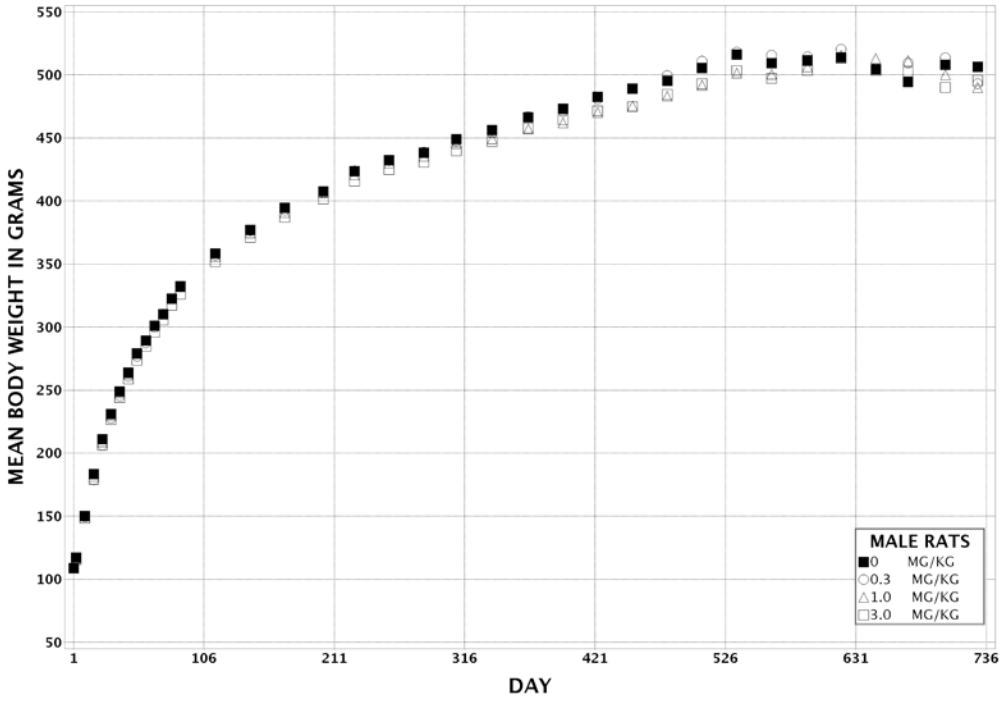
	Vehicle Control		0.3 mg/kg			1.0 mg/kg			3.0 mg/kg		
Day	Av. Wt. (g)	No. of Survivors	Av. Wt (g)	Wt. (% of Controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of Controls)	No. of Survivors	Av. Wt (g)	Wt. (% of Controls)	No. of Survivors
1	109	65	109	100	65	109	100	65	109	100	65
3	117	65	116	99	65	117	100	65	116	99	65
10	150	65	150	100	65	150	100	65	149	99	65
17[a]	184	60	179	97	60	182	99	60	179	98	60
24	211	60	206	98	60	209	99	60	206	98	60
31	231	60	228	99	60	230	100	60	227	98	60
38	249	60	245	99	60	248	100	60	244	98	60
45	264	60	261	99	60	263	100	60	259	98	60
52	279	60	277	99	60	279	100	60	274	98	60
59	290	60	288	99	60	290	100	60	285	98	60
66	301	60	300	100	60	302	100	60	296	98	60
73	310	60	310	100	60	311	100	60	306	99	60
80	323	60	323	100	60	323	100	60	318	98	60
87	332	60	332	100	60	332	100	60	326	98	60
115[a]	358	55	357	100	55	356	99	55	352	98	55
143	377	55	377	100	54	375	99	55	371	99	55
171	395	55	393	100	54	391	99	55	387	98	54
202	408	55	407	100	54	407	100	55	402	99	54
227	424	55	424	100	54	421	99	55	416	98	54
255	433	55	432	100	54	430	99	55	425	98	54
283	438	55	439	100	53	435	99	55	431	98	54
309	449	55	447	100	53	446	99	55	440	98	54
338	456	55	454	100	51	450	99	55	447	98	53
367[a]	466	50	467	100	45	457	98	50	458	98	48
395	473	50	471	100	45	462	98	50	464	98	48
423	483	50	481	100	45	470	97	49	471	98	48
451	489	49	489	100	43	476	97	48	475	97	48
479	496	49	500	101	42	483	98	47	485	98	47
507	506	48	511	101	42	492	97	46	493	98	47
535	516	48	518	100	39	502	97	44	504	98	45
563	509	47	516	101	37	501	98	41	497	98	45
592	512	44	515	101	33	506	99	40	503	98	42
619	514	42	521	101	33	516	100	38	513	100	41
647	505	39	505	100	32	513	102	37	504	100	38
673	494	36	510	103	24	511	103	33	503	102	33
703	508	26	514	101	19	500	99	32	490	97	29
Mean for Weeks											
1-13	239		237	99		239	100		235	98	
14-52	415		414	100		412	99		408	98	
53-101	498		501	101		491	99		489	99	

[a] Interim evaluations occurred during weeks 2, 13, and 53.

TABLE 7
Mean Body Weights and Survival of Female Rats in the 2-Year Dermal Study of Trimethylolpropane Triacrylate

	Vehicle Control		0.3 mg/kg			1.0 mg/kg			3.0 mg/kg		
Day	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	92	65	92	100	65	92	100	65	92	100	65
4	99	65	99	100	65	99	100	65	99	100	65
11	117	65	117	100	65	116	100	65	117	100	65
18[a]	129	60	130	101	60	130	101	60	130	101	60
25	140	60	141	100	60	141	100	60	140	100	60
32	153	60	153	100	60	153	100	60	153	100	60
39	161	60	162	100	60	162	100	60	161	100	60
46	166	60	166	100	60	166	100	60	166	100	60
53	172	60	172	100	60	172	100	60	171	100	60
60	179	60	180	101	60	179	100	60	179	100	60
67	183	60	184	100	60	183	100	60	183	100	60
74	190	60	190	101	60	190	100	60	189	100	60
81	194	60	195	101	60	194	100	60	192	99	60
88	196	60	196	100	60	196	100	60	196	100	60
116[a]	209	55	208	100	55	208	100	55	208	100	55
144	218	55	219	100	55	219	100	55	219	100	55
172	227	55	227	100	55	226	100	55	226	100	55
203	234	55	234	100	55	235	100	55	232	99	55
228	247	55	248	100	55	248	101	55	244	99	55
256	255	55	254	100	55	255	100	55	253	99	55
284	261	55	261	100	55	263	101	55	259	99	55
310	272	55	271	100	55	272	100	55	268	98	54
339	278	55	278	100	55	280	101	54	273	98	54
368[a]	289	50	289	100	50	291	101	49	283	98	49
396	298	50	296	100	50	301	101	48	293	98	48
424	309	50	308	100	49	311	101	48	302	98	47
452	314	50	315	100	49	317	101	47	308	98	46
480	324	50	324	100	49	322	100	46	318	98	44
508	332	49	334	101	49	330	99	44	326	98	44
536	337	49	343	102	49	341	101	43	333	99	44
564	337	46	341	101	49	340	101	43	329	98	43
592	339	45	346	102	48	340	101	41	334	99	43
620	343	41	350	102	47	349	102	38	342	100	41
648	342	38	349	102	44	345	101	36	340	100	40
674	346	34	347	100	40	342	99	33	339	98	38
704	353	31	348	99	36	345	98	27	348	99	35
Mean for Weeks											
1-13	155		156	100		155	100		155	100	
14-52	245		244	100		245	100		242	99	
53-101	328		330	101		329	101		323	99	

[a] Interim evaluations occurred during weeks 2, 13, and 53.



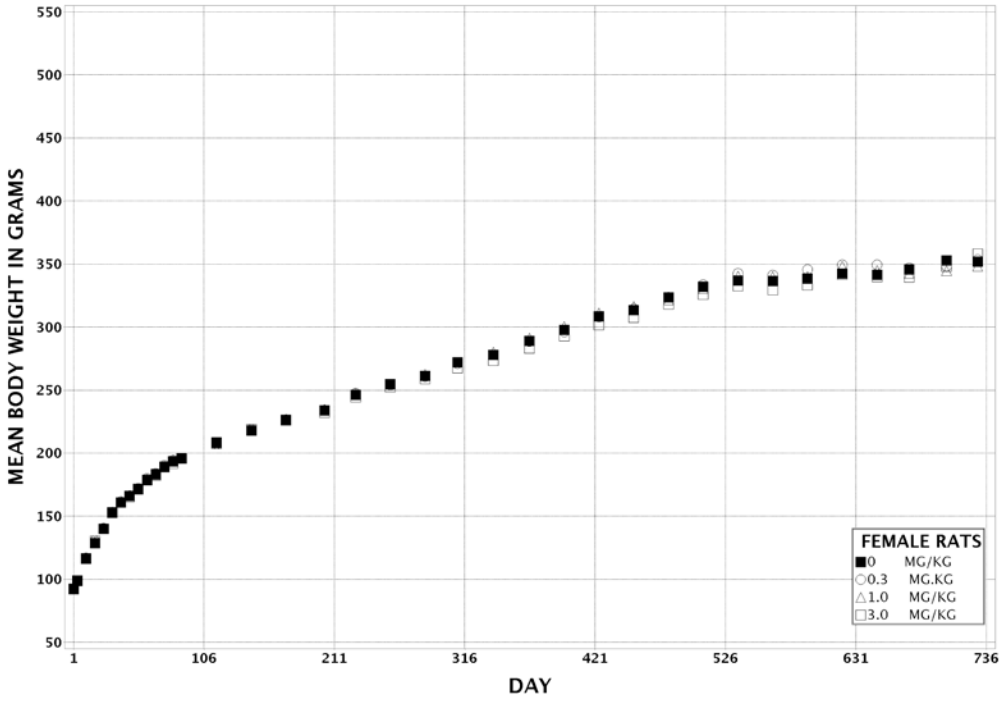


FIGURE 2
Growth Curves for Rats
Administered Trimethylolpropane Triacrylate Dermally for 2 Years

Pathology and Statistical Analyses

This section describes the statistically significant or biologically noteworthy changes in the incidences of malignant mesothelioma and neoplasms and nonneoplastic lesions of the skin. Summaries of the incidences of neoplasms and nonneoplastic lesions, statistical analyses of primary neoplasms that occurred with an incidence of at least 5% in at least one animal group, and historical incidences for the neoplasms mentioned in this section are presented in Appendix A for male rats and Appendix B for female rats.

Malignant Mesothelioma: In male rats, there was a positive trend in the incidences of malignant mesothelioma; the incidence in 3.0 mg/kg males was significantly greater than the vehicle control incidence and exceeded the historical control ranges for dermal studies and for all routes of administration (Tables 8, A2, and A3a). Microscopically, malignant mesotheliomas were papillary and consisted of one or more layers of neoplastic mesothelial cells covering pedunculated fibrovascular stalks (Plate 1). In all cases, they were present in the tunics around the testes with dissemination into the peritoneal cavity.

TABLE 8
Incidences of Malignant Mesothelioma in Male Rats in the 2-Year Dermal Study of Trimethylolpropane Triacrylate

	Vehicle Control	0.3 mg/kg	1.0 mg/kg	3.0 mg/kg
Overall rate[a,b]	0/50 (0%)	2/50 (4%)	2/50 (4%)	5/50 (10%)
Adjusted rate[c]	0.0%	5.7%	4.9%	11.8%
Terminal rate[d]	0/23 (0%)	1/18 (6%)	1/28 (4%)	1/23 (4%)
First incidence (days)	—[f]	529	728	591
Poly-3 test[e]	P=0.024	P=0.201	P=0.231	P=0.031

[a] Number of animals with malignant mesothelioma per number necropsied
[b] Historical incidence for 2-year dermal study vehicle controls (all vehicles) (mean ± standard deviation): 8/250 (3.2% ± 3.4%), range 0%-8%; all routes: 40/1,249 (3.2% ± 2.8%), range 0%-8%
[c] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[d] Observed incidence at terminal kill
[e] Beneath the vehicle control incidence is the P value associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the vehicle controls and that dosed group. The Poly-3 test accounts for the differential mortality in animals that do not reach terminal kill.
[f] Not applicable; no neoplasms in animal group

Skin: Nonneoplastic skin lesions in core study rats at the site of application included epidermal hyperplasia and hyperkeratosis (Tables 9, A4, and B4). The incidences of these lesions in male rats administered 1.0 or 3.0 mg/kg were significantly increased. In females at the site of application, the incidences of epidermal hyperplasia were significantly increased at 1.0 and 3.0 mg/kg, and the incidences of hyperkeratosis were significantly increased in all dosed groups. Microscopically, epidermal hyperplasia was defined as increased cell layers in the epidermis and considered minimal when the epidermis was thickened to three to four cell layers and mild when there was a thickening of the epidermis to five to six cell layers. Hyperkeratosis was defined as thickening of the stratum corneum with concurrent expansion of the stratum granulosum and was considered minimal if the stratum corneum layer was slightly thickened by a thin amount of loosely packed keratin and mild when thickened by a dense, compact band of keratin.

The following neoplasms were identified in core study males, as trace gross lesions remote from the site of application. Compared to the vehicle controls, male rats administered 0.3 mg/kg had increases in the incidences of basal cell adenoma (0/50, 3/50, 0/50, 2/50), basal cell carcinoma (0/50, 2/50, 1/50, 0/50), and basal cell adenoma or basal cell carcinoma (combined) (0/50, 5/50, 1/50, 2/50) (Tables A1 and A2). The incidence of basal cell adenoma or basal cell carcinoma (combined) was statistically significant in the 0.3 mg/kg group and exceeded the historical control range for all routes of study (0%-8%; Table A3b), but only by a single neoplasm.

TABLE 9
Incidences of Nonneoplastic Lesions of the Skin at the Site of Application in Core Study Rats in the 2-Year Dermal Study of Trimethylolpropane Triacrylate

	Vehicle Control	0.3 mg/kg	1.0 mg/kg	3.0 mg/kg
Male				
Number Examined Microscopically	50	49	50	50
Epidermis, Hyperplasia[a]	1 (1.0)[b]	0	12** (1.0)	28** (1.1)
Hyperkeratosis	2 (1.0)	4 (1.0)	33** (1.0)	49** (1.0)
Female				
Number Examined Microscopically	50	50	50	50
Epidermis, Hyperplasia	0	4 (1.3)	11** (1.0)	25** (1.0)
Hyperkeratosis	0	11** (1.0)	42** (1.0)	50** (1.0)

** P≤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

The increased incidence of basal cell adenoma or basal cell carcinoma (combined) was statistically significant in the 0.3 mg/kg group, but again, this is the lowest dose group. Additionally, there was no dose relationship for these lesions, the incidences of basal cell carcinoma alone were not statistically significant and did not exceed the historical control range for all routes of study (0%-6%), and none of these lesions was at the site of application. Therefore, the increased incidences of these lesions compared to concurrent controls were not considered treatment-related.

Interim evaluations of the proliferative skin effects of dermal exposure to trimethylolpropane triacrylate were conducted during weeks 2 and 13 and month 12 (Tables A4 and B3). Histopathologic evaluation of the skin from the site of application identified treatment-related increases in the incidences of epidermal hyperplasia at all three time points in both sexes. There were also treatment-related increases in the incidences of sebaceous gland hyperplasia at 2 and 13 weeks in the male rats, and at 13 weeks in the female rats. At 12 months, there were treatment-related increases in the incidences of hyperkeratosis in both sexes. The dosed rats had up to five layers of epidermal cells (control rats had one to two layers). Sebaceous gland hyperplasia was characterized by a slight increase in the size of the sebaceous glands relative to the vehicle controls. Hyperkeratosis was characterized by an increase in the amount of keratin on the epidermal surface. At all three time points, these changes were considered to be minor, but the increases in the incidences of these lesions were clearly dose related.

2-YEAR MOUSE STUDY

Survival

Estimates of 2-year survival probabilities for male and female mice are shown in Table 10 and in the Kaplan-Meier survival curves (Figure 3). Survival of all dosed groups of males and females was similar to that of the vehicle control groups.

TABLE 10
Survival of Mice in the 2-Year Dermal Study of Trimethylolpropane Triacrylate

	Vehicle Control	0.3 mg/kg	1.0 mg/kg	3.0 mg/kg
Male				
Animals initially in study	65	65	65	65
2-Week interim evaluation[a]	5	5	5	5
13-Week interim evaluation[a]	5	5	5	5
12-Month interim evaluation[a]	5	5	5	5
Moribund	8	7	10	4
Natural deaths	12	8	11	8
Animals surviving to study termination	30	35	29	38
Percent probability of survival at end of study[b]	60	70	58	76
Mean survival (days)[c]	665	687	688	700
Survival analysis[d]	P=0.159N	P=0.387N	P=1.000	P=0.118N
Female				
Animals initially in study	65	65	65	65
2-Week interim evaluation[a]	5	5	5	5
13-Week interim evaluation[a]	5	5	5	5
12-Month interim evaluation[a]	5	5	5	5
Accidental death[a]	0	1	0	0
Moribund	8	7	8	7
Natural deaths	3	11	12	13
Animals surviving to study termination	39	31	30[e]	30
Percent probability of survival at end of study	78	63	60	60
Mean survival (days)	710	682	685	693
Survival analysis	P=0.234	P=0.159	P=0.073	P=0.094

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

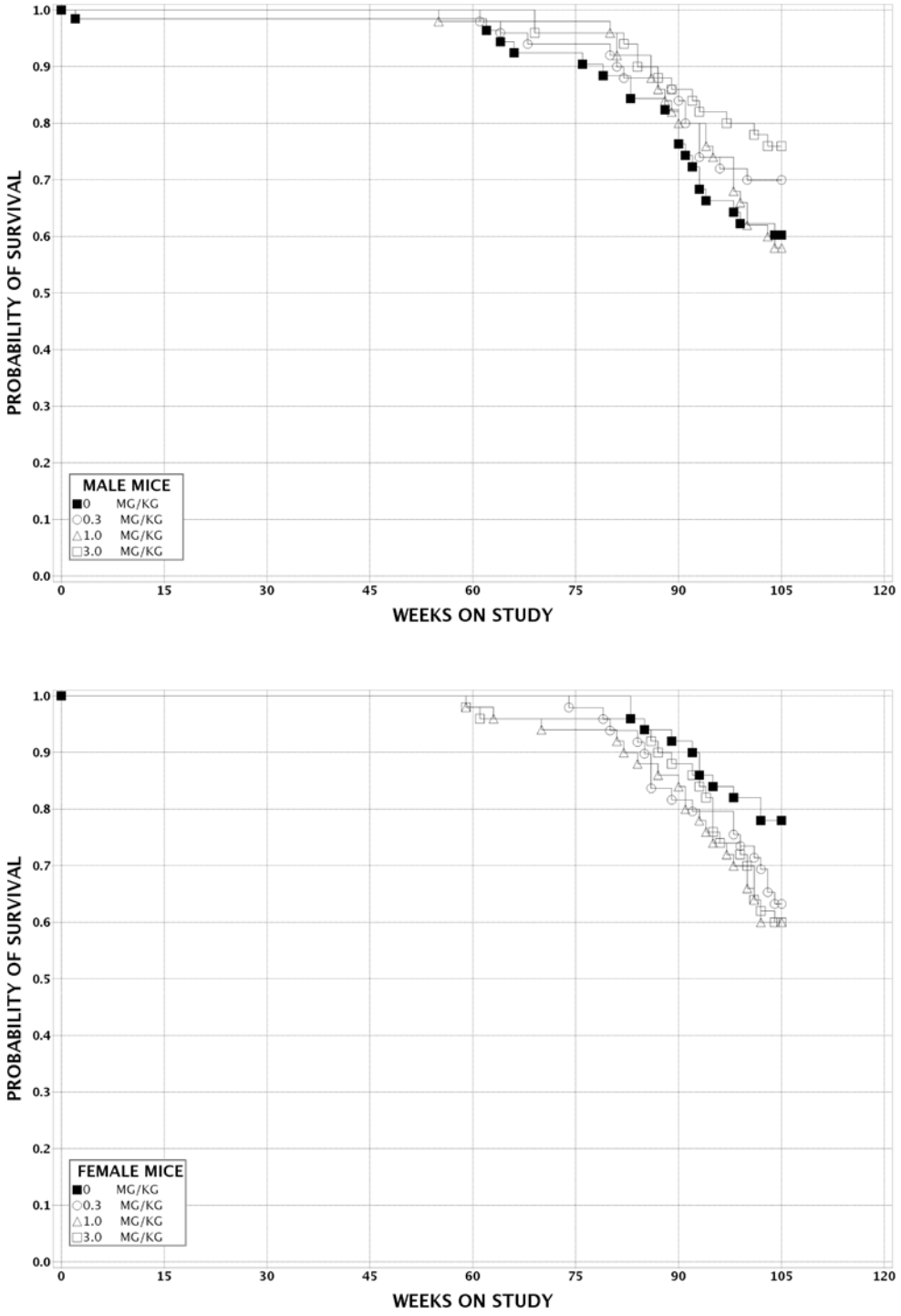
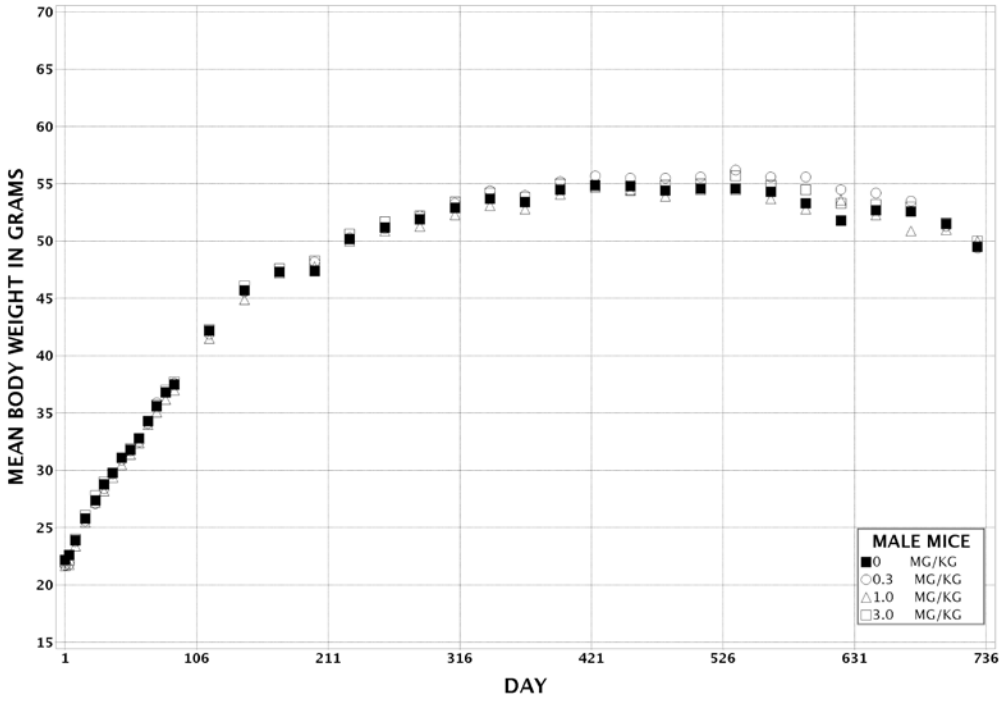


FIGURE 3
Kaplan-Meier Survival Curves for Mice
Administered Trimethylolpropane Triacrylate Dermally for 2 Years

Body Weights and Clinical Findings

Mean body weights of all dosed groups of male and female mice were within 10% of those of the vehicle control groups throughout the study (Figure 4, Tables 11 and 12). No chemical-related clinical findings were observed.



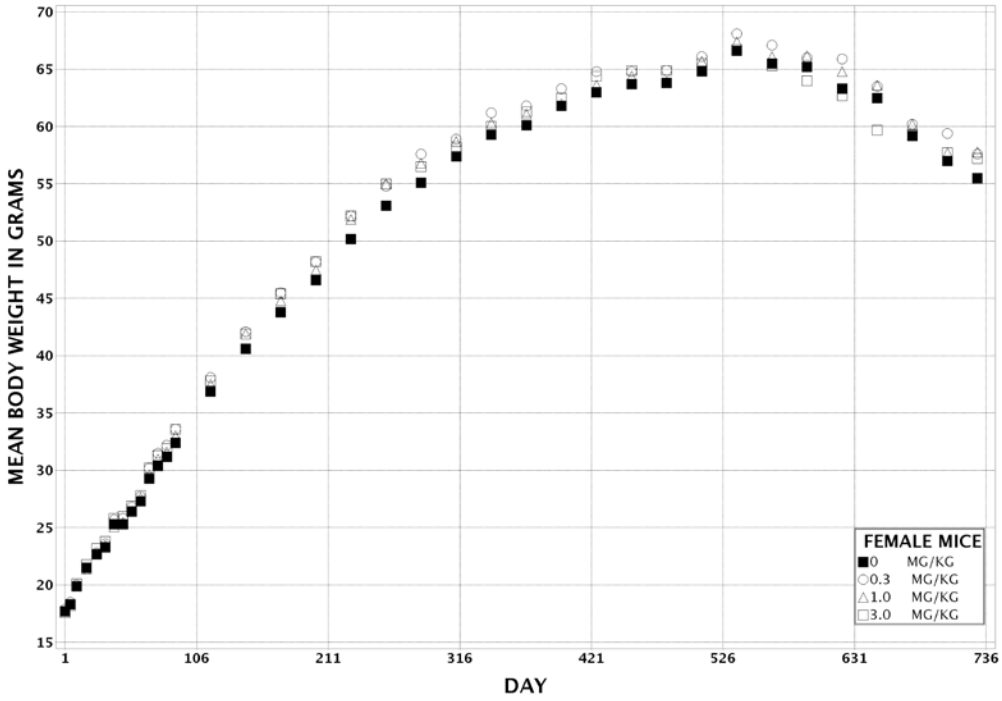


FIGURE 4
Growth Curves for Mice
Administered Trimethylolpropane Triacrylate Dermally for 2 Years

TABLE 11
Mean Body Weights and Survival of Male Mice in the 2-Year Dermal Study of Trimethylolpropane Triacrylate

	Vehicle Control		0.3 mg/kg			1.0 mg/kg			3.0 mg/kg		
Day	Av. Wt. (g)	No. of Survivors	Av. Wt (g)	Wt. (% of Controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of Controls)	No. of Survivors	Av. Wt (g)	Wt. (% of Controls)	No. of Survivors
1	22.2	65	21.7	98	65	21.7	98	65	22.0	99	65
4	22.6	65	21.8	97	65	21.8	97	65	22.2	99	65
9	23.9	64	23.8	100	65	23.4	98	65	24.0	101	65
17[a]	25.8	59	25.6	100	60	25.5	99	60	26.1	101	60
25	27.4	59	27.1	99	60	27.2	99	60	27.8	101	60
32	28.8	59	28.4	99	60	28.2	98	60	29.0	101	60
39	29.8	59	29.7	100	60	29.4	99	60	29.8	100	60
46	31.1	59	30.9	100	60	30.5	98	60	31.1	100	60
53	31.8	59	31.7	100	60	31.4	99	60	31.9	100	60
60	32.8	59	32.5	99	60	32.4	99	60	32.8	100	60
67	34.3	59	34.1	100	60	34.0	99	60	34.3	100	60
74	35.6	59	35.9	101	60	35.1	98	60	35.7	100	60
81	36.8	59	36.8	100	60	36.2	99	60	37.0	101	60
88	37.5	59	37.6	100	60	37.0	99	60	37.7	101	60
116[a]	42.2	54	41.9	99	55	41.5	98	55	42.3	100	55
144	45.7	54	45.6	100	55	44.9	98	55	46.1	101	55
172	47.3	54	47.3	100	55	47.2	100	55	47.6	101	55
200	47.4	54	48.2	102	55	47.8	101	55	48.3	102	55
228	50.2	54	50.3	100	55	50.0	100	55	50.6	101	55
256	51.2	54	51.1	100	55	50.9	99	55	51.7	101	55
284	51.9	54	52.2	101	55	51.3	99	55	52.2	101	55
312	52.9	54	53.3	101	55	52.3	99	55	53.4	101	55
340	53.7	54	54.4	101	55	53.1	99	55	54.2	101	55
368[a]	53.4	49	54.0	101	50	52.8	99	50	53.8	101	50
396	54.5	49	55.2	101	50	54.1	99	49	55.0	101	50
424	54.9	49	55.7	101	50	54.7	100	49	54.8	100	50
452	54.8	47	55.5	101	48	54.4	99	49	54.5	100	50
480	54.4	46	55.5	102	47	53.9	99	49	54.9	101	48
508	54.6	46	55.6	102	47	54.5	100	49	55.0	101	48
536	54.6	45	56.2	103	47	54.5	100	49	55.7	102	48
564	54.3	44	55.6	103	46	53.7	99	46	54.9	101	48
592	53.3	42	55.6	104	44	52.8	99	46	54.5	102	45
620	51.8	41	54.5	105	43	53.6	104	41	53.3	103	44
648	52.7	35	54.2	103	38	52.3	99	40	53.2	101	42
676	52.6	33	53.5	102	36	50.9	97	37	53.0	101	40
704	51.5	31	51.3	100	35	51.0	99	31	51.6	100	39
Mean for Weeks											
1-13	30.0		29.8	99		29.6	98		30.1	100	
14-52	49.2		49.4	100		48.8	99		49.6	101	
53-101	53.7		54.8	102		53.3	99		54.2	101	

[a] Interim evaluations occurred during weeks 2, 13, and 53.

TABLE 12
Mean Body Weights and Survival of Female Mice in the 2-Year Dermal Study of Trimethylolpropane Triacrylate

	Vehicle Control		0.3 mg/kg			1.0 mg/kg			3.0 mg/kg		
Day	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of Controls)	Av. Wt. (g)	Wt. (% of Controls)	Av. Wt. (g)	Wt. (% of Controls)	Wt. (% of Controls)	Day	Av. Wt. (g)
1	17.7	65	17.9	101	65	17.8	101	65	17.6	100	65
5	18.3	65	18.5	101	65	18.3	100	65	18.2	99	65
10	19.9	65	20.0	101	64	19.9	100	65	20.1	101	65
18[a]	21.5	60	21.4	100	59	21.4	100	60	21.8	102	60
26	22.7	60	22.8	101	59	22.7	100	60	23.2	102	60
33	23.3	60	23.6	101	59	23.5	101	60	23.8	102	60
40	25.3	60	25.7	102	59	25.1	99	60	25.8	102	60
47	25.3	60	25.8	102	59	25.5	101	60	26.0	103	60
54	26.4	60	26.8	102	59	26.4	100	60	26.9	102	60
61	27.3	60	27.7	102	59	27.6	101	60	27.8	102	60
68	29.3	60	30.2	103	59	29.6	101	60	30.2	103	60
75	30.4	60	31.5	104	59	31.0	102	60	31.3	103	60
82	31.2	60	32.2	103	59	31.6	102	60	31.9	103	60
89	32.4	60	33.6	104	59	33.0	102	60	33.6	104	60
117[a]	36.9	55	38.1	103	54	37.5	102	55	37.8	103	55
145	40.6	55	42.1	104	54	41.9	103	55	41.9	103	55
173	43.8	55	45.5	104	54	44.8	102	55	45.4	104	55
201	46.6	55	48.2	103	54	47.5	102	55	48.2	103	55
229	50.2	55	52.2	104	54	51.9	104	55	52.2	104	55
257	53.1	55	54.8	103	54	55.0	104	55	55.0	104	55
285	55.1	55	57.6	105	54	56.8	103	55	56.5	103	55
313	57.4	55	58.9	103	54	58.7	102	55	58.2	102	55
341	59.3	55	61.2	103	54	60.3	102	55	60.0	101	55
369[a]	60.1	50	61.8	103	49	61.1	102	50	61.3	102	50
397	61.8	50	63.3	102	49	62.0	100	50	62.5	101	50
425	63.0	50	64.8	103	49	63.6	101	49	64.4	102	48
453	63.7	50	64.8	102	49	64.4	101	48	64.9	102	48
481	63.8	50	64.9	102	49	63.9	100	48	64.9	102	48
509	64.8	50	66.1	102	49	65.7	101	47	65.5	101	48
537	66.6	50	68.1	102	48	67.4	101	47	66.7	100	48
565	65.5	50	67.1	103	46	66.1	101	46	65.3	100	48
593	65.2	47	66.0	101	44	66.2	102	44	64.0	98	47
621	63.3	46	65.9	104	40	64.8	102	43	62.7	99	44
649	62.5	43	63.5	102	39	63.6	102	39	59.7	95	42
677	59.2	42	60.2	102	39	60.2	102	36	59.3	100	37
705	57.0	41	59.4	104	35	57.7	101	32	57.7	101	33
Mean for Weeks											
1-13	25.1		25.6	102		25.2	101		25.6	102	
14-52	49.2		51.0	104		50.5	103		50.6	103	
53-101	62.8		64.3	102		63.6	101		63.0	100	

[a] Interim evaluations occurred during weeks 2, 13, and 53.

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 liver, uterus, skin, lung, adrenal medulla, and glandular stomach. Summaries of the incidences of neoplasms and nonneoplastic lesions, statistical analyses of primary neoplasms that occurred with an incidence of at least 5% in at least one animal group, and historical incidences for the neoplasms mentioned in this section are presented in Appendix C for male mice and Appendix D for female mice.

Liver: Although not significant, there were increased incidences of hepatoblastoma in the 0.3 and 3.0 mg/kg groups and hepatocholangiocarcinoma in the 1.0 and 3.0 mg/kg groups of females (Tables 13, D1, and D2). The historical control ranges for hepatoblastoma are low, while hepatocholangiocarcinoma has not been seen in historical controls (Tables 13 and D3a). Based on the rarity of these neoplasms in female mice and their absence in the concurrent vehicle controls, hepatoblastoma and hepatocholangiocarcinoma were considered to be treatment-related lesions. Female mice exposed to trimethylolpropane triacrylate showed positive trends in the incidences of hepatocellular carcinoma. However, increased incidences in treated groups were not significant and not dose related; therefore, this neoplasm is not treatment related.

The incidences of eosinophilic focus (0 mg/kg, 15/50; 0.3 mg/kg, 23/50; 1.0 mg/kg, 21/50; 3.0 mg/kg, 21/50) in 0.3 mg/kg females and Kupffer cell pigmentation (4/50, 5/50, 10/50, 4/50) in 1.0 mg/kg females were significantly greater than those in the vehicle controls (Table D4). The relationship of these nonneoplastic lesions to trimethylolpropane triacrylate administration is uncertain.

Microscopically, hepatocellular adenomas were usually solitary or multiple masses composed of well-differentiated hepatocytes with variable size and tinctorial characteristics. Hepatocellular carcinomas were noted to have trabecular patterns, with trabeculae at least three cells thick. Hepatocholangiocarcinomas were recorded as a pattern similar to hepatocellular carcinomas with small areas of ducts often containing both neoplastic hepatocytes and epithelial cells often inconspicuous in the primary tumor and more obvious in metastases, and containing large necrotic or cystic areas within tumors (Plate 2). Hepatoblastomas were noted as irregular masses with blood-filled

TABLE 13
Incidences of Neoplasms of the Liver in Female Mice in the 2-Year Dermal Study of Trimethylolpropane Triacrylate

	Vehicle Control	0.3 mg/kg	1.0 mg/kg	3.0 mg/kg
Number Examined Microscopically	50	50	50	50
Hepatoblastoma, Multiple[a]	0	1	0	0
Hepatoblastoma, (includes multiple)[b]	0	4	0	3
Hepatocholangiocarcinoma[c]	0	0	1	2
Hepatocellular Carcinoma, Multiple	3	3	5	2
Hepatocellular Carcinoma (includes multiple)[d]				
Overall rate[e]	12/50 (24%)	13/50 (26%)	10/50 (20%)	19/50 (38%)
Adjusted rate[f]	25.4%	28.4%	22.7%	41.3%
Terminal rate[g]	10/39 (26%)	6/31 (19%)	7/30 (23%)	12/30 (40%)
First incidence (days)	638	513	440	599
Poly-3 test[h]	P=0.045	P=0.461	P=0.479N	P=0.076

[a] Number of animals with neoplasm
[b] Historical incidence for 2-year dermal study vehicle controls (all vehicles) (mean ± standard deviation): 2/250 (0.8% ± 1.1%), range: 0%-2%; all routes: 4/1,195 (0.3% ± 0.8%), range: 0%-2%
[c] Historical incidence for 2-year dermal studies: 0/250; all routes: 0/1,195
[d] Historical incidence for 2-year dermal studies: 63/250 (25.2% ± 15.5%), range: 6%-46%; all routes: 144/1,195 (12.1% ± 10.8%), range: 0%-46%
[e] Number of animals with neoplasm per number of animals with liver examined microscopically
[f] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[g] Observed incidence at terminal kill
[h] Beneath the vehicle control incidence is the P value associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the vehicle controls and that dosed group. The Poly-3 test accounts for the differential mortality in animals that do not reach terminal sacrifice. A lower incidence in a dose group is indicated by **N**.

cystic spaces, necrosis and hemorrhage, and they generally had scant stroma and were composed of small, deeply basophilic cells with scant cytoplasm and elongated nuclei (hepatoblasts) (Plate 3).

Uterus: Incidences of uterine stromal polyp and stromal polyp or stromal sarcoma (combined) in female mice showed positive trends as well as significant increases in the 3.0 mg/kg group; the incidences in the 3.0 mg/kg females also exceeded the ranges in historical controls from dermal studies and from all routes of administration (Tables 14, D1, D2, and D3b).

Microscopically, stromal polyps were pedunculated masses that protruded into the lumen, were often lined by cuboidal to columnar epithelium, and were composed of abundant amounts of loose stroma containing stellate or

TABLE 14
Incidences of Neoplasms of the Uterus in Female Mice in the 2-Year Dermal Study of Trimethylolpropane Triacrylate

	Vehicle Control	0.3 mg/kg	1.0 mg/kg	3.0 mg/kg
Number Necropsied	50	50	50	50
Stromal Polyp[a]				
Overall rate[b]	0/50 (0%)	1/50 (2%)	2/50 (4%)	5/50 (10%)
Adjusted rate[c]	0.0%	2.3%	4.7%	11.1%
Terminal rate[d]	0/39 (0%)	1/31 (3%)	2/30 (7%)	4/30 (13%)
First incidence (days)	—[f]	729 (T)	729 (T)	409
Poly-3 test[e]	P=0.008	P=0.486	P=0.219	P=0.027
Stromal Sarcoma[g]	0	0	0	1
Stromal Polyp or Stromal Sarcoma[h]				
Overall rate	0/50 (0%)	1/50 (2%)	2/50 (4%)	6/50 (12%)
Adjusted rate	0.0%	2.3%	4.7%	13.3%
Terminal rate	0/39 (0%)	1/31 (3%)	2/30 (7%)	4/30 (13%)
First incidence (days)	—	729 (T)	729 (T)	409
Poly-3 test	P=0.002	P=0.486	P=0.219	P=0.014

(T) Terminal kill
[a] Historical incidence for 2-year dermal study vehicle controls (all vehicles) (mean ± standard deviation): 5/250 (2.0% ± 2.5%), range 0%-6%; all routes: 24/1,198 (2.0% ± 2.2%), range 0%–8%
[b] Number of animals with neoplasm per number of animals necropsied
[c] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[d] Observed incidence at terminal kill
[e] Beneath the vehicle control incidence is the P value associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the vehicle controls and that dosed group. The Poly-3 test accounts for the differential mortality in animals that do not reach terminal kill.
[f] Not applicable; no neoplasms in animal group
[g] Historical incidence for 2-year dermal studies: 0/250; all routes: 2/1,198 (0.2% ± 0.6%), range 0%-2%
[h] Historical incidence for 2-year dermal studies: 5/250 (2.0% ± 2.5%), range 0%-6%; all routes: 26/1,198 (2.2% ± 2.2%), range 0%-8%

spindle cells, numerous blood vessels, and ectatic endometrial glands (Plate 4). Stromal sarcomas were distinguished from stromal polyps by marked cellular pleomorphism.

Skin (Site of Application): Compared to the vehicle control incidences, the incidences of epidermal hyperplasia, melanocyte hyperplasia, and chronic inflammation were significantly increased in core study males and females administered 3.0 mg/kg; the incidences of epidermal hyperplasia in 1.0 mg/kg females and chronic inflammation in 1.0 mg/kg males were also significantly increased (Tables 15, C3, and D4). Microscopically, epidermal hyperplasia consisted of a slight increase in the number of cell layers of the epidermis. Melanocyte hyperplasia was characterized by rare-to-multiple aggregates of cells containing dark brown granules of pigment, which were typically found in the superficial dermis. Chronic inflammation was characterized predominantly by mononuclear cells, with occasional neutrophils in the dermis. Acute inflammation, which was much less common than chronic

inflammation, consisted mainly of neutrophils with fewer macrophages and lymphocytes in the dermis and epidermis adjacent to an eroded or ulcerated surface epithelium. Degenerate neutrophils, cell debris and necrotic epidermal cells, and proteinaceous fluid frequently formed a crust overlying the eroded or ulcerated epidermis. Interim evaluations of the proliferative skin effects of dermal exposure to trimethylolpropane triacrylate were conducted during weeks 2 and 13 and month 12 (Tables C3 and D4). Histopathologic evaluation of the skin from the site of application identified slight treatment-related increases in the incidences of hyperplasia and inflammation or chronic active inflammation at all three time points in both sexes. Additionally, there were treatment-related increases in the incidences of sebaceous gland hyperplasia at the 13-week time point in both sexes. The dosed mice had up to five layers of epidermal cells (vehicle control mice had one to two layers). Sebaceous gland hyperplasia was characterized by a slight increase in the size of the sebaceous glands relative to controls. The inflammation consisted of infiltrates of predominantly lymphocytes, with occasional macrophages, and the chronic active inflammation was characterized by infiltrates of predominantly macrophages with fewer neutrophils. The inflammatory cells were scattered throughout the dermis, multifocally in minimal inflammation, and more diffusely in mild and moderate inflammation. At all three time points, these changes were considered to be minor, but the increases in the incidences of these lesions were clearly dose related.

TABLE 15
Incidences of Nonneoplastic Lesions of the Skin at the Site of Application in Core Study Mice in the 2-Year Dermal Study of Trimethylolpropane Triacrylate

	Vehicle Control	0.3 mg/kg	1.0 mg/kg	3.0 mg/kg
Male				
Number Examined Microscopically	50	50	50	50
Epidermis, Hyperplasia[a]	10 (1.3)[b]	7 (1.9)	15 (1.2)	44** (1.7)
Hyperplasia, Melanocyte	0	0	0	19** (1.1)
Inflammation, Chronic	13 (1.2)	17 (1.1)	26** (1.1)	43** (1.3)
Female				
Number Examined Microscopically	50	50	50	50
Epidermis, Hyperplasia	7 (1.9)	7 (1.6)	15* (1.5)	34** (1.7)
Hyperplasia, Melanocyte	1 (1.0)	1 (4.0)	3 (1.7)	33** (1.3)
Inflammation, Chronic	37 (1.1)	36 (1.2)	43 (1.2)	48** (1.5)
Ulcer	0	0	3 (3.3)	3 (3.3)
Inflammation, Acute	1 (2.0)	1 (3.0)	2 (2.5)	4 (1.5)

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

Other Neoplastic Findings: In male mice administered 1.0 mg/kg trimethylolpropane triacrylate, there was a significant increase in the incidence of alveolar/bronchiolar adenoma (1/50, 6/50, 10/50, 4/50); however, the incidence of alveolar/bronchiolar carcinoma (12/50, 11/50, 3/50, 10/50) in this group was significantly decreased (Tables C1 and C2). The increased incidence of alveolar/bronchiolar adenoma was not considered to be a treatment-related effect of trimethylolpropane triacrylate due to the absence of a significant positive trend, because the combined incidences of adenoma or carcinoma (13/50, 17/50, 13/50, 14/50) were not significantly increased at any dose, and the incidences were within the historical control ranges for all routes of study [alveolar/bronchiolar adenoma: 172/1,150 (15.0% ± 6.9%), range 2%-30%; alveolar/bronchiolar carcinoma: 144/1,150 (12.5% ± 7.1%), range 4%-24%; alveolar/bronchiolar adenoma or carcinoma: 301/1,150 (26.2% ± 6.3%), range 14%-40%].

Other Nonneoplastic Findings: In male mice administered 3.0 mg/kg, there were significantly increased incidences of hyperplasia in the adrenal medulla (1/49, 4/49, 3/46, 10/50) and mineralization in the glandular stomach (1/48, 3/49, 2/44, 8/49) (Table C3). These are common background lesions, and the increased incidences were considered to be sporadic and most likely unrelated to trimethylolpropane triacrylate administration.

GENETIC TOXICOLOGY

Trimethylolpropane triacrylate (1,500 to 10,000 µg per plate; lot no. 08409HI) did not induce mutations in *Salmonella typhimurium* strains TA98 or TA100 or in *Escherichia coli* strain WP2 *uvrA*/pKM101, with or without 10% rat liver S9 mix (Table E1).

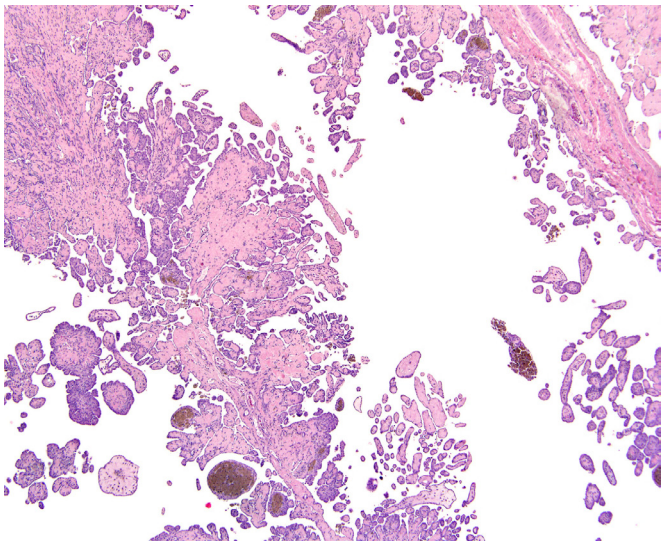


PLATE 1
Malignant mesothelioma in the mesentery of a male F344/N rat administered 3.0 mg/kg trimethylolpropane triacrylate in the 2-year dermal study. The malignant mesothelioma is papillary and consists of one or more layers of neoplastic mesothelial cells. H&E

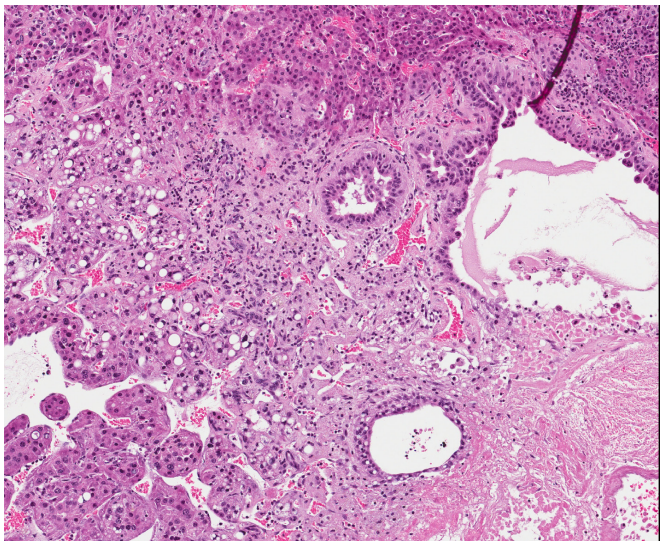


PLATE 2
Hepatocholangiocarcinoma in the liver of a male B6C3F1/N mouse administered 1.0 mg/kg trimethylolpropane triacrylate in the 2-year dermal study. The neoplasm contains both neoplastic hepatocytes and neoplastic bile duct epithelial cells with necrotic and cystic areas. H&E

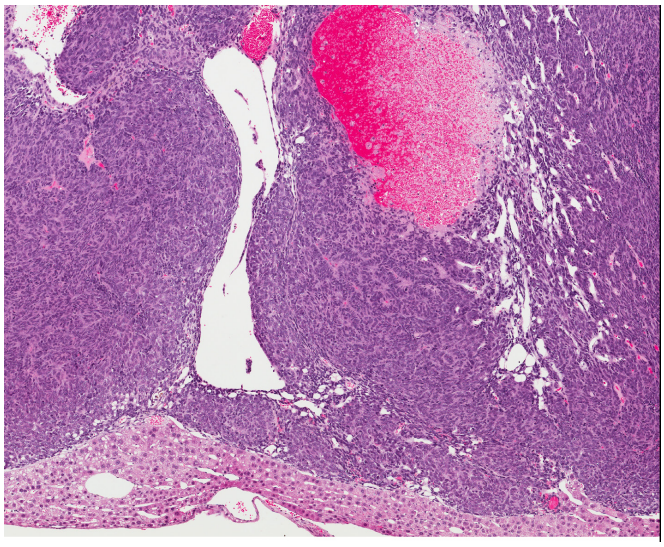


PLATE 3
Hepatoblastoma in the liver of a male B6C3F1/N mouse administered 3.0 mg/kg trimethylolpropane triacrylate in the 2-year dermal study. An expansile mass within the hepatic parenchyma is composed of small, deeply basophilic neoplastic cells and contains blood-filled cystic spaces. H&E

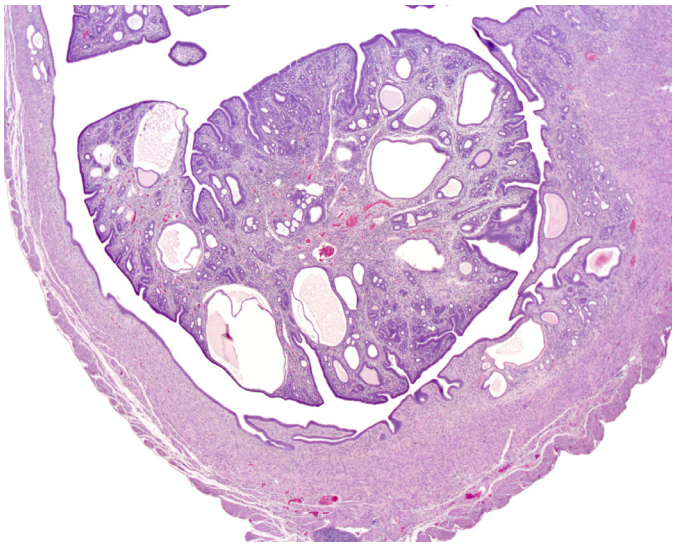


PLATE 4
Stromal polyp in the uterus of a female B6C3F1/N mouse administered 3.0 mg/kg trimethylolpropane triacrylate in the 2-year dermal study. The polyp is a pedunculated mass that protrudes into the lumen and contains marked cellular pleomorphism. H&E

DISCUSSION AND CONCLUSIONS

Trimethylolpropane triacrylate is a multifunctional monomer with a wide range of industrial applications. Trimethylolpropane triacrylate and pentaerythritol triacrylate were nominated for study by the National Cancer Institute for multi-dose dermal carcinogenicity studies with a high priority based on its high production volume and use, the potential for human exposure, and the lack of adequate chronic toxicity and carcinogenesis data. The compounds are representatives of multifunctional acrylates used and produced in much smaller quantities than the basic acrylates. From the available data in the literature, the critical effects of trimethylolpropane triacrylate and pentaerythritol triacrylate are skin and eye irritation (Mortensen, 1992; Kanerva *et al*., 1998; NTP, 2005a; Mancuso and Berdondini, 2008). Repeated dermal exposure to humans or animals leads to contact dermatitis and corrosion of the skin (Nethercott, 1978; Björkner *et al*., 1980; Dahlquist *et al*., 1983; Nethercott *et al*., 1983; Parker and Turk, 1983; Clemmensen, 1984; Maurice and Rycroft, 1986). Both chemicals are moderate to strong sensitizers in experimental animals and humans. In dermal carcinogenicity studies on 10 related acrylates and methacrylates, results were negative for trimethylolpropane triacrylate and pentaerythritol triacrylate associated carcinogenic activity in male mice (Andrews and Clary, 1986; Van Miller *et al*., 2003). The experimental designs of those studies were considered not to meet the current standards of chemical carcinogenicity evaluation. The NTP studies were performed in two phases. In the first phase, toxicity studies of trimethylolpropane triacrylate and pentaerythritol triacrylate were conducted in rats and mice, and carcinogenicity studies of these chemicals were conducted in a transgenic mouse model. In the second phase presented in this Technical Report, traditional 2-year studies were conducted in male and female rats and mice.

In the first phase, the 2-week and 3-month dermal studies showed that both trimethylolpropane triacrylate and pentaerythritol triacrylate affect the site of application (SOA) in F344/N rats and B6C3F$_1$ mice (NTP, 2005a,b). The microscopic examination of the skin (SOA) showed hyperplasia, hyperkeratosis, and inflammation; however, no systemic toxicity was observed. To test for carcinogenicity as well as to test the potential of the Tg.AC hemizygous mouse model, the carcinogenicity of trimethylolpropane triacrylate and pentaerythritol triacrylate was studied in the

Tg.AC hemizygous mouse model. Both chemicals produced neoplasms at the site of application in a dose-related fashion. Pentaerythritol triacrylate was found to be a more potent dermal carcinogen than trimethylolpropane triacrylate in the Tg.AC hemizygous mouse model. The results of transgenic mouse studies were presented to the NTP Board of Scientific Counselors' Technical Reports Review Subcommittee in the spring of 2002 as definitive studies for carcinogenicity; however, the Board did not accept the NTP recommendations because the Tg.AC hemizygous mouse was not considered a suitable model for carcinogenicity evaluation. Therefore, the reports were published as part of the new study report series on toxicity and carcinogenicity findings from genetically modified models rather than as part of the report series on general toxicity and carcinogenicity.

Because the Tg.AC hemizygous mouse model was not accepted as an alternative test system for evaluation of potential carcinogenic activity, NTP performed the traditional 2-year carcinogenicity studies of trimethylolpropane triacrylate reported in this Technical Report. Pentaerythritol triacrylate was not tested in 2-year studies because trimethylolpropane triacrylate and pentaerythritol triacrylate are structurally related and caused similar effects in the toxicity and transgenic mouse studies, and similar chronic effects were expected for both chemicals. Trimethylolpropane triacrylate was selected because its technical grade product has approximately 22% impurities compared to about 55% in pentaerythritol triacrylate preparations. The dose concentrations selected for 2-year studies were based on the 3-month dermal toxicity studies performed at doses ranging from 0.75 to 12 mg trimethylolpropane triacrylate /kg body weight in acetone. Nonneoplastic skin lesions observed at the site of application in those studies were epidermal hyperplasia, hyperkeratosis, necrosis, and chronic inflammation at or above 3.0 mg/kg in both rats and mice. Based on this information, the doses selected for 2-year dermal studies were 0, 0.3, 1.0, and 3.0 mg/kg.

In the 2-year studies, there were no differences in body weights or survival of dosed animals compared to the vehicle controls. There were no clinical findings of toxicity related to trimethylolpropane triacrylate administration. Trimethylolpropane triacrylate increased the incidences of epidermal hyperplasia, characteristic of tumor promotion (Rundhaug and Fischer, 2010), at the site of application in a dose-dependent manner in rats and mice at all the time points examined. Dose-dependent, significant increases in the incidences of hyperkeratosis at the site of application were observed in male and female rats. Both hyperplasia and hyperkeratosis are characteristics of chronic irritant

contact dermatitis (Berardesca and Distante, 1994). These results are consistent with the dermal irritant effect of trimethylolpropane triacrylate reported in the literature (Mortensen, 1992; Kanerva *et al*., 1998; NTP, 2005a). Skin irritation is an inflammatory response (Corsini and Galli, 1998). Inflammation affects all stages of carcinogenesis (Kundu and Surh, 2008). Reactive oxygen and nitrogen species formed by activated inflammatory cells can affect initiation stage. During the tumor promotion and progression stage, cell proliferation, apoptosis, and angiogenesis can be affected by inflammation. Whereas there was no treatment-related inflammation in the rats from 2 or 13 weeks or 12 months, it was observed in a dose-dependent manner in male and female mice at all the time points. However, severity of the chronic inflammation was minimal. The data are consistent with the study in the Tg.AC hemizygous mouse model where dose-related increases in the incidences of epidermal hyperplasia and minimal chronic inflammation were observed at the site of application; however, there were dose-related increases in the incidences of squamous cell papilloma at the site of application (NTP, 2005a). Although skin was identified as a target organ in the subchronic toxicity and transgenic mouse studies, (NTP, 2005a) trimethylolpropane triacrylate did not increase any treatment-related neoplasm in the skin of male or female rats or mice at the site of application in the current studies. These data are consistent with the previous study (Andrews and Clary, 1986), which found no evidence of dermal carcinogenic activity in male mice. However, there were increased incidences of tumors at sites other than skin in the current studies.

There were species and sex differences in neoplasm formation in response to topical trimethylolpropane triacrylate administration. Carcinogenic activity was observed in male rats and female mice. Malignant mesotheliomas were observed in male rats but not in females. Malignant mesothelioma is a neoplasm arising from the surface serosal cells of the pleural, peritoneal, and pericardial cavities and from the testicular tunica vaginalis (Attanoos and Gibbs, 1997, Maronpot *et al.*, 2009). It is a common spontaneous lesion of the peritoneal cavity in male F344/N rats, almost always arising from the epididymis or tunica vaginalis of the testis (Hall, 1990). In this study with trimethylolpropane triacrylate, all incidences were present in the tunics around the testes with dissemination into the peritoneal cavity. There was a positive trend in the incidences of mesothelioma; the incidence in 3.0 mg/kg males was significantly greater than in the concurrent vehicle controls receiving acetone. There is no NTP historical control data for dermal studies using an acetone vehicle; however, the incidences of mesothelioma exceeded the historical control ranges for dermal studies (all vehicles) and for all routes of exposure combined. Based on the

overall mesothelioma incidence in the current study, trimethylolpropane triacrylate was considered as having some evidence of carcinogenic activity in male rats.

There was no evidence of carcinogenic activity in male mice, but in female mice, the carcinogenic activity related to trimethylolpropane triacrylate administration was observed at two sites, liver and uterus. Incidences of hepatoblastoma and hepatocholangiocarcinoma of the liver were increased in the dosed groups. Hepatoblastomas were noted as irregular masses with blood-filled cystic spaces, necrosis and hemorrhage, and they generally had scant stroma composed of small, deeply basophilic cells with scant cytoplasm and elongated nuclei. Hepatoblastoma is a rare neoplasm in mice and spontaneous incidence in B6C3F1 mice has been reported to be less than 1% (Harada *et al.*, 1996; Turusov *et al*., 2002), which is comparable to the NTP historical control data. Hepatocholangiocarcinomas were recorded as a pattern similar to hepatocellular carcinomas with small areas of ducts often containing both neoplastic hepatocytes and epithelial cells often inconspicuous in the primary tumor and more obvious in metastases, and containing large necrotic or cystic areas within tumors. Spontaneous occurrence of this mixed tumor is very rare in mice. Hepatocholangiocarcinoma occurred in 1.0 and 3.0 mg/kg females. The incidences were not significantly increased but exceeded the historical control ranges for dermal studies (all vehicles) and for all routes including dermal. Since occurrence of hepatoblastoma and hepatocholangiocarcinoma is rare, it is concluded that there is some evidence of carcinogenic activity associated with the topical administration of trimethylolpropane triacrylate in female mice.

Incidences of uterine stromal polyp or stromal sarcoma (combined) in female mice occurred with a positive trend as well as a significant increase in the 3.0 mg/kg group. Stromal polyps were pedunculated masses that protruded into the lumen, often lined by cuboidal to columnar epithelium, and composed of abundant amounts of loose stroma containing stellate or spindle cells, numerous blood vessels, and ectatic endometrial glands. Stromal sarcomas were distinguished from stromal polyps by marked cellular pleomorphism. Uterine stromal polyps have been seen in control B6C3F1 mice (Tamano *et al.*, 1988) particularly in older mice, with a mean incidence of 2.0% ± 2.2% and a range of 0% to 8% among all studies in the NTP historical control database. However, the incidences in this study were dose related and the incidence in the 3.0 mg/kg group exceeded the historical control range for all routes and for all dermal studies regardless of vehicle. Additionally, the increasing trend and the increased incidence in the

3.0 mg/kg group relative to concurrent controls were statistically significant. Therefore, it was concluded that the increased incidences provided some evidence of carcinogenic activity related to trimethylolpropane triacrylate administration.

A number of polyfunctional acrylates were tested for carcinogenic activity by the industry (Andrews and Clary, 1986). In that study, male mice were topically administered 100 mg/kg trimethylolpropane triacrylate in mineral oil twice weekly for 80 weeks. The conclusion from that study was that skin was the major target of toxicity as shown by increased incidences of skin lesions in the treated animals; however, no skin or systemic tumors were observed. The current study showed increases of tumors at sites other than skin, suggesting systemic toxicity in trimethylolpropane triacrylate treated animals. In fact, NTP absorption and metabolism studies showed that [^{14}C]-trimethylolpropane triacrylate is well absorbed from skin in rats and mice, parent chemical/metabolites are distributed throughout the body, and excretion is mainly via urine (NTP, 2005a). Quantitation of parent trimethylolpropane triacrylate in blood was not possible due to the chemical instability of trimethylolpropane triacrylate in blood.

NTP and its industry and interagency partners performed a number of studies in transgenic mouse models in search of an alternate animal model requiring fewer animals and shorter study durations to identify chemical carcinogens. The results of those studies were analyzed to determine the suitability of models to replace traditional 2-year bioassays in mice. Analysis of Tg.AC hemizygous mouse studies showed 77% accuracy in identifying known human carcinogens (Pritchard *et al*., 2003). Trimethylolpropane triacrylate tested in the Tg.AC hemizygous mouse model demonstrated increased squamous cell papilloma formation at the site of dermal application in a dose-dependent manner (NTP, 2005a), suggesting that trimethylolpropane triacrylate was likely to be carcinogenic in a 2-year bioassay and that was proven to be true in the current study where trimethylolpropane triacrylate showed carcinogenic activity in male rats and female mice. This finding further supports the value of the Tg.AC hemizygous mouse model in predicting carcinogenic activity. However, in the 2-year study, trimethylolpropane triacrylate did not increase tumor formation at the site of application in the skin, and this discrepancy could be due to increased sensitivity of the Tg.AC hemizygous mouse skin to tumor promoters (Leder *et al*., 1990). The Tg.AC hemizygous mouse contains an oncogene, v-Ha-ras transgene (Leder *et al*., 1990), so this model is genetically

initiated and sensitive to the dermal tumor promoters. For example, abrasion (wounding) or application of a known tumor promoter was enough to induce papillomas in the skin in the Tg.AC hemizygous mouse model (Leder *et al*., 1990; Cannon *et al*., 1997). The Tg.AC hemizygous mouse model is expected to respond to both genotoxic and nongenotoxic carcinogens (Spalding *et al*., 2000; Tennant *et al*., 2001). The results from a limited number of genotoxicity assays with trimethylolpropane triacrylate are mixed. Evidence of trimethylolpropane triacrylate-induced chromosomal damage *in vitro* was seen in mouse lymphoma L5178Y $tk^{+/-}$ cells (Dearfield *et al.,* 1989; Moore *et al*., 1989; Cameron *et al*., 1991). However, no evidence of genotoxicity was seen with the bioassay lot of trimethylolpropane triacrylate in the Ames assay (bacterial mutagenicity test) (Appendix E), and no evidence of chromosomal damage was seen *in vivo* in male or female $B6C3F_1$ mice in a 3-month dermal study or Tg.AC hemizygous mice in a 6-month dermal study (NTP, 2005a). Thus, it is not possible, based on the current evidence, to assign a genotoxic or nongenotoxic mode of action to trimethylolpropane triacrylate.

CONCLUSIONS

Under the conditions of these 2-year dermal studies, there was *some evidence of carcinogenic activity* of trimethylolpropane triacrylate in male F344/N rats based on increased incidences of malignant mesothelioma. There was *no evidence of carcinogenic activity* of trimethylolpropane triacrylate in female F344/N rats administered 0.3, 1.0, or 3.0 mg/kg. There was *no evidence of carcinogenic activity* of trimethylolpropane triacrylate in male B6C3F1/N mice administered 0.3, 1.0, or 3.0 mg/kg. There was *some evidence of carcinogenic activity* of trimethylolpropane triacrylate in female B6C3F1/N mice based on increased incidences of uncommon malignant hepatic neoplasms (hepatoblastoma and hepatocholangiocarcinoma) and stromal polyp or stromal sarcoma of the uterus.

Dermal application of trimethylolpropane triacrylate for 2 years resulted in increased incidences of nonneoplastic lesions in the skin of male and female rats and mice.

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* Explanation of Levels of Evidence of Carcinogenic Activity is on page 10.

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

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

	Vehicle Control	0.3 mg/kg	1.0 mg/kg	3.0 mg/kg
Disposition Summary				
Animals initially in study	65	65	65	65
2-Week interim evaluation	5	5	5	5
13-Week interim evaluation	5	5	5	5
12-Month interim evaluation	5	5	5	5
Early deaths				
Accidental death		1		
Moribund	19	24	19	16
Natural deaths	8	7	3	11
Survivors				
Terminal kill	23	18	28	23
Animals examined microscopically	65	65	65	65
2-Week Interim Evaluation				
Integumentary System				
Skin	(5)	(5)	(5)	(5)
13-Week Interim Evaluation				
Integumentary System				
Skin	(5)	(5)	(5)	(5)
12-Month Interim Evaluation				
Integumentary System				
Skin	(5)	(5)	(5)	(5)
2-Year Study				
Alimentary System				
Intestine large, cecum	(50)	(50)	(49)	(50)
Intestine large, colon	(50)	(49)	(49)	(50)
Adenoma			1 (2%)	
Intestine large, rectum	(49)	(48)	(50)	(50)
Intestine small, duodenum	(50)	(49)	(50)	(50)
Intestine small, ileum	(49)	(47)	(48)	(48)
Intestine small, jejunum	(48)	(44)	(48)	(49)
Liver	(50)	(50)	(50)	(50)
Hepatocellular adenoma			1 (2%)	
Hepatocellular adenoma, multiple	1 (2%)	1 (2%)		
Hepatocellular carcinoma	1 (2%)			1 (2%)
Mesentery	(18)	(13)	(16)	(16)
Fibrosarcoma				1 (6%)
Lipoma			1 (6%)	
Osteosarcoma, metastatic, bone	1 (6%)			
Oral mucosa	(0)	(0)	(1)	(1)
Squamous cell papilloma				1 (100%)
Pancreas	(50)	(50)	(50)	(50)
Mixed tumor benign	1 (2%)		1 (2%)	
Acinus, adenoma	1 (2%)		3 (6%)	
Acinus, adenoma, multiple			1 (2%)	
Salivary glands	(50)	(50)	(50)	(50)
Carcinoma	1 (2%)			

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

	Vehicle Control	0.3 mg/kg	1.0 mg/kg	3.0 mg/kg
Alimentary System (continued)				
Stomach, forestomach	(50)	(50)	(50)	(50)
Stomach, glandular	(50)	(50)	(50)	(50)
Tongue	(1)	(1)	(0)	(0)
Squamous cell papilloma	1 (100%)			
Tooth	(0)	(1)	(0)	(0)
Cardiovascular System				
Blood vessel	(1)	(2)	(1)	(0)
Heart	(50)	(50)	(50)	(50)
Fibrous histiocytoma, metastatic, skeletal muscle			1 (2%)	
Endocrine System				
Adrenal cortex	(50)	(50)	(50)	(50)
Adenoma	1 (2%)	1 (2%)		
Osteosarcoma, metastatic, bone	1 (2%)			
Adrenal medulla	(49)	(50)	(50)	(50)
Pheochromocytoma benign	7 (14%)	8 (16%)	2 (4%)	6 (12%)
Pheochromocytoma benign, multiple	4 (8%)	4 (8%)	2 (4%)	3 (6%)
Pheochromocytoma malignant	1 (2%)	3 (6%)	1 (2%)	1 (2%)
Pheochromocytoma malignant, multiple				2 (4%)
Islets, pancreatic	(50)	(50)	(50)	(50)
Adenoma	15 (30%)	13 (26%)	9 (18%)	14 (28%)
Adenoma, multiple	3 (6%)	3 (6%)		
Parathyroid gland	(45)	(46)	(45)	(47)
Adenoma				1 (2%)
Pituitary gland	(49)	(50)	(49)	(50)
Pars distalis, adenoma	32 (65%)	40 (80%)	36 (73%)	30 (60%)
Pars distalis, adenoma, multiple	2 (4%)	1 (2%)	3 (6%)	4 (8%)
Pars distalis, carcinoma			1 (2%)	1 (2%)
Pars intermedia, adenoma				1 (2%)
Thyroid gland	(50)	(50)	(49)	(50)
C-cell, adenoma	8 (16%)	2 (4%)	6 (12%)	5 (10%)
C-cell, carcinoma	1 (2%)	1 (2%)		
Follicular cell, adenoma				1 (2%)
General Body System				
Tissue NOS	(1)	(0)	(2)	(0)
Fibroma			1 (50%)	
Fibrous histiocytoma, metastatic, skeletal muscle			1 (50%)	
Osteosarcoma, metastatic, bone	1 (100%)			
Genital System				
Epididymis	(50)	(50)	(50)	(50)
Preputial gland	(50)	(50)	(50)	(50)
Adenoma	3 (6%)	2 (4%)		2 (4%)
Carcinoma		1 (2%)	3 (6%)	
Prostate	(50)	(50)	(50)	(50)
Adenoma				1 (2%)
Seminal vesicle	(50)	(50)	(50)	(50)
Testes	(50)	(50)	(50)	(50)
Bilateral, interstitial cell, adenoma	8 (16%)	4 (8%)	11 (22%)	13 (26%)
Interstitial cell, adenoma	19 (38%)	13 (26%)	16 (32%)	15 (30%)

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

	Vehicle Control	0.3 mg/kg	1.0 mg/kg	3.0 mg/kg
Hematopoietic System				
Bone marrow	(49)	(50)	(49)	(50)
Osteosarcoma, metastatic, bone	1 (2%)			
Lymph node	(20)	(20)	(17)	(18)
Osteosarcoma, metastatic, bone	1 (5%)			
Lymph node, mandibular	(4)	(0)	(0)	(1)
Lymph node, mesenteric	(50)	(50)	(50)	(49)
Spleen	(50)	(50)	(49)	(49)
Thymus	(45)	(44)	(49)	(46)
Fibrous histiocytoma, metastatic, skeletal muscle			1 (2%)	
Thymoma benign			1 (2%)	
Integumentary System				
Mammary gland	(50)	(49)	(49)	(48)
Carcinoma		1 (2%)		
Fibroadenoma	1 (2%)	3 (6%)	2 (4%)	2 (4%)
Skin	(50)	(49)	(50)	(50)
Basal cell adenoma		3 (6%)		2 (4%)
Basal cell carcinoma		2 (4%)	1 (2%)	
Keratoacanthoma	3 (6%)	5 (10%)	2 (4%)	5 (10%)
Keratoacanthoma, multiple	1 (2%)			
Squamous cell papilloma	1 (2%)			
Squamous cell papilloma, multiple			1 (2%)	
Trichoepithelioma		1 (2%)		
Subcutaneous tissue, fibroma	4 (8%)	4 (8%)	10 (20%)	4 (8%)
Subcutaneous tissue, fibroma, multiple				2 (4%)
Subcutaneous tissue, lipoma	2 (4%)	1 (2%)	3 (6%)	3 (6%)
Subcutaneous tissue, schwannoma benign		1 (2%)		
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Chordoma				1 (2%)
Osteosarcoma	2 (4%)			1 (2%)
Skeletal muscle	(2)	(0)	(3)	(1)
Fibrous histiocytoma			1 (33%)	
Osteosarcoma, metastatic, bone	1 (50%)			
Sarcoma			1 (33%)	
Nervous System				
Brain	(50)	(50)	(50)	(50)
Carcinoma, metastatic, pituitary gland			1 (2%)	1 (2%)
Spinal cord	(2)	(3)	(5)	(3)

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

	Vehicle Control	0.3 mg/kg	1.0 mg/kg	3.0 mg/kg
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Alveolar/bronchiolar adenoma				2 (4%)
Alveolar/bronchiolar adenoma, multiple	1 (2%)			
Alveolar/bronchiolar carcinoma		2 (4%)		
Carcinoma	1 (2%)			
Fibrous histiocytoma, metastatic, skeletal muscle			1 (2%)	
Osteosarcoma, metastatic, bone	2 (4%)			1 (2%)
Pheochromocytoma malignant, metastatic, adrenal medulla				1 (2%)
Nose	(50)	(50)	(50)	(50)
Trachea	(50)	(50)	(50)	(50)
Special Senses System				
Eye	(50)	(50)	(50)	(50)
Harderian gland	(50)	(50)	(50)	(50)
Zymba gland	(1)	(2)	(1)	(3)
Adenoma	1 (100%)			
Carcinoma		2 (100%)	1 (100%)	3 (100%)
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Nephroblastoma		1 (2%)		
Osteosarcoma, metastatic, bone	1 (2%)			
Renal tubule, adenoma			1 (2%)	
Renal tubule, carcinoma		1 (2%)		
Urinary bladder	(50)	(50)	(50)	(50)
Systemic Lesions				
Multiple organs[b]	(50)	(50)	(50)	(50)
Leukemia mononuclear	26 (52%)	17 (34%)	14 (28%)	14 (28%)
Lymphoma malignant		1 (2%)	2 (4%)	2 (4%)
Mesothelioma malignant		2 (4%)	2 (4%)	5 (10%)
Neoplasm Summary				
Total animals with primary neoplasms[c]	50	48	50	50
Total primary neoplasms	153	144	141	149
Total animals with benign neoplasms	48	45	47	47
Total benign neoplasms	120	110	114	117
Total animals with malignant neoplasms	30	29	23	28
Total malignant neoplasms	33	34	27	32
Total animals with metastatic neoplasms	2		2	3
Total metastatic neoplasms	9		5	3

[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
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Dermal Study of Trimethylolpropane Triacrylate

	Vehicle Control	0.3 mg/kg	1.0 mg/kg	3.0 mg/kg
Adrenal Medulla: Benign Pheochromocytoma				
Overall rate[a]	11/49 (22%)	12/50 (24%)	4/50 (8%)	9/50 (18%)
Adjusted rate[b]	26.2%	32.5%	9.8%	21.5%
Terminal rate[c]	6/22 (27%)	5/18 (28%)	3/28 (11%)	5/23 (22%)
First incidence (days)	606	436	728	646
Poly-3 test[d]	P=0.272N	P=0.354	P=0.046N	P=0.401N
Adrenal Medulla: Malignant Pheochromocytoma				
Overall rate	1/49 (2%)	3/50 (6%)	1/50 (2%)	3/50 (6%)
Adjusted rate	2.4%	8.6%	2.5%	7.2%
Terminal rate	0/22 (0%)	2/18 (11%)	1/28 (4%)	1/23 (4%)
First incidence (days)	606	670	729 (T)	617
Poly-3 test	P=0.351	P=0.248	P=0.759	P=0.306
Adrenal Medulla: Benign or Malignant Pheochromocytoma				
Overall rate	12/49 (24%)	14/50 (28%)	5/50 (10%)	12/50 (24%)
Adjusted rate	28.3%	37.7%	12.2%	28.3%
Terminal rate	6/22 (27%)	6/18 (33%)	4/28 (14%)	6/23 (26%)
First incidence (days)	606	436	728	617
Poly-3 test	P=0.455N	P=0.253	P=0.058N	P=0.593
Mammary Gland: Fibroadenoma				
Overall rate	1/50 (2%)	3/50 (6%)	2/50 (4%)	2/50 (4%)
Adjusted rate	2.4%	8.5%	4.9%	4.9%
Terminal rate	0/23 (0%)	1/18 (6%)	1/28 (4%)	1/23 (4%)
First incidence (days)	591	552	728	704
Poly-3 test	P=0.584	P=0.245	P=0.488	P=0.490
Mammary Gland: Fibroadenoma or Carcinoma				
Overall rate	1/50 (2%)	4/50 (8%)	2/50 (4%)	2/50 (4%)
Adjusted rate	2.4%	11.3%	4.9%	4.9%
Terminal rate	0/23 (0%)	2/18 (11%)	1/28 (4%)	1/23 (4%)
First incidence (days)	591	552	728	704
Poly-3 test	P=0.573N	P=0.129	P=0.488	P=0.490
Pancreas: Adenoma				
Overall rate	1/50 (2%)	0/50 (0%)	4/50 (8%)	0/50 (0%)
Adjusted rate	2.4%	0.0%	9.8%	0.0%
Terminal rate	0/23 (0%)	0/18 (0%)	3/28 (11%)	0/23 (0%)
First incidence (days)	674	—[e]	715	—
Overall rate	P=0.403N	P=0.538N	P=0.169	P=0.505N
Pancreatic Islets: Adenoma				
Overall rate	18/50 (36%)	16/50 (32%)	9/50 (18%)	14/50 (28%)
Adjusted rate	41.7%	43.6%	21.1%	33.5%
Terminal rate	10/23 (44%)	9/18 (50%)	6/28 (21%)	9/23 (39%)
First incidence (days)	659	587	535	638
Poly-3 test	P=0.231N	P=0.521	P=0.031N	P=0.287N
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	34/49 (69%)	41/50 (82%)	39/49 (80%)	34/50 (68%)
Adjusted rate	73.8%	93.8%	84.2%	73.7%
Terminal rate	18/23 (78%)	17/18 (94%)	23/28 (82%)	18/23 (78%)
First incidence (days)	439	317	443	518
Poly-3 test	P=0.143N	P=0.005	P=0.152	P=0.591N

TABLE A2
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Dermal Study of Trimethylolpropane Triacrylate

	Vehicle Control	0.3 mg/kg	1.0 mg/kg	3.0 mg/kg
Pituitary Gland (Pars Distalis): Adenoma or Carcinoma				
Overall rate	34/49 (69%)	41/50 (82%)	40/49 (82%)	35/50 (70%)
Adjusted rate	73.8%	93.8%	84.9%	75.8%
Terminal rate	18/23 (78%)	17/18 (94%)	23/28 (82%)	18/23 (78%)
First incidence (days)	439	317	416	518
Poly-3 test	P=0.226N	P=0.005	P=0.130	P=0.508
Preputial Gland: Adenoma				
Overall rate	3/50 (6%)	2/50 (4%)	0/50 (0%)	2/50 (4%)
Adjusted rate	7.1%	5.8%	0.0%	4.8%
Terminal rate	2/23 (9%)	2/18 (11%)	0/28 (0%)	1/23 (4%)
First incidence (days)	652	729 (T)	—	582
Poly-3 test	P=0.488N	P=0.587N	P=0.124N	P=0.507N
Preputial Gland: Carcinoma				
Overall rate	0/50 (0%)	1/50 (2%)	3/50 (6%)	0/50 (0%)
Adjusted rate	0.0%	2.9%	7.2%	0.0%
Terminal rate	0/23 (0%)	1/18 (6%)	0/28 (0%)	0/23 (0%)
First incidence (days)	—	729 (T)	543	—
Poly-3 test	P=0.489N	P=0.463	P=0.118	—[f]
Preputial Gland: Adenoma or Carcinoma				
Overall rate	3/50 (6%)	2/50 (4%)	3/50 (6%)	2/50 (4%)
Adjusted rate	7.1%	5.8%	7.2%	4.8%
Terminal rate	2/23 (9%)	2/18 (11%)	0/28 (0%)	1/23 (4%)
First incidence (days)	652	729 (T)	543	582
Poly-3 test	P=0.448N	P=0.587N	P=0.661	P=0.507N
Skin: Keratoacanthoma				
Overall rate	4/50 (8%)	5/50 (10%)	2/50 (4%)	5/50 (10%)
Adjusted rate	9.4%	14.1%	4.9%	12.0%
Terminal rate	2/23 (9%)	2/18 (11%)	2/28 (7%)	2/23 (9%)
First incidence (days)	606	639	729 (T)	617
Poly-3 test	P=0.495	P=0.389	P=0.353N	P=0.491
Skin: Squamous Cell Papilloma or Keratoacanthoma				
Overall rate	5/50 (10%)	5/50 (10%)	3/50 (6%)	5/50 (10%)
Adjusted rate	11.8%	14.1%	7.3%	12.0%
Terminal rate	2/23 (9%)	2/18 (11%)	3/28 (11%)	2/23 (9%)
First incidence (days)	606	639	729 (T)	617
Poly-3 test	P=0.568N	P=0.514	P=0.377N	P=0.621
Skin: Basal Cell Adenoma				
Overall rate	0/50 (0%)	3/50 (6%)	0/50 (0%)	2/50 (4%)
Adjusted rate	0.0%	8.5%	0.0%	4.9%
Terminal rate	0/23 (0%)	2/18 (11%)	0/28 (0%)	1/23 (4%)
First incidence (days)	—	535	—	715
Poly-3 test	P=0.398	P=0.091	—	P=0.232
Skin: Trichoepithelioma or Basal Cell Adenoma				
Overall rate	0/50 (0%)	4/50 (8%)	0/50 (0%)	2/50 (4%)
Adjusted rate	0.0%	11.3%	0.0%	4.9%
Terminal rate	0/23 (0%)	3/18 (17%)	0/28 (0%)	1/23 (4%)
First incidence (days)	—	535	—	715
Poly-3 test	P=0.507	P=0.041	—	P=0.232

TABLE A2
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Dermal Study of Trimethylolpropane Triacrylate

	Vehicle Control	0.3 mg/kg	1.0 mg/kg	3.0 mg/kg
Skin: Basal Cell Adenoma or Basal Cell Carcinoma				
Overall rate	0/50 (0%)	5/50 (10%)	1/50 (2%)	2/50 (4%)
Adjusted rate	0.0%	14%	2.4%	4.9%
Terminal rate	0/23 (0%)	2/18 (11%)	0/28 (0%)	1/23 (4%)
First incidence (days)	—	535	693	715
Poly-3 test	P=0.610	P=0.019	P=0.496	P=0.232
Skin: Trichoepithelioma, Basal Cell Adenoma, or Basal Cell Carcinoma				
Overall rate	0/50 (0%)	6/50 (12%)	1/50 (2%)	2/50 (4%)
Adjusted rate	0.0%	16.8%	2.4%	4.9%
Terminal rate	0/23 (0%)	3/18 (17%)	0/28 (0%)	1/23 (4%)
First incidence (days)	—	535	693	715
Poly-3 test	P=0.549N	P=0.008	P=0.496	P=0.232
Skin: Squamous Cell Papilloma, Keratoacanthoma, Trichoepithelioma, Basal Cell Adenoma, or Basal Cell Carcinoma				
Overall rate	5/50 (10%)	11/50 (22%)	4/50 (8%)	7/50 (14%)
Adjusted rate	11.8%	30.1%	9.8%	16.7%
Terminal rate	2/23 (9%)	5/18 (28%)	3/28 (11%)	3/23 (13%)
First incidence (days)	606	535	693	617
Poly-3 test	P=0.517N	P=0.038	P=0.522N	P=0.367
Skin (Subcutaneous Tissue): Fibroma				
Overall rate	4/50 (8%)	4/50 (8%)	10/50 (20%)	6/50 (12%)
Adjusted rate	9.5%	11.3%	23.6%	14.5%
Terminal rate	2/23 (9%)	2/18 (11%)	5/28 (18%)	4/23 (17%)
First incidence (days)	652	529	543	674
Poly-3 test	P=0.366	P=0.546	P=0.070	P=0.355
Skin (Subcutaneous Tissue): Lipoma				
Overall rate	2/50 (4%)	1/50 (2%)	3/50 (6%)	3/50 (6%)
Adjusted rate	4.8%	2.9%	7.3%	7.2%
Terminal rate	2/23 (9%)	1/18 (6%)	3/28 (11%)	1/23 (4%)
First incidence (days)	729 (T)	729 (T)	729 (T)	626
Poly-3 test	P=0.359	P=0.564N	P=0.489	P=0.496
Testes: Adenoma				
Overall rate	27/50 (54%)	17/50 (34%)	27/50 (54%)	28/50 (56%)
Adjusted rate	59.7%	45.3%	62.7%	63.9%
Terminal rate	17/23 (74%)	9/18 (50%)	19/28 (68%)	16/23 (70%)
First incidence (days)	550	529	535	454
Poly-3 test	P=0.195	P=0.129N	P=0.470	P=0.422
Thyroid Gland (C-Cell): Adenoma				
Overall rate	8/50 (16%)	2/50 (4%)	6/49 (12%)	5/50 (10%)
Adjusted rate	18.6%	5.7%	14.6%	12.2%
Terminal rate	4/23 (17%)	1/18 (6%)	4/28 (14%)	4/23 (17%)
First incidence (days)	606	682	485	723
Poly-3 test	P=0.439N	P=0.087N	P=0.421N	P=0.303N
Thyroid Gland (C-Cell): Adenoma or Carcinoma				
Overall rate	8/50 (16%)	3/50 (6%)	6/49 (12%)	5/50 (10%)
Adjusted rate	18.6%	8.5%	14.6%	12.2%
Terminal rate	4/23 (17%)	1/18 (6%)	4/28 (14%)	4/23 (17%)
First incidence (days)	606	652	485	723
Poly-3 test	P=0.391N	P=0.171N	P=0.421N	P=0.303N

TABLE A2
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Dermal Study of Trimethylolpropane Triacrylate

	Vehicle Control	0.3 mg/kg	1.0 mg/kg	3.0 mg/kg
Zymbal's Gland: Carcinoma				
Overall rate	0/50 (0%)	2/50 (4%)	1/50 (2%)	3/50 (6%)
Adjusted rate	0.0%	5.5%	2.4%	7.3%
Terminal rate	0/23 (0%)	0/18 (0%)	0/28 (0%)	1/23 (4%)
First incidence (days)	—	365	626	669
Poly-3 test	P=0.131	P=0.207	P=0.497	P=0.115
Zymbal's Gland: Adenoma or Carcinoma				
Overall rate	1/50 (2%)	2/50 (4%)	1/50 (2%)	3/50 (6%)
Adjusted rate	2.4%	5.5%	2.4%	7.3%
Terminal rate	1/23 (4%)	0/18 (0%)	0/28 (0%)	1/23 (4%)
First incidence (days)	729 (T)	365	626	669
Poly-3 test	P=0.254	P=0.451	P=0.758	P=0.299
All Organs: Mononuclear Cell Leukemia				
Overall rate	26/50 (52%)	17/50 (34%)	14/50 (28%)	14/50 (28%)
Adjusted rate	57.6%	44.7%	31.9%	31.7%
Terminal rate	12/23 (52%)	7/18 (39%)	6/28 (21%)	5/23 (22%)
First incidence (days)	567	543	485	332
Poly-3 test	P=0.014N	P=0.163N	P=0.010N	P=0.009N
All Organs: Malignant Mesothelioma				
Overall rate	0/50 (0%)	2/50 (4%)	2/50 (4%)	5/50 (10%)
Adjusted rate	0.0%	5.7%	4.9%	11.8%
Terminal rate	0/23 (0%)	1/18 (6%)	1/28 (4%)	1/23 (4%)
First incidence (days)	—	529	728	591
Poly-3 test	P=0.024	P=0.201	P=0.231	P=0.031
All Organs: Benign Neoplasms				
Overall rate	48/50 (96%)	45/50 (90%)	47/50 (94%)	47/50 (94%)
Adjusted rate	97.3%	98.9%	98.2%	97.7%
Terminal rate	23/23 (100%)	18/18 (100%)	28/28 (100%)	22/23 (96%)
First incidence (days)	439	317	443	454
Poly-3 test	P=0.670N	P=0.598	P=0.699	P=0.722

TABLE A2
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Dermal Study of Trimethylolpropane Triacrylate

	Vehicle Control	0.3 mg/kg	1.0 mg/kg	3.0 mg/kg
All Organs: Malignant Neoplasms				
Overall rate	30/50 (60%)	29/50 (58%)	23/50 (46%)	28/50 (56%)
Adjusted rate	65.4%	69.5%	49.5%	59.6%
Terminal rate	14/23 (61%)	13/18 (72%)	10/28 (36%)	9/23 (39%)
First incidence (days)	567	318	416	157
Poly-3 test	P=0.271N	P=0.424	P=0.083N	P=0.352N
All Organs: Benign or Malignant Neoplasms				
Overall rate	50/50 (100%)	48/50 (96%)	50/50 (100%)	50/50 (100%)
Adjusted rate	100.0%	99.9%	100.0%	100.0%
Terminal rate	23/23 (100%)	18/18 (100%)	28/28 (100%)	23/23 (100%)
First incidence (days)	439	317	416	157
Poly-3 test	P=1.000	P=1.000	—	—

T) Terminal kill

[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, pancreas, pancreatic islets, pituitary gland, preputial gland, testes, and thyroid gland; for other tissues, denominator is number of animals necropsied.

[b] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality

[c] Observed incidence at terminal kill

[d] Beneath the vehicle control incidence is the P value associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the vehicle controls and that dosed group. The Poly-3 test accounts for the differential mortality in animals that do not reach terminal kill. 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 A3a
Historical Incidence of Malignant Mesothelioma in Control Male F344/N Rats[a]

Study (Study Start)	Incidence in Controls
Historical Incidence: Dermal Studies (all vehicles)	
Bis-(2-Chloroethoxy)methane (September 2002)	2/50
1,2-Dibromo-2,4-dicyanobutane (July 2002)	0/50
Methyl *trans*-styryl ketone (April 2004)	4/50
Pyrogallol (September 2004)	2/50
Trimethylolpropane triacrylate (January 2005)	0/50
Total (%)	8/250 (3.2%)
Mean ± standard deviation	3.2% ± 3.4%
Range	0%-8%
Overall Historical Incidence: All Routes	
Total (%)	40/1,249 (3.2%)
Mean ± standard deviation	3.2% ± 2.8%
Range	0%-8%

[a] Data as of October 2011

TABLE A4
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Dermal Study of Trimethylolpropane Triacrylate [a]

	Vehicle Control	0.3 mg/kg	1.0 mg/kg	3.0 mg/kg
Disposition Summary				
Animals initially in study	65	65	65	65
2-Week interim evaluation	5	5	5	5
13-Week interim evaluation	5	5	5	5
12-Month interim evaluation	5	5	5	5
Early deaths				
Accidental death		1		
Moribund	19	24	19	16
Natural deaths	8	7	3	11
Survivors				
Terminal kill	23	18	28	23
Animals examined microscopically	65	65	65	65
2-Week Interim Evaluation				
Integumentary System				
Skin	(5)	(5)	(5)	(5)
Site of application, hyperplasia	0	0	4 (80%)	5 (100%)
Site of application, sebaceous gland, hyperplasia	0	0	0	4 (80%)
13-Week Interim Evaluation				
Integumentary System				
Skin	(5)	(5)	(5)	(5)
Site of application, hyperplasia	0	0	3 (60%)	5 (100%)
Site of application, sebaceous gland, hyperplasia	0	1 (20%)	4 (80%)	5 (100%)
12-Month Interim Evaluation				
Integumentary System				
Skin	(5)	(5)	(5)	(5)
Site of application, hyperkeratosis	0	0	1 (20%)	2 (40%)
Site of application, hyperplasia	0	0	3 (60%)	3 (60%)
2-Year Study				
Alimentary System				
Intestine large, cecum	(50)	(50)	(49)	(50)
Edema	3 (6%)	1 (2%)	3 (6%)	1 (2%)
Inflammation, suppurative			1 (2%)	
Intestine large, colon	(50)	(49)	(49)	(50)
Intestine large, rectum	(49)	(48)	(50)	(50)
Edema	1 (2%)		1 (2%)	
Intestine small, duodenum	(50)	(49)	(50)	(50)
Epithelium, hyperplasia	8 (16%)	5 (10%)	3 (6%)	3 (6%)
Intestine small, ileum	(49)	(47)	(48)	(48)
Intestine small, jejunum	(48)	(44)	(48)	(49)
Ulcer			1 (2%)	
Epithelium, hyperplasia			1 (2%)	

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

TABLE A4
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Dermal Study of Trimethylolpropane Triacrylate

	Vehicle Control	0.3 mg/kg	1.0 mg/kg	3.0 mg/kg
Alimentary System (continued)				
Liver	(50)	(50)	(50)	(50)
Angiectasis	1 (2%)	1 (2%)	4 (8%)	
Basophilic focus	20 (40%)	19 (38%)	29 (58%)	23 (46%)
Clear cell focus	11 (22%)	10 (20%)	14 (28%)	16 (32%)
Degeneration, cystic	4 (8%)	2 (4%)	1 (2%)	3 (6%)
Eosinophilic focus	4 (8%)	4 (8%)	6 (12%)	4 (8%)
Fibrosis, focal			1 (2%)	
Hematopoietic cell proliferation	3 (6%)			3 (6%)
Hemorrhage			1 (2%)	
Hepatodiaphragmatic nodule	5 (10%)	5 (10%)	6 (12%)	11 (22%)
Infiltration cellular, mixed cell	5 (10%)	6 (12%)	5 (10%)	4 (8%)
Inflammation, suppurative	1 (2%)			1 (2%)
Inflammation, chronic				3 (6%)
Mixed cell focus	10 (20%)	8 (16%)	11 (22%)	11 (22%)
Necrosis	2 (4%)			
Necrosis, focal	2 (4%)	3 (6%)		1 (2%)
Thrombosis	1 (2%)	1 (2%)	1 (2%)	
Bile duct, hyperplasia	38 (76%)	27 (54%)	21 (42%)	30 (60%)
Centrilobular, necrosis	9 (18%)	11 (22%)	4 (8%)	3 (6%)
Hepatocyte, vacuolization cytoplasmic	17 (34%)	10 (20%)	12 (24%)	19 (38%)
Kupffer cell, pigmentation	1 (2%)	1 (2%)		
Oval cell, hyperplasia	2 (4%)			1 (2%)
Mesentery	(18)	(13)	(16)	(16)
Accessory spleen	3 (17%)	3 (23%)	1 (6%)	1 (6%)
Hemorrhage	1 (6%)			
Fat, necrosis	14 (78%)	10 (77%)	11 (69%)	11 (69%)
Oral mucosa	(0)	(0)	(1)	(1)
Cyst			1 (100%)	
Pancreas	(50)	(50)	(50)	(50)
Atrophy	25 (50%)	24 (48%)	24 (48%)	20 (40%)
Cyst	8 (16%)	9 (18%)	6 (12%)	8 (16%)
Necrosis		1 (2%)		
Acinus, cytoplasmic alteration	3 (6%)	5 (10%)	5 (10%)	5 (10%)
Acinus, hyperplasia, focal	3 (6%)	1 (2%)	1 (2%)	6 (12%)
Salivary glands	(50)	(50)	(50)	(50)
Atrophy	8 (16%)	7 (14%)	10 (20%)	6 (12%)
Necrosis		1 (2%)		
Stomach, forestomach	(50)	(50)	(50)	(50)
Edema	6 (12%)	7 (14%)	3 (6%)	1 (2%)
Foreign body				1 (2%)
Inflammation, chronic active	5 (10%)	4 (8%)	1 (2%)	2 (4%)
Perforation	4 (8%)			3 (6%)
Ulcer	9 (18%)	9 (18%)	10 (20%)	5 (10%)
Epithelium, hyperplasia	15 (30%)	12 (24%)	10 (20%)	14 (28%)
Stomach, glandular	(50)	(50)	(50)	(50)
Edema	3 (6%)		3 (6%)	
Erosion	9 (18%)	9 (18%)	5 (10%)	7 (14%)
Ulcer	4 (8%)		3 (6%)	2 (4%)
Glands, hyperplasia	2 (4%)	4 (8%)	1 (2%)	3 (6%)
Tongue	(1)	(1)	(0)	(0)
Epithelium, hyperplasia		1 (100%)		
Tooth	(0)	(1)	(0)	(0)
Malformation		1 (100%)		

TABLE A4
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Dermal Study of Trimethylolpropane Triacrylate

	Vehicle Control	0.3 mg/kg	1.0 mg/kg	3.0 mg/kg
Cardiovascular System				
Blood vessel	(1)	(2)	(1)	(0)
Hypertrophy		2 (100%)		
Inflammation, chronic		1 (50%)		
Thrombosis		1 (50%)		
Heart	(50)	(50)	(50)	(50)
Cardiomyopathy	46 (92%)	43 (86%)	44 (88%)	43 (86%)
Inflammation, suppurative	1 (2%)	1 (2%)		
Inflammation, chronic		1 (2%)		1 (2%)
Mineralization				1 (2%)
Thrombosis	10 (20%)	8 (16%)		2 (4%)
Endocrine System				
Adrenal cortex	(50)	(50)	(50)	(50)
Accessory adrenal cortical nodule	17 (34%)	14 (28%)	18 (36%)	23 (46%)
Atrophy	1 (2%)		1 (2%)	1 (2%)
Degeneration, fatty	25 (50%)	22 (44%)	27 (54%)	22 (44%)
Hematopoietic cell proliferation				1 (2%)
Hemorrhage		1 (2%)		
Hyperplasia, focal	4 (8%)	2 (4%)	4 (8%)	3 (6%)
Hyperplasia, diffuse		1 (2%)		2 (4%)
Hypertrophy, focal	11 (22%)	7 (14%)	10 (20%)	7 (14%)
Adrenal medulla	(49)	(50)	(50)	(50)
Hyperplasia	22 (45%)	19 (38%)	20 (40%)	19 (38%)
Islets, pancreatic	(50)	(50)	(50)	(50)
Hyperplasia	2 (4%)	1 (2%)	1 (2%)	1 (2%)
Parathyroid gland	(45)	(46)	(45)	(47)
Hyperplasia		2 (4%)		
Pituitary gland	(49)	(50)	(49)	(50)
Hyperplasia	1 (2%)			
Pigmentation	3 (6%)			
Pars distalis, angiectasis	3 (6%)	2 (4%)	8 (16%)	6 (12%)
Pars distalis, atrophy	3 (6%)			
Pars distalis, cyst	2 (4%)	3 (6%)	5 (10%)	4 (8%)
Pars distalis, hyperplasia	10 (20%)	5 (10%)	7 (14%)	12 (24%)
Pars distalis, hypertrophy, focal		2 (4%)		8 (16%)
Pars intermedia, angiectasis		1 (2%)	1 (2%)	2 (4%)
Pars intermedia, cyst	1 (2%)	2 (4%)		1 (2%)
Thyroid gland	(50)	(50)	(49)	(50)
Ultimobranchial cyst	2 (4%)	2 (4%)		
C-cell, hyperplasia	6 (12%)	5 (10%)	5 (10%)	6 (12%)
Follicle, cyst	2 (4%)	1 (2%)	2 (4%)	2 (4%)
Follicular cell, hyperplasia			1 (2%)	
General Body System				
Tissue NOS	(1)	(0)	(2)	(0)
Genital System				
Epididymis	(50)	(50)	(50)	(50)
Fibrosis			1 (2%)	1 (2%)
Granuloma sperm				1 (2%)
Inflammation, chronic	3 (6%)	3 (6%)	2 (4%)	7 (14%)

TABLE A4
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Dermal Study of Trimethylolpropane Triacrylate

	Vehicle Control	0.3 mg/kg	1.0 mg/kg	3.0 mg/kg
Genital System (continued)				
Preputial gland	(50)	(50)	(50)	(50)
Cyst			1 (2%)	
Hyperplasia			1 (2%)	3 (6%)
Inflammation, chronic	20 (40%)	15 (30%)	16 (32%)	18 (36%)
Prostate	(50)	(50)	(50)	(50)
Fibrosis			1 (2%)	
Inflammation, chronic	42 (84%)	36 (72%)	35 (70%)	41 (82%)
Epithelium, hyperplasia	4 (8%)	2 (4%)	4 (8%)	6 (12%)
Seminal vesicle	(50)	(50)	(50)	(50)
Inflammation, chronic				1 (2%)
Testes	(50)	(50)	(50)	(50)
Artery, inflammation, chronic	1 (2%)	3 (6%)		
Germinal epithelium, atrophy	23 (46%)	21 (42%)	25 (50%)	23 (46%)
Interstitial cell, hyperplasia	6 (12%)	5 (10%)	2 (4%)	6 (12%)
Hematopoietic System				
Bone marrow	(49)	(50)	(49)	(50)
Angiectasis			1 (2%)	
Depletion cellular			1 (2%)	
Hyperplasia	3 (6%)	8 (16%)	6 (12%)	6 (12%)
Infiltration cellular, histiocyte		1 (2%)		
Myelofibrosis	1 (2%)			
Necrosis		1 (2%)	1 (2%)	
Lymph node	(20)	(20)	(17)	(18)
Ectasia				1 (6%)
Deep cervical, ectasia	1 (5%)			
Deep cervical, hemorrhage			1 (6%)	
Deep cervical, hyperplasia, lymphoid	1 (5%)		1 (6%)	1 (6%)
Mediastinal, ectasia	5 (25%)	5 (25%)	4 (24%)	5 (28%)
Mediastinal, hemorrhage	1 (5%)	4 (20%)	3 (18%)	2 (11%)
Mediastinal, hyperplasia, lymphoid	3 (15%)	4 (20%)	4 (24%)	5 (28%)
Mediastinal, hyperplasia, plasma cell		2 (10%)		
Mediastinal, pigmentation	2 (10%)	1 (5%)		
Pancreatic, ectasia	3 (15%)	4 (20%)	3 (18%)	2 (11%)
Pancreatic, hemorrhage	1 (5%)		2 (12%)	
Pancreatic, hyperplasia, lymphoid	1 (5%)		3 (18%)	
Lymph node, mandibular	(4)	(0)	(0)	(1)
Ectasia	1 (25%)			
Lymph node, mesenteric	(50)	(50)	(50)	(49)
Angiectasis				1 (2%)
Ectasia	8 (16%)	2 (4%)	5 (10%)	6 (12%)
Hemorrhage	1 (2%)	5 (10%)	5 (10%)	3 (6%)
Hyperplasia, atypical	1 (2%)			
Hyperplasia, lymphoid	18 (36%)	20 (40%)	18 (36%)	19 (39%)
Necrosis	1 (2%)			
Pigmentation	1 (2%)	1 (2%)		
Spleen	(50)	(50)	(49)	(49)
Accessory spleen	1 (2%)			1 (2%)
Fibrosis	3 (6%)		2 (4%)	1 (2%)
Hematopoietic cell proliferation	10 (20%)	9 (18%)	9 (18%)	9 (18%)
Hemorrhage	1 (2%)			
Infiltration cellular, mixed cell		1 (2%)		
Necrosis	2 (4%)	1 (2%)	4 (8%)	1 (2%)
Pigmentation	1 (2%)	2 (4%)	1 (2%)	1 (2%)
Lymphoid follicle, atrophy	2 (4%)	1 (2%)	2 (4%)	2 (4%)
Lymphoid follicle, hyperplasia		1 (2%)		

TABLE A4
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Dermal Study of Trimethylolpropane Triacrylate

	Vehicle Control	0.3 mg/kg	1.0 mg/kg	3.0 mg/kg
Hematopoietic System (continued)				
Thymus	(45)	(44)	(49)	(46)
Atrophy		1 (2%)		
Integumentary System				
Mammary gland	(50)	(49)	(49)	(48)
Hyperplasia	37 (74%)	27 (55%)	35 (71%)	28 (58%)
Inflammation, chronic active			2 (4%)	
Skin	(50)	(49)	(50)	(50)
Cyst epithelial inclusion			3 (6%)	
Edema		1 (2%)		
Hemorrhage		1 (2%)		
Hyperkeratosis		1 (2%)		1 (2%)
Inflammation, chronic		1 (2%)		1 (2%)
Ulcer	6 (12%)	4 (8%)	10 (20%)	7 (14%)
Control, cyst epithelial inclusion			1 (2%)	
Control, edema		1 (2%)		
Epidermis, hyperplasia	4 (8%)	4 (8%)	5 (10%)	5 (10%)
Epidermis, site of application, hyperplasia	1 (2%)		12 (24%)	28 (56%)
Site of application, hyperkeratosis	2 (4%)	4 (8%)	33 (66%)	49 (98%)
Site of application, inflammation, chronic			1 (2%)	
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Fibrous osteodystrophy	1 (2%)	1 (2%)		2 (4%)
Fracture				1 (2%)
Femur, osteopetrosis			1 (2%)	
Skeletal muscle	(2)	(0)	(3)	(1)
Hemorrhage	1 (50%)			
Nervous System				
Brain	(50)	(50)	(50)	(50)
Compression	25 (50%)	26 (52%)	26 (52%)	16 (32%)
Hemorrhage	4 (8%)	1 (2%)	1 (2%)	2 (4%)
Necrosis	2 (4%)	1 (2%)	2 (4%)	4 (8%)
Meninges, fibrosis		1 (2%)		
Spinal cord	(2)	(3)	(5)	(3)
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Edema	1 (2%)	1 (2%)	1 (2%)	
Foreign body			1 (2%)	
Hemorrhage	3 (6%)	4 (8%)	1 (2%)	4 (8%)
Infiltration cellular, histiocyte	20 (40%)	18 (36%)	14 (28%)	18 (36%)
Inflammation, suppurative	1 (2%)	1 (2%)		
Inflammation, chronic	14 (28%)	12 (24%)	15 (30%)	10 (20%)
Metaplasia, osseous		2 (4%)	1 (2%)	1 (2%)
Pigmentation, hemosiderin	2 (4%)	2 (4%)		1 (2%)
Thrombosis	1 (2%)	1 (2%)	1 (2%)	
Alveolar epithelium, hyperplasia	10 (20%)	9 (18%)	8 (16%)	8 (16%)
Alveolar epithelium, metaplasia, squamous	1 (2%)		1 (2%)	
Bronchiole, hyperplasia			1 (2%)	
Pleura, fibrosis		1 (2%)		

TABLE A4
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Dermal Study of Trimethylolpropane Triacrylate

	Vehicle Control	0.3 mg/kg	1.0 mg/kg	3.0 mg/kg
Respiratory System (continued)				
Nose	(50)	(50)	(50)	(50)
Foreign body	23 (46%)	27 (54%)	26 (52%)	27 (54%)
Fungus	2 (4%)	4 (8%)	6 (12%)	3 (6%)
Hemorrhage		2 (4%)		
Inflammation, chronic	20 (40%)	19 (38%)	23 (46%)	21 (42%)
Respiratory epithelium, hyperplasia	11 (22%)	11 (22%)	14 (28%)	17 (34%)
Respiratory epithelium, metaplasia, squamous	2 (4%)	5 (10%)	6 (12%)	4 (8%)
Trachea	(50)	(50)	(50)	(50)
Inflammation, chronic	1 (2%)			
Special Senses System				
Eye	(50)	(50)	(50)	(50)
Cataract	3 (6%)	2 (4%)	2 (4%)	3 (6%)
Inflammation, suppurative			1 (2%)	
Inflammation, acute		1 (2%)	3 (6%)	
Inflammation, chronic	1 (2%)	1 (2%)		
Cornea, hyperplasia	1 (2%)			
Retina, degeneration	9 (18%)	2 (4%)	3 (6%)	3 (6%)
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Hydronephrosis				1 (2%)
Infarct	1 (2%)			
Inflammation, chronic			1 (2%)	
Nephropathy	48 (96%)	44 (88%)	47 (94%)	44 (88%)
Papilla, necrosis				2 (4%)
Renal tubule, accumulation, hyaline droplet	1 (2%)	1 (2%)	2 (4%)	
Renal tubule, dilatation	1 (2%)	2 (4%)	2 (4%)	
Renal tubule, necrosis	5 (10%)	3 (6%)	2 (4%)	1 (2%)
Renal tubule, pigmentation	6 (12%)	3 (6%)	1 (2%)	1 (2%)
Transitional epithelium, hyperplasia	1 (2%)		1 (2%)	
Urinary bladder	(50)	(50)	(50)	(50)
Calculus, gross observation only	1 (2%)			
Inflammation, chronic	1 (2%)			1 (2%)
Necrosis				1 (2%)

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

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

	Vehicle Control	0.3 mg/kg	1.0 mg/kg	3.0 mg/kg
Disposition Summary				
Animals initially in study	65	65	65	65
2-Week interim evaluation	5	5	5	5
13-Week interim evaluation	5	5	5	5
12-Month interim evaluation	5	5	5	5
Early deaths				
Moribund	10	12	17	10
Natural deaths	13	7	9	8
Survivors				
Died last week of study			1	
Terminal kill	27	31	23	32
Animals examined microscopically	65	65	65	65
2-Week Interim Evaluation				
Integumentary System				
Skin	(5)	(5)	(5)	(5)
13-Week Interim Evaluation				
Integumentary System				
Skin	(5)	(5)	(5)	(5)
12-Month Interim Evaluation				
Integumentary System				
Skin	(5)	(5)	(5)	(5)
2-Year Study				
Alimentary System				
Intestine large, cecum	(49)	(49)	(49)	(50)
Intestine small, duodenum	(50)	(50)	(50)	(50)
Intestine small, ileum	(45)	(49)	(48)	(49)
Intestine small, jejunum	(44)	(47)	(44)	(49)
Sarcoma, metastatic, kidney	1 (2%)			
Liver	(50)	(50)	(50)	(50)
Mesentery	(26)	(15)	(19)	(18)
Schwannoma malignant				1 (6%)
Pancreas	(50)	(50)	(49)	(50)
Sarcoma, metastatic, kidney	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)
Tongue	(1)	(1)	(0)	(0)
Squamous cell papilloma		1 (100%)		

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

	Vehicle Control	0.3 mg/kg	1.0 mg/kg	3.0 mg/kg
Cardiovascular System				
Heart	(50)	(50)	(50)	(50)
Sarcoma, metastatic, tissue NOS		1 (2%)		
Endocrine System				
Adrenal cortex	(50)	(50)	(50)	(50)
Adenoma		3 (6%)		
Adrenal medulla	(48)	(50)	(49)	(50)
Pheochromocytoma benign		1 (2%)	4 (8%)	1 (2%)
Pheochromocytoma complex				1 (2%)
Pheochromocytoma malignant, multiple			1 (2%)	
Islets, pancreatic	(50)	(50)	(49)	(50)
Adenoma	3 (6%)	1 (2%)	2 (4%)	2 (4%)
Parathyroid gland	(45)	(49)	(46)	(46)
Pituitary gland	(50)	(50)	(50)	(50)
Pars distalis, adenoma	34 (68%)	34 (68%)	24 (48%)	25 (50%)
Pars distalis, adenoma, multiple	2 (4%)	3 (6%)	1 (2%)	5 (10%)
Pars distalis, carcinoma	2 (4%)	2 (4%)	3 (6%)	2 (4%)
Pars intermedia, adenoma	1 (2%)	1 (2%)	1 (2%)	
Pars nervosa, craniopharyngioma	1 (2%)			
Thyroid gland	(50)	(50)	(50)	(50)
C-cell, adenoma	3 (6%)	3 (6%)	1 (2%)	5 (10%)
C-cell, carcinoma		1 (2%)	1 (2%)	1 (2%)
Follicular cell, adenoma			1 (2%)	1 (2%)
Follicular cell, carcinoma		1 (2%)		1 (2%)
General Body System				
Tissue NOS	(0)	(1)	(1)	(0)
Sarcoma		1 (100%)		
Genital System				
Clitoral gland	(50)	(50)	(50)	(49)
Adenoma	4 (8%)	4 (8%)	3 (6%)	4 (8%)
Carcinoma	4 (8%)	2 (4%)	4 (8%)	3 (6%)
Carcinoma, multiple	3 (6%)			
Ovary	(50)	(50)	(50)	(50)
Granulosa cell tumor malignant	1 (2%)			
Thecoma malignant			1 (2%)	
Uterus	(50)	(50)	(50)	(50)
Polyp stromal	9 (18%)	7 (14%)	7 (14%)	10 (20%)
Polyp stromal, multiple		2 (4%)	2 (4%)	
Vagina	(8)	(5)	(9)	(5)
Polyp	1 (13%)			1 (20%)
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(50)
Lymph node	(12)	(11)	(8)	(4)
Lymph node, mandibular	(4)	(0)	(0)	(0)
Lymph node, mesenteric	(50)	(50)	(50)	(50)
Spleen	(50)	(50)	(50)	(50)
Hemangiosarcoma				1 (2%)
Thymus	(47)	(47)	(46)	(50)
Thymoma benign		1 (2%)		1 (2%)

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

	Vehicle Control	0.3 mg/kg	1.0 mg/kg	3.0 mg/kg
Integumentary System				
Mammary gland	(50)	(50)	(50)	(50)
Adenoma	3 (6%)	1 (2%)	1 (2%)	
Adenoma, multiple	1 (2%)			
Carcinoma	3 (6%)	2 (4%)	1 (2%)	3 (6%)
Carcinoma, multiple		1 (2%)	1 (2%)	
Fibroadenoma	14 (28%)	18 (36%)	19 (38%)	13 (26%)
Fibroadenoma, multiple	8 (16%)	9 (18%)	7 (14%)	12 (24%)
Skin	(50)	(50)	(50)	(50)
Basal cell adenoma	1 (2%)			
Keratoacanthoma		1 (2%)	3 (6%)	2 (4%)
Trichoepithelioma				1 (2%)
Control, basal cell adenoma		1 (2%)		
Subcutaneous tissue, fibroma		3 (6%)	2 (4%)	
Subcutaneous tissue, schwannoma benign	1 (2%)	1 (2%)		
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Skeletal muscle	(0)	(1)	(1)	(0)
Sarcoma		1 (100%)		
Nervous System				
Brain	(50)	(50)	(50)	(50)
Carcinoma, metastatic, pituitary gland	1 (2%)	2 (4%)	3 (6%)	2 (4%)
Oligodendroglioma malignant		1 (2%)		
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Carcinoma, metastatic, pituitary gland			1 (2%)	
Carcinoma, metastatic, thyroid gland				1 (2%)
Pheochromocytoma malignant, metastatic, adrenal medulla			1 (2%)	
Sarcoma, metastatic, tissue NOS		1 (2%)		
Nose	(50)	(50)	(50)	(50)
Special Senses System				
Eye	(50)	(50)	(50)	(50)
Harderian gland	(50)	(50)	(50)	(50)
Zymbal's gland	(0)	(1)	(0)	(0)
Carcinoma		1 (100%)		
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Sarcoma	1 (2%)			
Transitional epithelium, carcinoma		1 (2%)		
Urinary bladder	(50)	(50)	(49)	(50)

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

	Vehicle Control	0.3 mg/kg	1.0 mg/kg	3.0 mg/kg
Systemic Lesions				
Multiple organs[b]	(50)	(50)	(50)	(50)
Leukemia mononuclear	12 (24%)	12 (24%)	17 (34%)	10 (20%)
Lymphoma malignant		2 (4%)		1 (2%)
Neoplasm Summary				
Total animals with primary neoplasms[c]	47	50	48	45
Total primary neoplasms	112	123	107	108
Total animals with benign neoplasms	43	47	42	42
Total benign neoplasms	86	95	78	84
Total animals with malignant neoplasms	21	21	26	21
Total malignant neoplasms	26	28	29	24
Total animals with metastatic neoplasms	2	3	4	3
Total metastatic neoplasms	3	4	5	3

[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
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Dermal Study of Trimethylolpropane Triacrylate

	Vehicle Control	0.3 mg/kg	1.0 mg/kg	3.0 mg/kg
Adrenal Cortex: Adenoma				
Overall rate[a]	0/50 (0%)	3/50 (6%)	0/50 (0%)	0/50 (0%)
Adjusted rate[b]	0.0%	6.6%	0.0%	0.0%
Terminal rate[c]	0/27 (0%)	2/31 (7%)	0/24 (0%)	0/32 (0%)
First incidence (days)	—[e]	655	—	—
Poly-3 test[d]	P=0.243N	P=0.130	—[f]	—
Adrenal Medulla: Benign Pheochromocytoma				
Overall rate	0/48 (0%)	1/50 (2%)	4/49 (8%)	1/50 (2%)
Adjusted rate	0.0%	2.2%	10.2%	2.4%
Terminal rate	0/26 (0%)	1/31 (3%)	3/23 (13%)	1/32 (3%)
First incidence (days)	—	729 (T)	598	729 (T)
Poly-3 test	P=0.512	P=0.521	P=0.055	P=0.507
Adrenal Medulla: Benign, Complex, or Malignant Pheochromocytoma				
Overall rate	0/48 (0%)	1/50 (2%)	5/49 (10%)	2/50 (4%)
Adjusted rate	0.0%	2.2%	12.5%	4.7%
Terminal rate	0/26 (0%)	1/31 (3%)	3/23 (13%)	2/32 (6%)
First incidence (days)	—	729 (T)	511	729 (T)
Poly-3 test	P=0.288	P=0.521	P=0.028	P=0.245
Clitoral Gland: Adenoma				
Overall rate	4/50 (8%)	4/50 (8%)	3/50 (6%)	4/49 (8%)
Adjusted rate	9.4%	8.7%	7.5%	9.7%
Terminal rate	3/27 (11%)	1/31 (3%)	1/24 (4%)	3/31 (10%)
First incidence (days)	726	594	652	715
Poly-3 test	P=0.543	P=0.602N	P=0.533N	P=0.625
Clitoral Gland: Carcinoma				
Overall rate	7/50 (14%)	2/50 (4%)	4/50 (8%)	3/49 (6%)
Adjusted rate	16.3%	4.3%	10.0%	7.2%
Terminal rate	5/27 (19%)	1/31 (3%)	3/24 (13%)	2/31 (7%)
First incidence (days)	698	399	715	669
Poly-3 test	P=0.325N	P=0.062N	P=0.302N	P=0.169N
Clitoral Gland: Adenoma or Carcinoma				
Overall rate	10/50 (20%)	6/50 (12%)	7/50 (14%)	7/49 (14%)
Adjusted rate	23.3%	12.8%	17.4%	16.8%
Terminal rate	8/27 (30%)	2/31 (7%)	4/24 (17%)	5/31 (16%)
First incidence (days)	698	399	652	669
Poly-3 test	P=0.476N	P=0.151N	P=0.344N	P=0.318N
Mammary Gland: Fibroadenoma				
Overall rate	22/50 (44%)	27/50 (54%)	26/50 (52%)	25/50 (50%)
Adjusted rate	49.3%	57.9%	60.8%	57.5%
Terminal rate	13/27 (48%)	19/31 (61%)	15/24 (63%)	20/32 (63%)
First incidence (days)	616	650	502	594
Poly-3 test	P=0.363	P=0.264	P=0.184	P=0.284
Mammary Gland: Adenoma				
Overall rate	4/50 (8%)	1/50 (2%)	1/50 (2%)	0/50 (0%)
Adjusted rate	9.1%	2.2%	2.5%	0.0%
Terminal rate	2/27 (7%)	1/31 (3%)	0/24 (0%)	0/32 (0%)
First incidence (days)	497	729 (T)	693	—
Poly-3 test	P=0.075N	P=0.168N	P=0.207N	P=0.064N

TABLE B2
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Dermal Study of Trimethylolpropane Triacrylate

	Vehicle Control	0.3 mg/kg	1.0 mg/kg	3.0 mg/kg
Mammary Gland: Fibroadenoma or Adenoma				
Overall rate	25/50 (50%)	27/50 (54%)	27/50 (54%)	25/50 (50%)
Adjusted rate	54.7%	57.9%	62.9%	57.5%
Terminal rate	14/27 (52%)	19/31 (61%)	15/24 (63%)	20/32 (63%)
First incidence (days)	497	650	502	594
Poly-3 test	P=0.492	P=0.459	P=0.278	P=0.479
Mammary Gland: Carcinoma				
Overall rate	3/50 (6%)	3/50 (6%)	2/50 (4%)	3/50 (6%)
Adjusted rate	6.9%	6.6%	5.0%	7.0%
Terminal rate	1/27 (4%)	2/31 (7%)	1/24 (4%)	2/32 (6%)
First incidence (days)	625	715	652	652
Poly-3 test	P=0.577	P=0.643N	P=0.537N	P=0.653
Mammary Gland: Adenoma or Carcinoma				
Overall rate	6/50 (12%)	4/50 (8%)	3/50 (6%)	3/50 (6%)
Adjusted rate	13.6%	8.8%	7.5%	7.0%
Terminal rate	3/27 (11%)	3/31 (10%)	1/24 (4%)	2/32 (6%)
First incidence (days)	497	715	652	652
Poly-3 test	P=0.274N	P=0.353N	P=0.288N	P=0.259N
Mammary Gland: Fibroadenoma, Adenoma, or Carcinoma				
Overall rate	25/50 (50%)	28/50 (56%)	29/50 (58%)	26/50 (52%)
Adjusted rate	54.7%	60.0%	67.1%	59.4%
Terminal rate	14/27 (52%)	20/31 (65%)	16/24 (67%)	20/32 (63%)
First incidence (days)	497	650	502	594
Poly-3 test	P=0.450	P=0.375	P=0.153	P=0.406
Pancreatic Islets: Adenoma				
Overall rate	3/50 (6%)	1/50 (2%)	2/49 (4%)	2/50 (4%)
Adjusted rate	7.0%	2.2%	5.1%	4.7%
Terminal rate	2/27 (7%)	1/31 (3%)	1/23 (4%)	1/32 (3%)
First incidence (days)	722	729 (T)	704	690
Poly-3 test	P=0.603N	P=0.285N	P=0.543N	P=0.504N
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	36/50 (72%)	37/50 (74%)	25/50 (50%)	30/50 (60%)
Adjusted rate	73.2%	76.6%	57.9%	66.6%
Terminal rate	15/27 (56%)	24/31 (77%)	16/24 (67%)	20/32 (63%)
First incidence (days)	497	577	472	298
Poly-3 test	P=0.200N	P=0.442	P=0.084N	P=0.315N
Pituitary Gland (Pars Distalis): Carcinoma				
Overall rate	2/50 (4%)	2/50 (4%)	3/50 (6%)	2/50 (4%)
Adjusted rate	4.6%	4.4%	7.5%	4.6%
Terminal rate	0/27 (0%)	0/31 (0%)	1/24 (4%)	0/32 (0%)
First incidence (days)	543	650	682	379
Poly-3 test	P=0.611N	P=0.677N	P=0.463	P=0.692N
Pituitary Gland (Pars Distalis): Adenoma or Carcinoma				
Overall rate	38/50 (76%)	39/50 (78%)	27/50 (54%)	32/50 (64%)
Adjusted rate	76.0%	80.1%	62.0%	68.6%
Terminal rate	15/27 (56%)	24/31 (77%)	16/24 (67%)	20/32 (63%)
First incidence (days)	497	577	472	298
Poly-3 test	P=0.157N	P=0.401	P=0.102N	P=0.279N

TABLE B2
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Dermal Study of Trimethylolpropane Triacrylate

	Vehicle Control	0.3 mg/kg	1.0 mg/kg	3.0 mg/kg
Skin: Keratoacanthoma				
Overall rate	0/50 (0%)	1/50 (2%)	3/50 (6%)	2/50 (4%)
Adjusted rate	0.0%	2.2%	7.5%	4.7%
Terminal rate	0/27 (0%)	1/31 (3%)	1/24 (4%)	2/32 (6%)
First incidence (days)	—	729 (T)	690	729 (T)
Poly-3 test	P=0.241	P=0.512	P=0.107	P=0.234
Skin: Keratoacanthoma, Trichoepithelioma, or Basal Cell Adenoma				
Overall rate	1/50 (2%)	2/50 (4%)	3/50 (6%)	3/50 (6%)
Adjusted rate	2.3%	4.4%	7.5%	7.1%
Terminal rate	1/27 (4%)	2/31 (7%)	1/24 (4%)	2/32 (6%)
First incidence (days)	729 (T)	729 (T)	690	704
Poly-3 test	P=0.273	P=0.520	P=0.282	P=0.302
Skin (Subcutaneous Tissue): Fibroma				
Overall rate	0/50 (0%)	3/50 (6%)	2/50 (4%)	0/50 (0%)
Adjusted rate	0.0%	6.6%	5.0%	0.0%
Terminal rate	0/27 (0%)	2/31 (7%)	1/24 (4%)	0/32 (0%)
First incidence (days)	—	655	598	—
Poly-3 test	P=0.285N	P=0.130	P=0.224	—
Thyroid Gland (C-Cell): Adenoma				
Overall rate	3/50 (6%)	3/50 (6%)	1/50 (2%)	5/50 (10%)
Adjusted rate	7.0%	6.6%	2.5%	11.8%
Terminal rate	2/27 (7%)	1/31 (3%)	1/24 (4%)	5/32 (16%)
First incidence (days)	652	704	729 (T)	729 (T)
Poly-3 test	P=0.207	P=0.637N	P=0.333N	P=0.346
Thyroid Gland (C-Cell): Adenoma or Carcinoma				
Overall rate	3/50 (6%)	4/50 (8%)	1/50 (2%)	6/50 (12%)
Adjusted rate	7.0%	8.8%	2.5%	14.2%
Terminal rate	2/27 (7%)	2/31 (7%)	1/24 (4%)	6/32 (19%)
First incidence (days)	652	704	729 (T)	729 (T)
Poly-3 test	P=0.149	P=0.530	P=0.333N	P=0.232
Uterus: Stromal Polyp				
Overall rate	9/50 (18%)	9/50 (18%)	9/50 (18%)	10/50 (20%)
Adjusted rate	20.3%	19.7%	22.0%	23.2%
Terminal rate	5/27 (19%)	6/31 (19%)	6/24 (25%)	8/32 (25%)
First incidence (days)	597	680	571	448
Poly-3 test	P=0.401	P=0.576N	P=0.532	P=0.475
All Organs: Mononuclear Cell Leukemia				
Overall rate	12/50 (24%)	12/50 (24%)	17/50 (34%)	10/50 (20%)
Adjusted rate	27.5%	25.9%	38.6%	23.5%
Terminal rate	9/27 (33%)	5/31 (16%)	4/24 (17%)	8/32 (25%)
First incidence (days)	625	638	449	690
Poly-3 test	P=0.394N	P=0.524N	P=0.187	P=0.428N
All Organs: Benign Neoplasms				
Overall rate	43/50 (86%)	47/50 (94%)	42/50 (84%)	42/50 (84%)
Adjusted rate	87.5%	96.2%	91.7%	90.8%
Terminal rate	22/27 (82%)	30/31 (97%)	23/24 (96%)	30/32 (94%)
First incidence (days)	497	577	472	298
Poly-3 test	P=0.570N	P=0.100	P=0.363	P=0.420

TABLE B2
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Dermal Study of Trimethylolpropane Triacrylate

	Vehicle Control	0.3 mg/kg	1.0 mg/kg	3.0 mg/kg
All Organs: Malignant Neoplasms				
Overall rate	21/50 (42%)	21/50 (42%)	26/50 (52%)	21/50 (42%)
Adjusted rate	47.1%	44.0%	58.0%	47.0%
Terminal rate	13/27 (48%)	10/31 (32%)	10/24 (42%)	14/32 (44%)
First incidence (days)	543	399	449	379
Poly-3 test	P=0.507	P=0.465N	P=0.200	P=0.582N
All Organs: Benign or Malignant Neoplasms				
Overall rate	47/50 (94%)	50/50 (100%)	48/50 (96%)	45/50 (90%)
Adjusted rate	94.0%	100.0%	99.5%	94.0%
Terminal rate	24/27 (89%)	31/31 (100%)	24/24 (100%)	30/32 (94%)
First incidence (days)	497	399	449	298
Poly-3 test	P=0.300N	P=0.119	P=0.158	P=0.670N

(T) Terminal kill

[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, clitoral gland, pancreatic islets, pituitary gland, and thyroid gland; for other tissues, denominator is number of animals necropsied.

[b] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality

[c] Observed incidence at terminal kill

[d] Beneath the vehicle control incidence is the P value associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the vehicle controls and that dosed group. The Poly-3 test accounts for the differential mortality in animals that do not reach terminal kill. 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 B3
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Dermal Study of Trimethylolpropane Triacrylate [a]

	Vehicle Control	0.3 mg/kg	1.0 mg/kg	3.0 mg/kg
Disposition Summary				
Animals initially in study	65	65	65	65
2-Week interim evaluation	5	5	5	5
13-Week interim evaluation	5	5	5	5
12-Month interim evaluation	5	5	5	5
Early deaths				
Moribund	10	12	17	10
Natural deaths	13	7	9	8
Survivors				
Died last week of study			1	
Terminal kill	27	31	23	32
Animals examined microscopically	65	65	65	65
2-Week Interim Evaluation				
Integumentary System				
Skin	(5)	(5)	(5)	(5)
Site of application, hyperplasia	0	0	3 (60%)	4 (80%)
Site of application, inflammation, chronic active	0	0	1 (20%)	0
13-Week Interim Evaluation				
Integumentary System				
Skin	(5)	(5)	(5)	(5)
Site of application, hyperplasia	0	2 (40%)	1 (20%)	4 (80%)
Site of application, sebaceous gland, hyperplasia	0	0	0	4 (80%)
12-Month Interim Evaluation				
Integumentary System				
Skin	(5)	(5)	(5)	(5)
Site of application, hyperkeratosis	0	0	3 (60%)	5 (100%)
Site of application, hyperplasia	0	1 (20%)	0	2 (40%)
Site of application, inflammation	0	0	0	1 (20%)
2-Year Study				
Alimentary System				
Intestine large, cecum	(49)	(49)	(49)	(50)
Edema	1 (2%)		3 (6%)	
Intestine small, duodenum	(50)	(50)	(50)	(50)
Epithelium, hyperplasia		1 (2%)	4 (8%)	
Intestine small, ileum	(45)	(49)	(48)	(49)
Intestine small, jejunum	(44)	(47)	(44)	(49)

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

TABLE B3
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Dermal Study of Trimethylolpropane Triacrylate

	Vehicle Control	0.3 mg/kg	1.0 mg/kg	3.0 mg/kg
Alimentary System (continued)				
Liver	(50)	(50)	(50)	(50)
Angiectasis	4 (8%)	2 (4%)		3 (6%)
Basophilic focus	43 (86%)	45 (90%)	38 (76%)	45 (90%)
Clear cell focus	9 (18%)	5 (10%)	2 (4%)	7 (14%)
Cyst	1 (2%)			
Eosinophilic focus	8 (16%)	9 (18%)	7 (14%)	4 (8%)
Fatty change	4 (8%)	7 (14%)	6 (12%)	5 (10%)
Hematopoietic cell proliferation	2 (4%)	2 (4%)	1 (2%)	
Hepatodiaphragmatic nodule	11 (22%)	9 (18%)	2 (4%)	9 (18%)
Infiltration cellular, mixed cell	7 (14%)	7 (14%)	9 (18%)	12 (24%)
Inflammation, chronic				1 (2%)
Mixed cell focus	9 (18%)	9 (18%)	4 (8%)	8 (16%)
Necrosis, focal	2 (4%)	5 (10%)	4 (8%)	
Thrombosis			1 (2%)	
Bile duct, hyperplasia		2 (4%)	4 (8%)	2 (4%)
Centrilobular, necrosis	2 (4%)	3 (6%)	3 (6%)	
Hepatocyte, eosinophilic focus				1 (2%)
Hepatocyte, mitotic alteration				2 (4%)
Hepatocyte, vacuolization cytoplasmic	3 (6%)	7 (14%)	12 (24%)	6 (12%)
Kupffer cell, pigmentation		1 (2%)		
Mesentery	(26)	(15)	(19)	(18)
Accessory spleen	4 (15%)		2 (11%)	1 (6%)
Fibrosis	1 (4%)		1 (5%)	
Hemorrhage		1 (7%)		
Thrombosis			1 (5%)	
Fat, necrosis	22 (85%)	13 (87%)	16 (84%)	15 (83%)
Pancreas	(50)	(50)	(49)	(50)
Atrophy	10 (20%)	13 (26%)	16 (33%)	8 (16%)
Cyst	3 (6%)	4 (8%)	3 (6%)	6 (12%)
Metaplasia, hepatocyte		1 (2%)		
Acinus, cytoplasmic alteration	4 (8%)	2 (4%)	3 (6%)	
Acinus, hyperplasia, focal	1 (2%)	2 (4%)	3 (6%)	2 (4%)
Salivary glands	(50)	(50)	(50)	(50)
Atrophy	5 (10%)	5 (10%)	3 (6%)	2 (4%)
Necrosis	1 (2%)			
Stomach, forestomach	(50)	(50)	(50)	(50)
Edema	3 (6%)	2 (4%)	7 (14%)	2 (4%)
Erosion		1 (2%)		
Inflammation, chronic active	4 (8%)	2 (4%)	5 (10%)	4 (8%)
Perforation			2 (4%)	
Ulcer	5 (10%)	1 (2%)	9 (18%)	2 (4%)
Epithelium, hyperplasia	6 (12%)	3 (6%)	12 (24%)	7 (14%)
Stomach, glandular	(50)	(50)	(50)	(50)
Erosion	1 (2%)	5 (10%)	5 (10%)	3 (6%)
Ulcer	1 (2%)		3 (6%)	1 (2%)
Glands, hyperplasia		2 (4%)	2 (4%)	1 (2%)
Tongue	(1)	(1)	(0)	(0)
Epithelium, hyperplasia	1 (100%)			
Cardiovascular System				
Heart	(50)	(50)	(50)	(50)
Cardiomyopathy	38 (76%)	44 (88%)	34 (68%)	30 (60%)
Thrombosis		3 (6%)	2 (4%)	

TABLE B3
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Dermal Study of Trimethylolpropane Triacrylate

	Vehicle Control	0.3 mg/kg	1.0 mg/kg	3.0 mg/kg
Endocrine System				
Adrenal cortex	(50)	(50)	(50)	(50)
Accessory adrenal cortical nodule	7 (14%)	6 (12%)	4 (8%)	8 (16%)
Atrophy	1 (2%)	1 (2%)		
Degeneration, fatty	18 (36%)	23 (46%)	23 (46%)	22 (44%)
Hemorrhage		1 (2%)		
Hyperplasia	1 (2%)			
Hyperplasia, focal	8 (16%)	6 (12%)	3 (6%)	9 (18%)
Hyperplasia, diffuse			1 (2%)	
Hypertrophy, focal	7 (14%)	11 (22%)	12 (24%)	7 (14%)
Necrosis	2 (4%)	1 (2%)		
Adrenal medulla	(48)	(50)	(49)	(50)
Hyperplasia	5 (10%)	3 (6%)	4 (8%)	1 (2%)
Necrosis	1 (2%)			
Islets, pancreatic	(50)	(50)	(49)	(50)
Hyperplasia	2 (4%)	1 (2%)		
Parathyroid gland	(45)	(49)	(46)	(46)
Hyperplasia	1 (2%)			
Pituitary gland	(50)	(50)	(50)	(50)
Pigmentation			1 (2%)	
Pars distalis, angiectasis	9 (18%)	10 (20%)	14 (28%)	10 (20%)
Pars distalis, cyst	14 (28%)	18 (36%)	19 (38%)	24 (48%)
Pars distalis, hyperplasia	9 (18%)	11 (22%)	17 (34%)	9 (18%)
Pars distalis, hypertrophy, focal			1 (2%)	1 (2%)
Pars intermedia, angiectasis	3 (6%)	5 (10%)	2 (4%)	4 (8%)
Pars intermedia, cyst	3 (6%)	1 (2%)	3 (6%)	7 (14%)
Pars intermedia, hyperplasia	1 (2%)			
Thyroid gland	(50)	(50)	(50)	(50)
Ultimobranchial cyst		1 (2%)	2 (4%)	
C-cell, hyperplasia	5 (10%)	8 (16%)	8 (16%)	4 (8%)
Follicle, cyst		1 (2%)	2 (4%)	1 (2%)
Follicular cell, hyperplasia	1 (2%)			
General Body System				
Tissue NOS	(0)	(1)	(1)	(0)
Genital System				
Clitoral gland	(50)	(50)	(50)	(49)
Cyst	3 (6%)	2 (4%)	2 (4%)	
Hyperplasia	10 (20%)	6 (12%)	3 (6%)	2 (4%)
Inflammation, chronic	5 (10%)	7 (14%)	2 (4%)	4 (8%)
Ovary	(50)	(50)	(50)	(50)
Cyst	6 (12%)	5 (10%)	8 (16%)	7 (14%)
Uterus	(50)	(50)	(50)	(50)
Hyperplasia, cystic	10 (20%)	7 (14%)	12 (24%)	3 (6%)
Cervix, myometrium, hypertrophy		1 (2%)		
Vagina	(8)	(5)	(9)	(5)
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(50)
Hyperplasia	3 (6%)	5 (10%)	2 (4%)	1 (2%)
Infiltration cellular, histiocyte				2 (4%)
Myelofibrosis	2 (4%)	1 (2%)	2 (4%)	1 (2%)

TABLE B3
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Dermal Study of Trimethylolpropane Triacrylate

	Vehicle Control	0.3 mg/kg	1.0 mg/kg	3.0 mg/kg
Hematopoietic System (continued)				
Lymph node	(12)	(11)	(8)	(4)
Bronchial, hyperplasia	1 (8%)			
Bronchial, pigmentation	1 (8%)			
Mediastinal, ectasia	3 (25%)	2 (18%)	1 (13%)	
Mediastinal, hemorrhage	4 (33%)	4 (36%)	2 (25%)	2 (50%)
Mediastinal, hyperplasia, lymphoid	3 (25%)	7 (64%)	1 (13%)	1 (25%)
Mediastinal, pigmentation	5 (42%)	6 (55%)	2 (25%)	2 (50%)
Pancreatic, hemorrhage	1 (8%)			
Pancreatic, pigmentation	1 (8%)			
Lymph node, mandibular	(4)	(0)	(0)	(0)
Ectasia	1 (25%)			
Lymph node, mesenteric	(50)	(50)	(50)	(50)
Ectasia			1 (2%)	2 (4%)
Hemorrhage	1 (2%)	1 (2%)	1 (2%)	2 (4%)
Hyperplasia, lymphoid	26 (52%)	20 (40%)	14 (28%)	19 (38%)
Pigmentation	1 (2%)	1 (2%)	1 (2%)	3 (6%)
Spleen	(50)	(50)	(50)	(50)
Fibrosis	1 (2%)		1 (2%)	
Hematopoietic cell proliferation	10 (20%)	13 (26%)	17 (34%)	13 (26%)
Infiltration cellular, mixed cell				1 (2%)
Necrosis			1 (2%)	1 (2%)
Pigmentation	8 (16%)	5 (10%)	6 (12%)	6 (12%)
Lymphoid follicle, atrophy		1 (2%)	1 (2%)	1 (2%)
Thymus	(47)	(47)	(46)	(50)
Cyst	1 (2%)			
Integumentary System				
Mammary gland	(50)	(50)	(50)	(50)
Hyperplasia	48 (96%)	48 (96%)	45 (90%)	44 (88%)
Inflammation, chronic		1 (2%)		
Skin	(50)	(50)	(50)	(50)
Cyst epithelial inclusion	1 (2%)			
Edema		1 (2%)		1 (2%)
Ulcer	2 (4%)	3 (6%)		2 (4%)
Epidermis, hyperplasia	1 (2%)	4 (8%)		2 (4%)
Epidermis, site of application, hyperplasia		4 (8%)	11 (22%)	25 (50%)
Site of application, hyperkeratosis		11 (22%)	42 (84%)	50 (100%)
Site of application, ulcer		2 (4%)		
Subcutaneous tissue, necrosis				1 (2%)
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Fibrous osteodystrophy			1 (2%)	
Femur, osteopetrosis		1 (2%)		
Skeletal muscle	(0)	(1)	(1)	(0)
Cyst			1 (100%)	
Nervous System				
Brain	(50)	(50)	(50)	(50)
Compression	31 (62%)	24 (48%)	18 (36%)	21 (42%)
Hemorrhage	3 (6%)	4 (8%)	4 (8%)	1 (2%)
Necrosis	1 (2%)	4 (8%)	1 (2%)	

TABLE B3
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Dermal Study of Trimethylolpropane Triacrylate

	Vehicle Control	0.3 mg/kg	1.0 mg/kg	3.0 mg/kg
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Edema	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Foreign body				2 (4%)
Hemorrhage	4 (8%)	5 (10%)	10 (20%)	4 (8%)
Infiltration cellular, histiocyte	23 (46%)	24 (48%)	28 (56%)	21 (42%)
Inflammation, chronic	14 (28%)	22 (44%)	15 (30%)	13 (26%)
Inflammation, chronic active			1 (2%)	
Metaplasia, osseous			1 (2%)	
Pigmentation, hemosiderin	11 (22%)	16 (32%)	14 (28%)	12 (24%)
Alveolar epithelium, hyperplasia	3 (6%)	5 (10%)	3 (6%)	2 (4%)
Nose	(50)	(50)	(50)	(50)
Foreign body	5 (10%)	5 (10%)	2 (4%)	2 (4%)
Inflammation, chronic	8 (16%)	5 (10%)	4 (8%)	5 (10%)
Respiratory epithelium, hyperplasia	2 (4%)	3 (6%)		
Respiratory epithelium, metaplasia, squamous	2 (4%)	1 (2%)		
Special Senses System				
Eye	(50)	(50)	(50)	(50)
Cataract	2 (4%)	6 (12%)	5 (10%)	4 (8%)
Inflammation, acute	2 (4%)	1 (2%)	1 (2%)	
Cornea, hyperplasia	1 (2%)			
Retina, degeneration	6 (12%)	10 (20%)	11 (22%)	5 (10%)
Harderian gland	(50)	(50)	(50)	(50)
Inflammation, chronic	1 (2%)	3 (6%)		
Zymbal's gland	(0)	(1)	(0)	(0)
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Cyst	1 (2%)		2 (4%)	
Infarct	1 (2%)	1 (2%)	2 (4%)	
Inflammation, suppurative			1 (2%)	
Inflammation, chronic			1 (2%)	
Nephropathy	38 (76%)	39 (78%)	36 (72%)	35 (70%)
Renal tubule, accumulation, hyaline droplet	2 (4%)	2 (4%)	1 (2%)	
Renal tubule, dilatation	2 (4%)			
Renal tubule, necrosis		1 (2%)	1 (2%)	
Renal tubule, pigmentation	2 (4%)	1 (2%)	3 (6%)	1 (2%)
Transitional epithelium, hyperplasia		2 (4%)	3 (6%)	1 (2%)
Urinary bladder	(50)	(50)	(49)	(50)
Edema	1 (2%)			
Transitional epithelium, hyperplasia			1 (2%)	

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

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

	Vehicle Control	0.3 mg/kg	1.0 mg/kg	3.0 mg/kg
Disposition Summary				
Animals initially in study	65	65	65	65
2-Week interim evaluation	5	5	5	5
13-Week interim evaluation	5	5	5	5
12-Month interim evaluation	5	5	5	5
Early deaths				
Moribund	8	7	10	4
Natural deaths	12	8	11	8
Survivors				
Terminal kill	30	35	29	38
Animals examined microscopically	65	65	65	65
2-Week Interim Evaluation				
Integumentary System				
Skin	(5)	(5)	(5)	(5)
13-Week Interim Evaluation				
Integumentary System				
Skin	(5)	(5)	(5)	(5)
12-Month Interim Evaluation				
Integumentary System				
Skin	(5)	(5)	(5)	(5)
2-Year Study				
Alimentary System				
Esophagus	(50)	(50)	(50)	(49)
Gallbladder	(38)	(41)	(37)	(43)
Carcinoma, metastatic, pancreas	1 (3%)			
Intestine large, cecum	(42)	(43)	(40)	(44)
Adenoma	1 (2%)	1 (2%)		
Carcinoma			1 (3%)	
Intestine large, colon	(44)	(44)	(41)	(46)
Intestine large, rectum	(45)	(44)	(41)	(47)
Intestine small, duodenum	(40)	(43)	(40)	(46)
Adenoma		1 (2%)		
Intestine small, ileum	(42)	(43)	(40)	(45)
Intestine small, jejunum	(40)	(42)	(40)	(44)
Carcinoma	2 (5%)		4 (10%)	1 (2%)
Hepatocholangiocarcinoma, metastatic, liver			1 (3%)	

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

	Vehicle Control	0.3 mg/kg	1.0 mg/kg	3.0 mg/kg
Alimentary System (continued)				
Liver	(50)	(50)	(50)	(50)
Alveolar/bronchiolar carcinoma, metastatic, lung	1 (2%)			
Carcinoma, metastatic, pancreas	1 (2%)			
Hemangioma			1 (2%)	
Hemangiosarcoma	2 (4%)	1 (2%)	4 (8%)	5 (10%)
Hepatoblastoma	4 (8%)	4 (8%)	3 (6%)	5 (10%)
Hepatoblastoma, multiple	1 (2%)	1 (2%)	1 (2%)	
Hepatocellular adenoma	12 (24%)	14 (28%)	14 (28%)	15 (30%)
Hepatocellular adenoma, multiple	22 (44%)	21 (42%)	18 (36%)	19 (38%)
Hepatocellular carcinoma	13 (26%)	13 (26%)	15 (30%)	14 (28%)
Hepatocellular carcinoma, multiple	9 (18%)	1 (2%)	4 (8%)	11 (22%)
Hepatocholangiocarcinoma	2 (4%)		3 (6%)	
Mesentery	(9)	(8)	(11)	(6)
Carcinoma, metastatic, pancreas	1 (11%)			
Hemangiosarcoma			1 (9%)	
Hepatoblastoma, metastatic, liver			1 (9%)	
Hepatocellular carcinoma, metastatic, liver			1 (9%)	
Hepatocholangiocarcinoma, metastatic, liver			1 (9%)	
Oral mucosa	(0)	(1)	(0)	(0)
Pancreas	(50)	(49)	(45)	(50)
Carcinoma	1 (2%)			
Hepatoblastoma, metastatic, liver			1 (2%)	
Hepatocholangiocarcinoma, metastatic, liver	1 (2%)		1 (2%)	
Salivary glands	(50)	(50)	(50)	(50)
Stomach, forestomach	(50)	(49)	(48)	(50)
Carcinoma, metastatic, pancreas	1 (2%)			
Squamous cell papilloma	3 (6%)	1 (2%)		
Stomach, glandular	(48)	(49)	(44)	(49)
Cardiovascular System				
Blood vessel	(1)	(0)	(0)	(1)
Heart	(50)	(50)	(50)	(50)
Alveolar/bronchiolar carcinoma, metastatic, lung	1 (2%)			
Hemangiosarcoma	1 (2%)			1 (2%)
Hepatocellular carcinoma, metastatic, liver		1 (2%)		
Hepatocholangiocarcinoma, metastatic, liver	1 (2%)			
Endocrine System				
Adrenal cortex	(50)	(49)	(47)	(50)
Carcinoma, metastatic, liver	1 (2%)			
Subcapsular, adenoma	6 (12%)	10 (20%)	4 (9%)	4 (8%)
Adrenal medulla	(49)	(49)	(46)	(50)
Pheochromocytoma benign				1 (2%)
Islets, pancreatic	(50)	(49)	(44)	(50)
Adenoma		5 (10%)	1 (2%)	
Parathyroid gland	(48)	(48)	(48)	(50)

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

	Vehicle Control	0.3 mg/kg	1.0 mg/kg	3.0 mg/kg
Endocrine System (continued)				
Pituitary gland	(50)	(48)	(49)	(50)
Pars intermedia, adenoma			1 (2%)	
Thyroid gland	(50)	(47)	(46)	(48)
Hepatocholangiocarcinoma, metastatic, liver	1 (2%)			
Follicular cell, adenoma		1 (2%)	1 (2%)	1 (2%)
General Body System				
Tissue NOS	(2)	(1)	(1)	(0)
Carcinoma, metastatic, pancreas	1 (50%)			
Hepatoblastoma, metastatic, liver			1 (100%)	
Genital System				
Coagulating gland	(0)	(0)	(1)	(0)
Epididymis	(49)	(50)	(50)	(50)
Alveolar/bronchiolar carcinoma, metastatic, lung	1 (2%)			
Carcinoma, metastatic, pancreas	1 (2%)			
Preputial gland	(50)	(50)	(50)	(50)
Prostate	(50)	(49)	(49)	(50)
Seminal vesicle	(50)	(50)	(49)	(50)
Carcinoma, metastatic, pancreas	1 (2%)			
Testes	(50)	(50)	(50)	(50)
Interstitial cell, adenoma	1 (2%)	2 (4%)	1 (2%)	
Hematopoietic System				
Bone marrow	(50)	(49)	(50)	(50)
Hemangiosarcoma	1 (2%)	1 (2%)	1 (2%)	
Lymph node	(5)	(6)	(2)	(1)
Mediastinal, carcinoma, metastatic, harderian gland				1 (100%)
Mediastinal, carcinoma, metastatic, pancreas	1 (20%)			
Lymph node, mandibular	(48)	(48)	(46)	(46)
Carcinoma, metastatic, Harderian gland				2 (4%)
Lymph node, mesenteric	(48)	(47)	(45)	(50)
Hemangiosarcoma	1 (2%)			
Spleen	(49)	(48)	(45)	(49)
Hemangiosarcoma	4 (8%)	1 (2%)	1 (2%)	1 (2%)
Thymus	(48)	(48)	(44)	(47)
Hemangiosarcoma		1 (2%)		
Hepatocholangiocarcinoma, metastatic, liver	1 (2%)			

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

	Vehicle Control	0.3 mg/kg	1.0 mg/kg	3.0 mg/kg
Integumentary System				
Skin	(50)	(50)	(50)	(50)
Hemangioma				1 (2%)
Hemangiosarcoma			1 (2%)	
Squamous cell papilloma	1 (2%)			
Pinna, neural crest tumor		1 (2%)		1 (2%)
Site of application, subcutaneous tissue, hemangiosarcoma	1 (2%)	1 (2%)		
Subcutaneous tissue, fibrous histiocytoma			1 (2%)	
Subcutaneous tissue, hemangiosarcoma	1 (2%)		2 (4%)	
Subcutaneous tissue, hepatocholangiocarcinoma, metastatic, liver	1 (2%)			
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Carcinoma, metastatic, Harderian gland				1 (2%)
Skeletal muscle	(3)	(2)	(6)	(1)
Alveolar/bronchiolar carcinoma, metastatic, lung	1 (33%)			
Carcinoma, metastatic, pancreas	1 (33%)			
Hemangiosarcoma		1 (50%)	1 (17%)	
Hepatoblastoma, metastatic, liver			1 (17%)	
Hepatocholangiocarcinoma, metastatic, liver	1 (33%)			
Sarcoma			1 (17%)	
Schwannoma malignant, metastatic, spinal cord			1 (17%)	
Nervous System				
Brain	(50)	(50)	(50)	(50)
Hepatocholangiocarcinoma, metastatic, liver			1 (2%)	
Meningioma benign		1 (2%)		
Oligodendroglioma malignant	1 (2%)			
Peripheral nerve	(2)	(1)	(4)	(1)
Spinal cord	(2)	(1)	(4)	(0)
Schwannoma malignant			1 (25%)	
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Alveolar/bronchiolar adenoma	1 (2%)	5 (10%)	9 (18%)	4 (8%)
Alveolar/bronchiolar adenoma, multiple		1 (2%)	1 (2%)	
Alveolar/bronchiolar carcinoma	10 (20%)	9 (18%)	3 (6%)	8 (16%)
Alveolar/bronchiolar carcinoma, multiple	2 (4%)	2 (4%)		2 (4%)
Carcinoma, metastatic, harderian gland				2 (4%)
Carcinoma, metastatic, pancreas	1 (2%)			
Hemangiosarcoma		1 (2%)		
Hepatoblastoma, metastatic, liver		1 (2%)	1 (2%)	1 (2%)
Hepatocellular carcinoma, metastatic, liver	8 (16%)	2 (4%)	7 (14%)	10 (20%)
Hepatocholangiocarcinoma, metastatic, liver	2 (4%)		2 (4%)	
Nose	(50)	(50)	(50)	(50)
Carcinoma, metastatic, harderian gland				1 (2%)
Trachea	(50)	(50)	(50)	(50)

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

	Vehicle Control	0.3 mg/kg	1.0 mg/kg	3.0 mg/kg
Special Senses System				
Eye	(48)	(47)	(41)	(47)
Harderian gland	(50)	(49)	(49)	(50)
Adenoma	8 (16%)	7 (14%)	4 (8%)	5 (10%)
Carcinoma	3 (6%)			2 (4%)
Bilateral, adenoma		1 (2%)		
Urinary System				
Kidney	(48)	(46)	(42)	(49)
Alveolar/bronchiolar carcinoma, metastatic, lung	1 (2%)			
Carcinoma, metastatic, pancreas	1 (2%)			
Hemangiosarcoma				1 (2%)
Hepatocholangiocarcinoma, metastatic, liver	1 (2%)		1 (2%)	
Renal tubule, adenoma	2 (4%)			
Renal tubule, carcinoma, metastatic, lung	1 (2%)			
Urethra	(0)	(1)	(2)	(3)
Urinary bladder	(47)	(48)	(42)	(49)
Systemic Lesions				
Multiple organs[b]	(50)	(50)	(50)	(50)
Histiocytic sarcoma		3 (6%)		
Leukemia granulocytic			1 (2%)	
Lymphoma malignant	2 (4%)	3 (6%)	4 (8%)	2 (4%)
Neoplasm Summary				
Total animals with primary neoplasms[c]	46	48	47	44
Total primary neoplasms	118	115	108	104
Total animals with benign neoplasms	37	41	36	37
Total benign neoplasms	57	71	55	50
Total animals with malignant neoplasms	38	28	32	36
Total malignant neoplasms	61	43	53	53
Total animals with metastatic neoplasms	12	3	12	13
Total metastatic neoplasms	35	4	21	18
Total animals with uncertain neoplasms-benign or malignant		1		1
Total uncertain neoplasms		1		1

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

TABLE C2
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Dermal Study of Trimethylolpropane Triacrylate

	Vehicle Control	0.3 mg/kg	1.0 mg/kg	3.0 mg/kg
Adrenal Cortex: Adenoma				
Overall rate[a]	6/50 (12%)	10/49 (20%)	4/47 (9%)	4/50 (8%)
Adjusted rate[b]	14.6%	22.9%	9.7%	8.8%
Terminal rate[c]	5/30 (17%)	9/35 (26%)	4/29 (14%)	4/38 (11%)
First incidence (days)	725	568	729 (T)	729 (T)
Poly-3 test[d]	P=0.103N	P=0.241	P=0.365N	P=0.310N
Harderian Gland: Adenoma				
Overall rate	8/50 (16%)	8/50 (16%)	4/50 (8%)	5/50 (10%)
Adjusted rate	18.5%	18.1%	9.3%	10.8%
Terminal rate	4/30 (13%)	6/35 (17%)	4/29 (14%)	2/38 (5%)
First incidence (days)	460	556	729 (T)	583
Poly-3 test	P=0.172N	P=0.590N	P=0.174N	P=0.231N
Harderian Gland: Carcinoma				
Overall rate	3/50 (6%)	0/50 (0%)	0/50 (0%)	2/50 (4%)
Adjusted rate	7.3%	0.0%	0.0%	4.4%
Terminal rate	2/30 (7%)	0/35 (0%)	0/29 (0%)	1/38 (3%)
First incidence (days)	690	—[e]	—	675
Poly-3 test	P=0.567	P=0.109N	P=0.110N	P=0.455N
Harderian Gland: Adenoma or Carcinoma				
Overall rate	11/50 (22%)	8/50 (16%)	4/50 (8%)	7/50 (14%)
Adjusted rate	25.4%	18.1%	9.3%	15.1%
Terminal rate	6/30 (20%)	6/35 (17%)	4/29 (14%)	3/38 (8%)
First incidence (days)	460	556	729 (T)	583
Poly-3 test	P=0.214N	P=0.286N	P=0.042N	P=0.168N
Small Intestine (Jejunum): Carcinoma				
Overall rate	2/50 (4%)	0/50 (0%)	4/50 (8%)	1/50 (2%)
Adjusted rate	4.9%	0.0%	9.2%	2.2%
Terminal rate	2/30 (7%)	0/35 (0%)	3/29 (10%)	1/38 (3%)
First incidence (days)	729 (T)	—	657	729 (T)
Poly-3 test	P=0.529N	P=0.225N	P=0.363	P=0.466N
Small Intestine (Duodenum or Jejunum): Adenoma or Carcinoma				
Overall rate	2/50 (4%)	1/50 (2%)	4/50 (8%)	1/50 (2%)
Adjusted rate	4.9%	2.3%	9.2%	2.2%
Terminal rate	2/30 (7%)	1/35 (3%)	3/29 (10%)	1/38 (3%)
First incidence (days)	729 (T)	729 (T)	657	729 (T)
Poly-3 test	P=0.425N	P=0.481N	P=0.363	P=0.466N
Liver: Hemangiosarcoma				
Overall rate	2/50 (4%)	1/50 (2%)	4/50 (8%)	5/50 (10%)
Adjusted rate	4.9%	2.3%	9.2%	10.6%
Terminal rate	2/30 (7%)	0/35 (0%)	2/29 (7%)	1/38 (3%)
First incidence (days)	729 (T)	568	657	480
Poly-3 test	P=0.113	P=0.477N	P=0.363	P=0.274
Liver: Hepatocellular Adenoma				
Overall rate	34/50 (68%)	35/50 (70%)	32/50 (64%)	34/50 (68%)
Adjusted rate	76.2%	76.0%	69.1%	71.6%
Terminal rate	24/30 (80%)	28/35 (80%)	21/29 (72%)	27/38 (71%)
First incidence (days)	530	442	561	583
Poly-3 test	P=0.345N	P=0.593N	P=0.290N	P=0.391N

TABLE C2
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Dermal Study of Trimethylolpropane Triacrylate

	Vehicle Control	0.3 mg/kg	1.0 mg/kg	3.0 mg/kg
Liver: Hepatocellular Carcinoma				
Overall rate	22/50 (44%)	14/50 (28%)	19/50 (38%)	25/50 (50%)
Adjusted rate	49.5%	31.0%	41.8%	53.6%
Terminal rate	14/30 (47%)	11/35 (31%)	11/29 (38%)	21/38 (55%)
First incidence (days)	429	425	380	480
Poly-3 test	P=0.102	P=0.054N	P=0.298N	P=0.428
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rate	37/50 (74%)	39/50 (78%)	40/50 (80%)	40/50 (80%)
Adjusted rate	80.9%	82.5%	83.0%	83.0%
Terminal rate	25/30 (83%)	30/35 (86%)	24/29 (83%)	32/38 (84%)
First incidence (days)	429	425	380	480
Poly-3 test	P=0.489	P=0.528	P=0.502	P=0.504
Liver: Hepatoblastoma				
Overall rate	5/50 (10%)	5/50 (10%)	4/50 (8%)	5/50 (10%)
Adjusted rate	12.1%	11.5%	9.2%	11.0%
Terminal rate	3/30 (10%)	4/35 (11%)	3/29 (10%)	4/38 (11%)
First incidence (days)	686	648	681	622
Poly-3 test	P=0.537N	P=0.597N	P=0.471N	P=0.568N
Liver: Hepatocellular Carcinoma or Hepatoblastoma				
Overall rate	26/50 (52%)	18/50 (36%)	21/50 (42%)	28/50 (56%)
Adjusted rate	58.1%	39.6%	46.2%	59.5%
Terminal rate	16/30 (53%)	14/35 (40%)	13/29 (45%)	23/38 (61%)
First incidence (days)	429	425	380	480
Poly-3 test	P=0.161	P=0.056N	P=0.173N	P=0.529
Liver: Hepatocellular Adenoma, Hepatocellular Carcinoma, or Hepatoblastoma				
Overall rate	38/50 (76%)	40/50 (80%)	41/50 (82%)	41/50 (82%)
Adjusted rate	82.8%	84.6%	85.1%	85.0%
Terminal rate	25/30 (83%)	31/35 (89%)	25/29 (86%)	33/38 (87%)
First incidence (days)	429	425	380	480
Poly-3 test	P=0.482	P=0.517	P=0.492	P=0.493
Liver: Hepatocholangiocarcinoma				
Overall rate	2/50 (4%)	0/50 (0%)	3/50 (6%)	0/50 (0%)
Adjusted rate	4.8%	0.0%	6.8%	0.0%
Terminal rate	0/30 (0%)	0/35 (0%)	0/29 (0%)	0/38 (0%)
First incidence (days)	632	—	605	—
Poly-3 test	P=0.275N	P=0.228N	P=0.523	P=0.219N
Lung: Aveolar/bronchiolar Adenoma				
Overall rate	1/50 (2%)	6/50 (12%)	10/50 (20%)	4/50 (8%)
Adjusted rate	2.4%	13.6%	23.0%	8.8%
Terminal rate	0/30 (0%)	4/35 (11%)	8/29 (28%)	3/38 (8%)
First incidence (days)	629	567	662	718
Poly-3 test	P=0.561	P=0.066	P=0.005	P=0.207
Lung: Aveolar/bronchiolar Carcinoma				
Overall rate	12/50 (24%)	11/50 (22%)	3/50 (6%)	10/50 (20%)
Adjusted rate	27.4%	24.8%	7.0%	21.7%
Terminal rate	6/30 (20%)	8/35 (23%)	3/29 (10%)	9/38 (24%)
First incidence (days)	429	568	729 (T)	479
Poly-3 test	P=0.371N	P=0.488N	P=0.010N	P=0.354N

TABLE C2
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Dermal Study of Trimethylolpropane Triacrylate

	Vehicle Control	0.3 mg/kg	1.0 mg/kg	3.0 mg/kg
Lung: Aveolar/bronchiolar Adenoma or Carcinoma				
Overall rate	13/50 (26%)	17/50 (34%)	13/50 (26%)	14/50 (28%)
Adjusted rate	29.4%	37.6%	29.8%	30.4%
Terminal rate	6/30 (20%)	12/35 (34%)	11/29 (38%)	12/38 (32%)
First incidence (days)	429	567	662	479
Poly-3 test	P=0.440N	P=0.275	P=0.575	P=0.550
Pancreatic Islets: Adenoma				
Overall rate	0/50 (0%)	5/49 (10%)	1/44 (2%)	0/50 (0%)
Adjusted rate	0.0%	11.5%	2.5%	0.0%
Terminal rate	0/30 (0%)	4/35 (11%)	0/29 (0%)	0/38 (0%)
First incidence (days)	—	649	626	—
Poly-3 test	P=0.116N	P=0.035	P=0.492	—[f]
Skin: Hemangiosarcoma				
Overall rate	2/50 (4%)	1/50 (2%)	3/50 (6%)	0/50 (0%)
Adjusted rate	4.8%	2.3%	6.9%	0.0%
Terminal rate	1/30 (3%)	1/35 (3%)	2/29 (7%)	0/38 (0%)
First incidence (days)	645	729 (T)	717	—
Poly-3 test	P=0.200N	P=0.484N	P=0.520	P=0.218N
Spleen: Hemangiosarcoma				
Overall rate	4/49 (8%)	1/48 (2%)	1/45 (2%)	1/49 (2%)
Adjusted rate	9.8%	2.4%	2.5%	2.2%
Terminal rate	3/30 (10%)	1/35 (3%)	0/29 (0%)	0/38 (0%)
First incidence (days)	655	729 (T)	717	480
Poly-3 test	P=0.220N	P=0.164N	P=0.182N	P=0.148N
Stomach (Forestomach): Squamous Cell Papilloma				
Overall rate	3/50 (6%)	1/50 (2%)	0/50 (0%)	0/50 (0%)
Adjusted rate	7.2%	2.3%	0.0%	0.0%
Terminal rate	2/30 (7%)	1/35 (3%)	0/29 (0%)	0/38 (0%)
First incidence (days)	610	729 (T)	—	—
Poly-3 test	P=0.094N	P=0.289N	P=0.111N	P=0.104N
All Organs: Hemangiosarcoma				
Overall rate	6/50 (12%)	4/50 (8%)	8/50 (16%)	6/50 (12%)
Adjusted rate	14.4%	9.1%	18.3%	12.8%
Terminal rate	4/30 (13%)	3/35 (9%)	5/29 (17%)	2/38 (5%)
First incidence (days)	645	568	657	480
Poly-3 test	P=0.560	P=0.336N	P=0.423	P=0.534N
All Organs: Hemangioma or Hemangiosarcoma				
Overall rate	6/50 (12%)	4/50 (8%)	9/50 (18%)	7/50 (14%)
Adjusted rate	14.4%	9.1%	20.4%	14.9%
Terminal rate	4/30 (13%)	3/35 (9%)	5/29 (17%)	3/38 (8%)
First incidence (days)	645	568	614	480
Poly-3 test	P=0.433	P=0.336N	P=0.327	P=0.592
All Organs: Histocytic Sarcoma				
Overall rate	0/50 (0%)	3/50 (6%)	0/50 (0%)	0/50 (0%)
Adjusted rate	0.0%	6.7%	0.0%	0.0%
Terminal rate	0/30 (0%)	0/35 (0%)	0/29 (0%)	0/38 (0%)
First incidence (days)	—	567	—	—
Poly-3 test	P=0.224N	P=0.134	—	—

TABLE C2
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Dermal Study of Trimethylolpropane Triacrylate

	Vehicle Control	0.3 mg/kg	1.0 mg/kg	3.0 mg/kg
All Organs: Malignant Lymphoma				
Overall rate	2/50 (4%)	3/50 (6%)	4/50 (8%)	2/50 (4%)
Adjusted rate	4.9%	6.9%	9.1%	4.4%
Terminal rate	2/30 (7%)	2/35 (6%)	3/29 (10%)	1/38 (3%)
First incidence (days)	729 (T)	698	556	675
Poly-3 test	P=0.458N	P=0.526	P=0.366	P=0.657N
All Organs: Benign Neoplasms				
Overall rate	37/50 (74%)	41/50 (82%)	36/50 (72%)	37/50 (74%)
Adjusted rate	80.5%	86.5%	77.0%	77.9%
Terminal rate	25/30 (83%)	31/35 (89%)	24/29 (83%)	30/38 (79%)
First incidence (days)	460	442	561	583
Poly-3 test	P=0.281N	P=0.300	P=0.434N	P=0.476N
All Organs: Malignant Neoplasms				
Overall rate	38/50 (76%)	28/50 (56%)	32/50 (64%)	36/50 (72%)
Adjusted rate	79.0%	58.8%	67.9%	73.6%
Terminal rate	21/30 (70%)	18/35 (51%)	18/29 (62%)	27/38 (71%)
First incidence (days)	429	425	380	479
Poly-3 test	P=0.395	P=0.024N	P=0.154N	P=0.348N
All Organs: Benign or Malignant Neoplasms				
Overall rate	46/50 (92%)	48/50 (96%)	47/50 (94%)	44/50 (88%)
Adjusted rate	94.6%	97.4%	95.1%	89.9%
Terminal rate	28/30 (93%)	34/35 (97%)	28/29 (97%)	35/38 (92%)
First incidence (days)	429	425	380	479
Poly-3 test	P=0.105N	P=0.418	P=0.643	P=0.306N

(T)Terminal kill

[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, liver, lung, pancreatic islets, and spleen; for other tissues, denominator is number of animals necropsied.

[b] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality

[c] Observed incidence at terminal kill

[d] Beneath the vehicle control incidence is the P value associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the vehicle controls and that dosed group. The Poly-3 test accounts for the differential mortality in animals that do not reach terminal kill. 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 C3
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Dermal Study of Trimethylolpropane Triacrylate [a]

	Vehicle Control	0.3 mg/kg	1.0 mg/kg	3.0 mg/kg
Disposition Summary				
Animals initially in study	65	65	65	65
2-Week interim evaluation	5	5	5	5
13-Week interim evaluation	5	5	5	5
12-Month interim evaluation	5	5	5	5
Early deaths				
Moribund	8	7	10	4
Natural deaths	12	8	11	8
Survivors				
Terminal kill	30	35	29	38
Animals examined microscopically	65	65	65	65
2-Week Interim Evaluation				
Integumentary System				
Skin	(5)	(5)	(5)	(5)
Site of application, hyperplasia	0	2 (40%)	1 (20%)	5 (100%)
Site of application, inflammation, chronic active	0	2 (40%)	1 (20%)	5 (100%)
13-Week Interim Evaluation				
Integumentary System				
Skin	(5)	(5)	(5)	(5)
Site of application, hyperplasia	0	1 (20%)	2 (40%)	5 (100%)
Site of application, inflammation, chronic active	0	0	2 (40%)	5 (100%)
Site of application, sebaceous gland, hyperplasia	0	0	0	5 (100%)
12-Month Interim Evaluation				
Integumentary System				
Skin	(5)	(5)	(5)	(5)
Site of application, hyperplasia	1 (20%)	0	3 (60%)	5 (100%)
Site of application, inflammation	0	0	0	4 (80%)
2-Year Study				
Alimentary System				
Esophagus	(50)	(50)	(50)	(49)
Inflammation, chronic active				1 (2%)
Gallbladder	(38)	(41)	(37)	(43)
Intestine large, cecum	(42)	(43)	(40)	(44)
Edema			1 (3%)	
Hemorrhage				1 (2%)
Necrosis			1 (3%)	
Thrombosis			1 (3%)	
Intestine large, colon	(44)	(44)	(41)	(46)
Diverticulum				1 (2%)
Intestine large, rectum	(45)	(44)	(41)	(47)
Inflammation, acute			1 (2%)	
Intestine small, duodenum	(40)	(43)	(40)	(46)
Edema			1 (3%)	
Inflammation, chronic			1 (3%)	

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

TABLE C3
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Dermal Study of Trimethylolpropane Triacrylate

	Vehicle Control	0.3 mg/kg	1.0 mg/kg	3.0 mg/kg
Alimentary System (continued)				
Intestine small, ileum	(42)	(43)	(40)	(45)
Hemorrhage	1 (2%)			
Hyperplasia, lymphoid			1 (3%)	
Inflammation, acute		2 (5%)	2 (5%)	
Inflammation, chronic active		1 (2%)		
Necrosis	1 (2%)	1 (2%)	1 (3%)	
Thrombosis			1 (3%)	
Epithelium, hyperplasia		1 (2%)		
Muscularis, hyperplasia		1 (2%)		
Intestine small, jejunum	(40)	(42)	(40)	(44)
Hemorrhage			1 (3%)	
Hyperplasia, lymphoid	1 (3%)		3 (8%)	
Inflammation, granulomatous				1 (2%)
Inflammation, acute		1 (2%)	1 (3%)	
Inflammation, chronic active				1 (2%)
Mineralization		1 (2%)		
Necrosis		2 (5%)	1 (3%)	
Muscularis, hyperplasia		1 (2%)		
Liver	(50)	(50)	(50)	(50)
Amyloid deposition			1 (2%)	
Angiectasis		1 (2%)	1 (2%)	1 (2%)
Basophilic focus	2 (4%)	2 (4%)	6 (12%)	4 (8%)
Clear cell focus	24 (48%)	23 (46%)	18 (36%)	24 (48%)
Congestion	2 (4%)		1 (2%)	
Cytoplasmic alteration			1 (2%)	
Eosinophilic focus	18 (36%)	23 (46%)	26 (52%)	19 (38%)
Fatty change	1 (2%)		2 (4%)	
Fibrosis		1 (2%)		
Hematopoietic cell proliferation	2 (4%)	3 (6%)		3 (6%)
Hemorrhage	2 (4%)		1 (2%)	
Infarct				1 (2%)
Inflammation, chronic		3 (6%)		2 (4%)
Inflammation, chronic active	4 (8%)	7 (14%)	6 (12%)	4 (8%)
Mineralization			1 (2%)	1 (2%)
Mixed cell focus	2 (4%)	2 (4%)	2 (4%)	1 (2%)
Necrosis	1 (2%)			2 (4%)
Necrosis, focal	11 (22%)	10 (20%)	11 (22%)	6 (12%)
Tension lipidosis		2 (4%)		1 (2%)
Thrombosis		1 (2%)	1 (2%)	2 (4%)
Bile duct, cyst	1 (2%)			
Centrilobular, necrosis	2 (4%)		5 (10%)	1 (2%)
Hepatocyte, vacuolization cytoplasmic	1 (2%)	3 (6%)	2 (4%)	3 (6%)
Kupffer cell, hyperplasia			1 (2%)	
Kupffer cell, pigmentation	2 (4%)	2 (4%)	4 (8%)	4 (8%)
Oval cell, hyperplasia			1 (2%)	
Mesentery	(9)	(8)	(11)	(6)
Fibrosis			1 (9%)	
Fat, necrosis	8 (89%)	8 (100%)	8 (73%)	6 (100%)
Oral mucosa	(0)	(1)	(0)	(0)
Pancreas	(50)	(49)	(45)	(50)
Atrophy	2 (4%)	3 (6%)	5 (11%)	3 (6%)
Cyst	1 (2%)		1 (2%)	1 (2%)
Hemorrhage	1 (2%)			
Hyperplasia, lymphoid	7 (14%)	12 (24%)	19 (42%)	8 (16%)
Infiltration cellular, lipocyte				1 (2%)
Inflammation, chronic		1 (2%)		
Inflammation, chronic active				1 (2%)
Necrosis				1 (2%)

TABLE C3
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Dermal Study of Trimethylolpropane Triacrylate

	Vehicle Control	0.3 mg/kg	1.0 mg/kg	3.0 mg/kg
Alimentary System (continued)				
Salivary glands	(50)	(50)	(50)	(50)
Atrophy	1 (2%)		1 (2%)	3 (6%)
Hyperplasia, lymphoid	36 (72%)	38 (76%)	37 (74%)	40 (80%)
Mineralization	2 (4%)		1 (2%)	
Pigmentation	1 (2%)			
Stomach, forestomach	(50)	(49)	(48)	(50)
Cyst			1 (2%)	
Edema	3 (6%)	2 (4%)	1 (2%)	
Erosion	1 (2%)	1 (2%)		2 (4%)
Hemorrhage				1 (2%)
Inflammation		1 (2%)		
Inflammation, acute		1 (2%)		
Inflammation, chronic	2 (4%)	1 (2%)	2 (4%)	1 (2%)
Inflammation, chronic active	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Necrosis	1 (2%)			
Ulcer	9 (18%)	4 (8%)	5 (10%)	5 (10%)
Epithelium, hyperplasia	11 (22%)	10 (20%)	8 (17%)	10 (20%)
Stomach, glandular	(48)	(49)	(44)	(49)
Congestion				1 (2%)
Cyst	14 (29%)	19 (39%)	16 (36%)	21 (43%)
Dysplasia			1 (2%)	
Erosion	4 (8%)	3 (6%)	2 (5%)	2 (4%)
Foreign body	1 (2%)			
Hemorrhage	1 (2%)			
Inflammation, granulomatous	1 (2%)			
Inflammation, acute		2 (4%)	1 (2%)	2 (4%)
Inflammation, chronic		1 (2%)	1 (2%)	
Inflammation, chronic active		1 (2%)	2 (5%)	
Metaplasia				1 (2%)
Metaplasia, squamous	3 (6%)		5 (11%)	1 (2%)
Mineralization	1 (2%)	3 (6%)	2 (5%)	8 (16%)
Necrosis		2 (4%)		1 (2%)
Ulcer	1 (2%)		4 (9%)	1 (2%)
Glands, ectasia	5 (10%)	9 (18%)	5 (11%)	6 (12%)
Glands, hyperplasia, cystic				1 (2%)
Cardiovascular System				
Blood vessel	(1)	(0)	(0)	(1)
Inflammation, chronic				1 (100%)
Thrombosis				1 (100%)
Heart	(50)	(50)	(50)	(50)
Cardiomyopathy	22 (44%)	27 (54%)	28 (56%)	30 (60%)
Inflammation, acute			3 (6%)	
Inflammation, chronic active			1 (2%)	
Mineralization		1 (2%)	3 (6%)	1 (2%)
Thrombosis		2 (4%)	1 (2%)	1 (2%)
Myocardium, necrosis	2 (4%)		1 (2%)	

TABLE C3
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Dermal Study of Trimethylolpropane Triacrylate

	Vehicle Control	0.3 mg/kg	1.0 mg/kg	3.0 mg/kg
Endocrine System				
Adrenal cortex	(50)	(49)	(47)	(50)
Accessory adrenal cortical nodule	5 (10%)	4 (8%)	1 (2%)	3 (6%)
Degeneration, hydropic		1 (2%)		
Hyperplasia				1 (2%)
Hypertrophy, focal	14 (28%)	24 (49%)	17 (36%)	17 (34%)
Necrosis				1 (2%)
Capsule, hyperplasia	37 (74%)	33 (67%)	36 (77%)	41 (82%)
Adrenal medulla	(49)	(49)	(46)	(50)
Hyperplasia	1 (2%)	4 (8%)	3 (7%)	10 (20%)
Islets, pancreatic	(50)	(49)	(44)	(50)
Hyperplasia	26 (52%)	33 (67%)	21 (48%)	34 (68%)
Parathyroid gland	(48)	(48)	(48)	(50)
Amyloid deposition			1 (2%)	
Cyst	2 (4%)	3 (6%)	3 (6%)	1 (2%)
Pituitary gland	(50)	(48)	(49)	(50)
Pars distalis, cyst		3 (6%)	4 (8%)	2 (4%)
Pars distalis, hyperplasia, focal		1 (2%)	1 (2%)	1 (2%)
Thyroid gland	(50)	(47)	(46)	(48)
Cyst			1 (2%)	
Hemorrhage			1 (2%)	
Inflammation, chronic		1 (2%)		
Follicle, degeneration, focal	14 (28%)	15 (32%)	20 (43%)	14 (29%)
Follicular cell, hyperplasia, focal		1 (2%)	1 (2%)	1 (2%)
General Body System				
Tissue NOS	(2)	(1)	(1)	(0)
Fibrosis	1 (50%)	1 (100%)		
Necrosis	1 (50%)			
Genital System				
Coagulating gland	(0)	(0)	(1)	(0)
Necrosis			1 (100%)	
Epididymis	(49)	(50)	(50)	(50)
Angiectasis	1 (2%)			
Atrophy			1 (2%)	
Fibrosis			1 (2%)	
Granuloma sperm		2 (4%)		
Inflammation, chronic	6 (12%)	16 (32%)	14 (28%)	10 (20%)
Necrosis		1 (2%)		
Preputial gland	(50)	(50)	(50)	(50)
Cyst	2 (4%)	4 (8%)	5 (10%)	6 (12%)
Inflammation, chronic	16 (32%)	17 (34%)	18 (36%)	18 (36%)
Inflammation, chronic active	1 (2%)			
Bilateral, cyst	1 (2%)			
Prostate	(50)	(49)	(49)	(50)
Fibrosis		1 (2%)		
Infiltration cellular, lymphoid	1 (2%)			
Inflammation, suppurative			1 (2%)	1 (2%)
Inflammation, chronic	21 (42%)	24 (49%)	23 (47%)	26 (52%)
Necrosis		1 (2%)	1 (2%)	2 (4%)

TABLE C3
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Dermal Study of Trimethylolpropane Triacrylate

	Vehicle Control	0.3 mg/kg	1.0 mg/kg	3.0 mg/kg
Genital System (continued)				
Seminal vesicle	(50)	(50)	(49)	(50)
Infiltration cellular, lymphoid	1 (2%)			
Inflammation, suppurative			1 (2%)	
Inflammation, chronic	8 (16%)	10 (20%)	7 (14%)	6 (12%)
Inflammation, chronic active		1 (2%)		
Necrosis		1 (2%)	1 (2%)	
Epithelium, hyperplasia		1 (2%)		
Testes	(50)	(50)	(50)	(50)
Hemorrhage		1 (2%)	1 (2%)	
Inflammation, chronic		1 (2%)		
Mineralization			1 (2%)	
Thrombosis				1 (2%)
Germinal epithelium, atrophy	4 (8%)	6 (12%)	5 (10%)	7 (14%)
Interstitial cell, hyperplasia		6 (12%)	3 (6%)	
Hematopoietic System				
Bone marrow	(50)	(49)	(50)	(50)
Depletion cellular			1 (2%)	
Hemorrhage			1 (2%)	
Hyperplasia	1 (2%)	2 (4%)	1 (2%)	2 (4%)
Infiltration cellular, histiocyte				1 (2%)
Necrosis	1 (2%)		1 (2%)	1 (2%)
Lymph node	(5)	(6)	(2)	(1)
Hyperplasia, lymphoid	3 (60%)		1 (50%)	
Pigmentation	1 (20%)		1 (50%)	
Bronchial, hyperplasia, lymphoid		1 (17%)		
Iliac, hyperplasia, lymphoid		1 (17%)		
Mediastinal, ectasia	1 (20%)			
Mediastinal, hyperplasia, lymphoid	1 (20%)			1 (100%)
Pancreatic, hyperplasia, lymphoid		1 (17%)		
Renal, hemorrhage		1 (17%)		
Lymph node, mandibular	(48)	(48)	(46)	(46)
Atrophy		1 (2%)		
Ectasia	1 (2%)			1 (2%)
Hemorrhage	1 (2%)			
Hyperplasia, lymphoid	13 (27%)	20 (42%)	14 (30%)	7 (15%)
Inflammation, granulomatous				1 (2%)
Mineralization				1 (2%)
Lymph node, mesenteric	(48)	(47)	(45)	(50)
Angiectasis				1 (2%)
Atrophy	2 (4%)	2 (4%)	1 (2%)	1 (2%)
Congestion	1 (2%)			
Ectasia		2 (4%)		2 (4%)
Hematopoietic cell proliferation		1 (2%)		1 (2%)
Hemorrhage	3 (6%)	5 (11%)	7 (16%)	6 (12%)
Hyperplasia, lymphoid	27 (56%)	30 (64%)	28 (62%)	30 (60%)
Infiltration cellular, lipocyte				1 (2%)
Inflammation, acute			2 (4%)	1 (2%)
Inflammation, chronic		1 (2%)		
Inflammation, chronic active			1 (2%)	

TABLE C3
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Dermal Study of Trimethylolpropane Triacrylate

	Vehicle Control	0.3 mg/kg	1.0 mg/kg	3.0 mg/kg
Hematopoietic System (continued)				
Spleen	(49)	(48)	(45)	(49)
Angiectasis	1 (2%)			
Fibrosis	1 (2%)			
Hematopoietic cell proliferation	15 (31%)	16 (33%)	23 (51%)	19 (39%)
Hyperplasia, lymphoid		2 (4%)	1 (2%)	2 (4%)
Necrosis		1 (2%)	1 (2%)	1 (2%)
Pigmentation	1 (2%)	1 (2%)	2 (4%)	1 (2%)
Lymphoid follicle, atrophy		2 (4%)	1 (2%)	
Lymphoid follicle, hyperplasia	18 (37%)	25 (52%)	17 (38%)	21 (43%)
Thymus	(48)	(48)	(44)	(47)
Cyst	8 (17%)	14 (29%)	13 (30%)	15 (32%)
Hemorrhage			2 (5%)	
Hyperplasia, lymphoid	3 (6%)	9 (19%)	6 (14%)	3 (6%)
Epithelial cell, hyperplasia		1 (2%)		
Integumentary System				
Skin	(50)	(50)	(50)	(50)
Cyst epithelial inclusion	1 (2%)			
Edema				1 (2%)
Erosion			1 (2%)	
Hyperkeratosis	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Infiltration cellular, melanocyte		1 (2%)		
Inflammation, chronic				2 (4%)
Inflammation, chronic active		1 (2%)	1 (2%)	
Mineralization		1 (2%)		
Necrosis		1 (2%)		
Ulcer	1 (2%)			
Control, fibrosis			1 (2%)	
Control, hyperkeratosis	17 (34%)	24 (48%)	22 (44%)	21 (42%)
Control, hyperplasia, melanocyte			1 (2%)	
Control, inflammation, acute	1 (2%)			
Control, inflammation, chronic	8 (16%)	10 (20%)	13 (26%)	16 (32%)
Control, vacuolization cytoplasmic			1 (2%)	
Control, hair follicle, dilatation		1 (2%)		1 (2%)
Control, subcutaneous tissue, hemorrhage		1 (2%)		
Control epidermis, hyperplasia	2 (4%)		3 (6%)	3 (6%)
Epidermis, hyperplasia	1 (2%)			
Epidermis, site of application, hyperplasia	10 (20%)	7 (14%)	15 (30%)	44 (88%)
Hair follicle, site of application, dilatation		1 (2%)	1 (2%)	
Lip, inflammation, acute			1 (2%)	
Prepuce, ulcer		1 (2%)		
Sebaceous gland, hyperplasia	1 (2%)			
Sebaceous gland, site of application, hyperplasia		1 (2%)		
Site of application, erosion				1 (2%)
Site of application, fibrosis		1 (2%)		
Site of application, hemorrhage		1 (2%)		
Site of application, hyperkeratosis	45 (90%)	50 (100%)	49 (98%)	50 (100%)
Site of application, hyperplasia, melanocyte				19 (38%)
Site of application, inflammation, acute	1 (2%)	2 (4%)		3 (6%)
Site of application, inflammation, chronic	13 (26%)	17 (34%)	26 (52%)	43 (86%)
Site of application, ulcer		2 (4%)		2 (4%)
Site of application, vacuolization cytoplasmic			1 (2%)	1 (2%)

TABLE C3
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Dermal Study of Trimethylolpropane Triacrylate

	Vehicle Control	0.3 mg/kg	1.0 mg/kg	3.0 mg/kg
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Osteopetrosis		1 (2%)		
Cranium, osteopetrosis	1 (2%)			1 (2%)
Skeletal muscle	(3)	(2)	(6)	(1)
Angiectasis			1 (17%)	
Degeneration	2 (67%)			
Hemorrhage			1 (17%)	1 (100%)
Inflammation, chronic		1 (50%)		
Inflammation, chronic active	1 (33%)			
Necrosis			1 (17%)	
Capillary, hyperplasia			1 (17%)	
Nervous System				
Brain	(50)	(50)	(50)	(50)
Congestion	1 (2%)	1 (2%)		
Demyelination		1 (2%)		2 (4%)
Gliosis	1 (2%)			1 (2%)
Hemorrhage	4 (8%)	3 (6%)	3 (6%)	5 (10%)
Hyperplasia, lymphoid	1 (2%)		1 (2%)	1 (2%)
Inflammation, acute	1 (2%)			
Inflammation, chronic	1 (2%)			
Necrosis	2 (4%)		3 (6%)	
Peripheral nerve	(2)	(1)	(4)	(1)
Degeneration	1 (50%)	1 (100%)	3 (75%)	1 (100%)
Spinal cord	(2)	(1)	(4)	(0)
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Congestion	1 (2%)		2 (4%)	
Fibrosis				1 (2%)
Hemorrhage	7 (14%)	5 (10%)	3 (6%)	4 (8%)
Hyperplasia, lymphoid	1 (2%)		1 (2%)	
Infiltration cellular, histiocyte	13 (26%)	14 (28%)	9 (18%)	13 (26%)
Inflammation, suppurative	1 (2%)	1 (2%)		1 (2%)
Inflammation, chronic	1 (2%)			1 (2%)
Metaplasia, osseous	5 (10%)	1 (2%)		
Mineralization	`1 (2%)		1 (2%)	2 (4%)
Thrombosis	4 (8%)	1 (2%)	3 (6%)	2 (4%)
Alveolar epithelium, hyperplasia	6 (12%)	9 (18%)	7 (14%)	5 (10%)
Glands, hyperplasia	1 (2%)			
Nose	(50)	(50)	(50)	(50)
Foreign body		1 (2%)	2 (4%)	
Hemorrhage	1 (2%)			
Inflammation, chronic	7 (14%)	11 (22%)	5 (10%)	9 (18%)
Polyp, inflammatory	2 (4%)	1 (2%)		
Glands, atrophy				1 (2%)
Goblet cell, hyperplasia			1 (2%)	
Respiratory epithelium, hyperplasia	1 (2%)	1 (2%)		3 (6%)
Trachea	(50)	(50)	(50)	(50)
Hemorrhage				1 (2%)
Inflammation, chronic			1 (2%)	
Necrosis			1 (2%)	

TABLE C3
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Dermal Study of Trimethylolpropane Triacrylate

	Vehicle Control	0.3 mg/kg	1.0 mg/kg	3.0 mg/kg
Special Senses System				
Eye	(48)	(47)	(41)	(47)
Atrophy	1 (2%)			2 (4%)
Cataract	1 (2%)		1 (2%)	
Inflammation, chronic	1 (2%)	1 (2%)	2 (5%)	2 (4%)
Inflammation, chronic active		1 (2%)		
Cornea, hyperplasia	1 (2%)	2 (4%)	1 (2%)	2 (4%)
Lens, degeneration		1 (2%)		1 (2%)
Harderian gland	(50)	(49)	(49)	(50)
Hyperplasia, focal	3 (6%)	6 (12%)	3 (6%)	3 (6%)
Inflammation, chronic	26 (52%)	23 (47%)	20 (41%)	28 (56%)
Urinary System				
Kidney	(48)	(46)	(42)	(49)
Amyloid deposition			1 (2%)	
Casts protein	2 (4%)	1 (2%)	1 (2%)	2 (4%)
Cyst	13 (27%)	13 (28%)	13 (31%)	9 (18%)
Dilatation				1 (2%)
Glomerulosclerosis	1 (2%)		2 (5%)	
Hyperplasia, lymphoid	34 (71%)	38 (83%)	31 (74%)	36 (73%)
Infarct	3 (6%)	3 (7%)	3 (7%)	4 (8%)
Inflammation, suppurative	1 (2%)	1 (2%)	3 (7%)	1 (2%)
Inflammation, chronic				1 (2%)
Metaplasia, osseous	9 (19%)	3 (7%)	5 (12%)	3 (6%)
Mineralization	17 (35%)	29 (63%)	17 (40%)	31 (63%)
Nephropathy	39 (81%)	41 (89%)	38 (90%)	42 (86%)
Thrombosis			1 (2%)	1 (2%)
Artery, inflammation, suppurative	1 (2%)			
Papilla, necrosis	2 (4%)	2 (4%)		1 (2%)
Pelvis, dilatation	3 (6%)	3 (7%)	1 (2%)	5 (10%)
Renal tubule, accumulation, hyaline droplet	1 (2%)			
Renal tubule, dilatation, focal	16 (33%)	15 (33%)	14 (33%)	22 (45%)
Renal tubule, dilatation, diffuse	1 (2%)	1 (2%)	1 (2%)	4 (8%)
Renal tubule, hyperplasia				2 (4%)
Renal tubule, necrosis	1 (2%)	1 (2%)	2 (5%)	1 (2%)
Renal tubule, pigmentation			2 (5%)	
Transitional epithelium, hyperplasia		1 (2%)		1 (2%)
Urethra	(0)	(1)	(2)	(3)
Inflammation, acute				1 (33%)
Necrosis				2 (67%)
Bulbourethral gland, infiltration cellular			1 (50%)	2 (67%)
Bulbourethral gland, necrosis		1 (100%)	1 (50%)	
Transitional epithelium, hyperplasia				1 (33%)
Urinary bladder	(47)	(48)	(42)	(49)
Edema		1 (2%)		2 (4%)
Hemorrhage	1 (2%)			2 (4%)
Hyperplasia, lymphoid	18 (38%)	22 (46%)	16 (38%)	19 (39%)
Inflammation, chronic		1 (2%)		2 (4%)
Inflammation, chronic active		1 (2%)		
Mineralization			1 (2%)	
Necrosis	1 (2%)	2 (4%)	1 (2%)	1 (2%)
Ulcer				1 (2%)
Muscularis, degeneration		1 (2%)		
Transitional epithelium, hyperplasia	1 (2%)	1 (2%)		2 (4%)

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

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

	Vehicle Control	0.3 mg/kg	1.0 mg/kg	3.0 mg/kg
Disposition Summary				
Animals initially in study	65	65	65	65
2-Week interim evaluation	5	5	5	5
13-Week interim evaluation	5	5	5	5
12-Month interim evaluation	5	5	5	5
Early deaths				
Accidental death		1		
Moribund	8	7	8	7
Natural deaths	3	11	12	13
Survivors				
Died last week of study			1	
Terminal kill	39	31	29	30
Animals examined microscopically	65	65	65	65
2-Week Interim Evaluation				
Integumentary System				
Skin	(5)	(5)	(5)	(5)
13-Week Interim Evaluation				
Integumentary System				
Skin	(5)	(5)	(5)	(5)
12-Month Interim Evaluation				
Integumentary System				
Skin	(5)	(5)	(5)	(5)
2-Year Study				
Alimentary System				
Esophagus	(50)	(50)	(50)	(50)
Gallbladder	(46)	(41)	(39)	(40)
Intestine large, cecum	(47)	(42)	(40)	(42)
Intestine large, colon	(47)	(44)	(41)	(44)
Liposarcoma, metastatic, mesentery				1 (2%)
Intestine large, rectum	(48)	(44)	(40)	(43)
Intestine small, duodenum	(47)	(42)	(40)	(39)
Adenoma				1 (3%)
Carcinoma	1 (2%)	1 (2%)		1 (3%)
Intestine small, ileum	(48)	(42)	(40)	(40)
Intestine small, jejunum	(47)	(41)	(41)	(40)
Carcinoma		1 (2%)		1 (3%)

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

	Vehicle Control	0.3 mg/kg	1.0 mg/kg	3.0 mg/kg
Alimentary System (continued)				
Liver	(50)	(50)	(50)	(50)
Carcinoma, metastatic, pancreas		1 (2%)		
Fibrosarcoma, metastatic, skin			1 (2%)	
Hemangiosarcoma			3 (6%)	2 (4%)
Hepatoblastoma		3 (6%)		3 (6%)
Hepatoblastoma, multiple		1 (2%)		
Hepatocellular adenoma	11 (22%)	5 (10%)	9 (18%)	10 (20%)
Hepatocellular adenoma, multiple	23 (46%)	29 (58%)	22 (44%)	26 (52%)
Hepatocellular carcinoma	9 (18%)	10 (20%)	5 (10%)	17 (34%)
Hepatocellular carcinoma, multiple	3 (6%)	3 (6%)	5 (10%)	2 (4%)
Hepatocholangiocarcinoma			1 (2%)	2 (4%)
Liposarcoma, metastatic, mesentery				1 (2%)
Osteosarcoma, metastatic, bone				1 (2%)
Sarcoma, metastatic, skeletal muscle			1 (2%)	
Sarcoma, metastatic, skin			1 (2%)	1 (2%)
Sarcoma, metastatic, uncertain primary site	1 (2%)			
Sarcoma, metastatic, uterus	1 (2%)			
Mesentery	(24)	(25)	(25)	(14)
Carcinoma, metastatic, pancreas		1 (4%)		
Fibrous histiocytoma, metastatic, skeletal muscle			1 (4%)	
Hemangioma			1 (4%)	
Hemangiosarcoma			1 (4%)	
Hepatoblastoma, metastatic, liver		1 (4%)		
Hepatocholangiocarcinoma, metastatic, liver			1 (4%)	1 (7%)
Liposarcoma				1 (7%)
Osteosarcoma, metastatic, bone				1 (7%)
Sarcoma, metastatic, skeletal muscle			1 (4%)	
Sarcoma, metastatic, skin			1 (4%)	
Sarcoma, metastatic, uncertain primary site	1 (4%)			
Sarcoma, metastatic, uterus	1 (4%)			
Pancreas	(49)	(50)	(46)	(49)
Carcinoma		1 (2%)		
Hepatoblastoma, metastatic, liver		1 (2%)		
Hepatocholangiocarcinoma, metastatic, liver			1 (2%)	1 (2%)
Liposarcoma, metastatic, mesentery				1 (2%)
Sarcoma, metastatic, skeletal muscle			1 (2%)	
Sarcoma, metastatic, skin			1 (2%)	
Sarcoma, metastatic, uncertain primary site	1 (2%)			
Salivary glands	(50)	(50)	(50)	(49)
Stomach, forestomach	(50)	(50)	(47)	(50)
Carcinoma, metastatic, pancreas		1 (2%)		
Liposarcoma, metastatic, mesentery				1 (2%)
Sarcoma, metastatic, uterus	1 (2%)			
Squamous cell papilloma	2 (4%)			
Stomach, glandular	(49)	(46)	(43)	(47)
Liposarcoma, metastatic, mesentery				1 (2%)
Sarcoma, metastatic, skeletal muscle			1 (2%)	
Sarcoma, metastatic, skin			1 (2%)	
Cardiovascular System				
Heart	(50)	(50)	(50)	(50)
Hemangiosarcoma		1 (2%)		
Sarcoma, metastatic, uncertain primary site	1 (2%)			

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

	Vehicle Control	0.3 mg/kg	1.0 mg/kg	3.0 mg/kg
Endocrine System				
Adrenal cortex	(50)	(50)	(46)	(50)
Sarcoma, metastatic, skin			1 (2%)	
Sarcoma, metastatic, uncertain primary site	2 (4%)			
Subcapsular, adenoma		1 (2%)		
Adrenal medulla	(50)	(48)	(45)	(50)
Pheochromocytoma benign		1 (2%)	1 (2%)	1 (2%)
Pheochromocytoma malignant	2 (4%)			
Islets, pancreatic	(49)	(50)	(46)	(49)
Adenoma	2 (4%)		1 (2%)	1 (2%)
Parathyroid gland	(47)	(47)	(44)	(48)
Carcinoma			1 (2%)	
Pituitary gland	(49)	(47)	(49)	(50)
Pars distalis, adenoma	7 (14%)	5 (11%)	8 (16%)	
Pars distalis, carcinoma		1 (2%)		
Pars intermedia, adenoma		1 (2%)	1 (2%)	
Thyroid gland	(49)	(49)	(45)	(48)
Follicular cell, adenoma		1 (2%)		1 (2%)
Follicular cell, carcinoma			1 (2%)	
General Body System				
Tissue NOS	(3)	(2)	(4)	(0)
Carcinoma, metastatic, pancreas		1 (50%)		
Fibrosarcoma	1 (33%)			
Hepatocholangiocarcinoma, metastatic, liver			1 (25%)	
Osteosarcoma, metastatic, bone			1 (25%)	
Sarcoma, metastatic, uterus	1 (33%)			
Genital System				
Clitoral gland	(49)	(48)	(49)	(49)
Squamous cell carcinoma, metastatic, vagina		1 (2%)		
Ovary	(47)	(49)	(45)	(48)
Carcinoma, metastatic, pancreas		1 (2%)		
Cystadenocarcinoma	1 (2%)			
Cystadenoma	1 (2%)	1 (2%)	1 (2%)	
Sarcoma, metastatic, uncertain primary site	1 (2%)			
Uterus	(50)	(50)	(50)	(50)
Polyp stromal		1 (2%)	2 (4%)	5 (10%)
Sarcoma	1 (2%)			
Sarcoma stromal				1 (2%)
Vagina	(0)	(1)	(1)	(1)
Polyp				1 (100%)
Squamous cell carcinoma		1 (100%)		

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

	Vehicle Control	0.3 mg/kg	1.0 mg/kg	3.0 mg/kg
Hematopoietic System				
Bone marrow	(50)	(50)	(49)	(50)
Hemangiosarcoma			1 (2%)	
Sarcoma, metastatic, skin		1 (2%)		
Lymph node	(10)	(7)	(16)	(10)
Fibrosarcoma, metastatic, skin			1 (6%)	
Sarcoma, metastatic, skin			1 (6%)	
Iliac, osteosarcoma, metastatic, bone			1 (6%)	
Iliac, sarcoma, metastatic, uncertain primary site	1 (10%)			
Mediastinal, hepatocholangiocarcinoma, metastatic, liver				1 (10%)
Mediastinal, sarcoma, metastatic, skeletal muscle			1 (6%)	
Mediastinal, sarcoma, metastatic, skin			1 (6%)	
Mediastinal, sarcoma, metastatic, uterus	1 (10%)			
Pancreatic, hepatoblastoma, metastatic, liver		1 (14%)		
Renal, sarcoma, metastatic, uncertain primary site	1 (10%)			
Lymph node, mandibular	(50)	(48)	(48)	(48)
Lymph node, mesenteric	(45)	(46)	(42)	(49)
Hemangiosarcoma				1 (2%)
Spleen	(49)	(48)	(44)	(48)
Hemangioma			1 (2%)	
Hemangiosarcoma		1 (2%)	1 (2%)	
Liposarcoma, metastatic, mesentery				1 (2%)
Sarcoma, metastatic, skin			1 (2%)	
Sarcoma, metastatic, uncertain primary site	1 (2%)			
Thymus	(47)	(49)	(44)	(44)
Hepatocholangiocarcinoma, metastatic, liver			1 (2%)	
Liposarcoma, metastatic, mesentery				1 (2%)
Sarcoma, metastatic, uncertain primary site	1 (2%)			
Thymoma malignant	1 (2%)			
Integumentary System				
Mammary gland	(50)	(50)	(50)	(50)
Carcinoma			1 (2%)	
Skin	(50)	(50)	(50)	(50)
Carcinoma, metastatic, pancreas		1 (2%)		
Fibroma				1 (2%)
Sarcoma	1 (2%)			
Squamous cell papilloma	1 (2%)			
Control, subcutaneous tissue, hemangioma				1 (2%)
Site of application, mast cell tumor benign			1 (2%)	1 (2%)
Subcutaneous tissue, fibrosarcoma	3 (6%)		1 (2%)	
Subcutaneous tissue, hemangiosarcoma	2 (4%)	1 (2%)		2 (4%)
Subcutaneous tissue, melanoma benign	1 (2%)			
Subcutaneous tissue, neural crest tumor	1 (2%)			
Subcutaneous tissue, sarcoma		1 (2%)	1 (2%)	1 (2%)

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

	Vehicle Control	0.3 mg/kg	1.0 mg/kg	3.0 mg/kg
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Hemangiosarcoma			1 (2%)	
Osteosarcoma			2 (4%)	2 (4%)
Sarcoma, metastatic, skin		1 (2%)		
Skeletal muscle	(8)	(3)	(4)	(3)
Carcinoma, metastatic, pancreas		1 (33%)		
Fibrous histiocytoma			1 (25%)	
Hepatoblastoma, metastatic, liver		1 (33%)		
Hepatocholangiocarcinoma, metastatic, liver			1 (25%)	1 (33%)
Liposarcoma, metastatic, mesentery				1 (33%)
Osteosarcoma, metastatic, bone			1 (25%)	1 (33%)
Sarcoma	2 (25%)		1 (25%)	
Sarcoma, metastatic, uncertain primary site	1 (13%)			
Sarcoma, metastatic, uterus	1 (13%)			
Nervous System				
Brain	(50)	(50)	(50)	(50)
Osteosarcoma, metastatic, bone			1 (2%)	
Peripheral nerve	(3)	(2)	(0)	(1)
Spinal cord	(3)	(2)	(0)	(1)
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Alveolar/bronchiolar adenoma	3 (6%)	2 (4%)	3 (6%)	2 (4%)
Alveolar/bronchiolar carcinoma	2 (4%)	5 (10%)	5 (10%)	1 (2%)
Carcinoma, metastatic, pancreas		1 (2%)		
Carcinoma, metastatic, thyroid gland			1 (2%)	
Fibrosarcoma, metastatic, skin			1 (2%)	
Hepatoblastoma, metastatic, liver		1 (2%)		
Hepatocellular carcinoma, metastatic, liver	3 (6%)	3 (6%)	3 (6%)	5 (10%)
Hepatocholangiocarcinoma, metastatic, liver			1 (2%)	2 (4%)
Liposarcoma, metastatic, mesentery				1 (2%)
Osteosarcoma, metastatic, bone			1 (2%)	2 (4%)
Sarcoma, metastatic, uncertain primary site	2 (4%)			
Sarcoma, metastatic, uterus	1 (2%)			
Nose	(50)	(50)	(50)	(50)
Special Senses System				
Eye	(48)	(45)	(43)	(45)
Harderian gland	(50)	(50)	(48)	(49)
Adenoma	5 (10%)	10 (20%)	11 (23%)	3 (6%)
Carcinoma	2 (4%)		2 (4%)	1 (2%)

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

	Vehicle Control	0.3 mg/kg	1.0 mg/kg	3.0 mg/kg
Urinary System				
Kidney	(49)	(46)	(43)	(47)
Fibrosarcoma, metastatic, skin			1 (2%)	
Fibrous histiocytoma, metastatic, skeletal muscle			1 (2%)	
Liposarcoma, metastatic, mesentery				1 (2%)
Sarcoma, metastatic, uncertain primary site	1 (2%)			
Urinary bladder	(48)	(48)	(46)	(48)
Carcinoma, metastatic, pancreas		1 (2%)		
Systemic Lesions				
Multiple organs[b]	(50)	(50)	(50)	(50)
Histiocytic sarcoma	2 (4%)	1 (2%)		2 (4%)
Lymphoma malignant	20 (40%)	13 (26%)	17 (34%)	17 (34%)
Neoplasm Summary				
Total animals with primary neoplasms[c]	47	45	47	49
Total primary neoplasms	110	102	113	111
Total animals with benign neoplasms	41	39	37	40
Total benign neoplasms	56	57	62	54
Total animals with malignant neoplasms	38	32	37	33
Total malignant neoplasms	53	45	51	57
Total animals with metastatic neoplasms	6	7	11	10
Total metastatic neoplasms	25	20	34	27
Total animals with malignant neoplasms of uncertain primary site	2			
Total animals with uncertain neoplasms-benign or malignant	1			
Total uncertain neoplasms	1			

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

TABLE D2
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Dermal Study of Trimethylolpropane Triacrylate

	Vehicle Control	0.3 mg/kg	1.0 mg/kg	3.0 mg/kg
Harderian Gland: Adenoma				
Overall rate[a]	5/50 (10%)	10/50 (20%)	11/50 (22%)	3/50 (6%)
Adjusted rate[b]	10.7%	22.6%	25.2%	6.8%
Terminal rate[c]	5/39 (13%)	8/31 (26%)	8/30 (27%)	2/30 (7%)
First incidence (days)	729 (T)	598	627	670
Poly-3 test[d]	P=0.123N	P=0.106	P=0.061	P=0.384N
Harderian Gland: Adenoma or Carcinoma				
Overall rate	7/50 (14%)	10/50 (20%)	13/50 (26%)	4/50 (8%)
Adjusted rate	15.0%	22.6%	29.7%	9.0%
Terminal rate	7/39 (18%)	8/31 (26%)	9/30 (30%)	3/30 (10%)
First incidence (days)	729 (T)	598	627	670
Poly-3 test	P=0.126N	P=0.255	P=0.074	P=0.290N
Small Intestine (Duodenum or Jejunum): Adenoma or Carcinoma				
Overall rate	1/50 (2%)	2/50 (4%)	0/50 (0%)	3/50 (6%)
Adjusted rate	2.1%	4.6%	0.0%	6.8%
Terminal rate	1/39 (3%)	2/31 (7%)	0/30 (0%)	2/30 (7%)
First incidence (days)	729 (T)	729 (T)	—[e]	728
Poly-3 test	P=0.214	P=0.475	P=0.516N	P=0.286
Liver: Hemangiosarcoma				
Overall rate	0/50 (0%)	0/50 (0%)	3/50 (6%)	2/50 (4%)
Adjusted rate	0.0%	0.0%	6.9%	4.5%
Terminal rate	0/39 (0%)	0/31 (0%)	2/30 (7%)	1/30 (3%)
First incidence (days)	—	—	633	702
Poly-3 test	P=0.145	—[f]	P=0.106	P=0.226
Liver: Hepatocellular Adenoma				
Overall rate	34/50 (68%)	34/50 (68%)	31/50 (62%)	36/50 (72%)
Adjusted rate	70.1%	74.2%	71.2%	77.9%
Terminal rate	27/39 (69%)	23/31 (74%)	27/30 (90%)	26/30 (87%)
First incidence (days)	576	583	657	599
Poly-3 test	P=0.245	P=0.412	P=0.546	P=0.255
Liver: Hepatocellular Carcinoma				
Overall rate	12/50 (24%)	13/50 (26%)	10/50 (20%)	19/50 (38%)
Adjusted rate	25.4%	28.4%	22.7%	41.3%
Terminal rate	10/39 (26%)	6/31 (19%)	7/30 (23%)	12/30 (40%)
First incidence (days)	638	513	440	599
Poly-3 test	P=0.045	P=0.461	P=0.479N	P=0.076
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rate	37/50 (74%)	36/50 (72%)	33/50 (66%)	42/50 (84%)
Adjusted rate	75.7%	77.5%	74.1%	89.5%
Terminal rate	29/39 (74%)	24/31 (77%)	27/30 (90%)	30/30 (100%)
First incidence (days)	576	513	440	599
Poly-3 test	P=0.036	P=0.517	P=0.524N	P=0.055
Liver: Hepatoblastoma				
Overall rate	0/50 (0%)	4/50 (8%)	0/50 (0%)	3/50 (6%)
Adjusted rate	0.0%	9.1%	0.0%	6.8%
Terminal rate	0/39 (0%)	2/31 (7%)	0/30 (0%)	3/30 (10%)
First incidence (days)	—	617	—	729 (T)
Poly-3 test	P=0.267	P=0.053	—	P=0.109

TABLE D2
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Dermal Study of Trimethylolpropane Triacrylate

	Vehicle Control	0.3 mg/kg	1.0 mg/kg	3.0 mg/kg
Liver: Hepatocellular Carcinoma or Hepatoblastoma				
Overall rate	12/50 (24%)	17/50 (34%)	10/50 (20%)	19/50 (38%)
Adjusted rate	25.4%	36.8%	22.7%	41.3%
Terminal rate	10/39 (26%)	8/31 (26%)	7/30 (23%)	12/30 (40%)
First incidence (days)	638	513	440	599
Poly-3 test	P=0.103	P=0.164	P=0.479N	P=0.076
Liver: Hepatocellular Adenoma, Hepatocellular Carcinoma, or Hepatoblastoma				
Overall rate	37/50 (74%)	38/50 (76%)	33/50 (66%)	42/50 (84%)
Adjusted rate	75.7%	81.1%	74.1%	89.5%
Terminal rate	29/39 (74%)	25/31 (81%)	27/30 (90%)	30/30 (100%)
First incidence (days)	576	513	440	599
Poly-3 test	P=0.052	P=0.346	P=0.524N	P=0.055
Lung: Alveolar/bronchiolar Adenoma				
Overall rate	3/50 (6%)	2/50 (4%)	3/50 (6%)	2/50 (4%)
Adjusted rate	6.4%	4.5%	7.0%	4.5%
Terminal rate	2/39 (5%)	1/31 (3%)	2/30 (7%)	2/30 (7%)
First incidence (days)	647	513	674	729 (T)
Poly-3 test	P=0.499N	P=0.529N	P=0.623	P=0.528N
Lung: Alveolar/bronchiolar Carcinoma				
Overall rate	2/50 (4%)	5/50 (10%)	5/50 (10%)	1/50 (2%)
Adjusted rate	4.3%	11.3%	11.5%	2.3%
Terminal rate	2/39 (5%)	1/31 (3%)	3/30 (10%)	1/30 (3%)
First incidence (days)	729 (T)	599	627	729 (T)
Poly-3 test	P=0.218N	P=0.196	P=0.188	P=0.519N
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rate	5/50 (10%)	7/50 (14%)	8/50 (16%)	3/50 (6%)
Adjusted rate	10.7%	15.6%	18.3%	6.8%
Terminal rate	4/39 (10%)	2/31 (7%)	5/30 (17%)	3/30 (10%)
First incidence (days)	647	513	627	729 (T)
Poly-3 test	P=0.219N	P=0.349	P=0.229	P=0.391N
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	7/49 (14%)	5/47 (11%)	8/49 (16%)	0/50 (0%)
Adjusted rate	15.2%	12.1%	19.1%	0.0%
Terminal rate	6/38 (16%)	4/30 (13%)	8/29 (28%)	0/30 (0%)
First incidence (days)	638	557	729 (T)	—
Poly-3 test	P=0.012N	P=0.453N	P=0.423	P=0.009N
Pituitary Gland (Pars Distalis): Adenoma or Carcinoma				
Overall rate	7/49 (14%)	6/47 (13%)	8/49 (16%)	0/50 (0%)
Adjusted rate	15.2%	14.4%	19.1%	0.0%
Terminal rate	6/38 (16%)	4/30 (13%)	8/29 (28%)	0/30 (0%)
First incidence (days)	638	557	729 (T)	—
Poly-3 test	P=0.009N	P=0.577N	P=0.423	P=0.009N
Skin (Subcutaneous Tissue): Fibrosarcoma				
Overall rate	3/50 (6%)	0/50 (0%)	1/50 (2%)	0/50 (0%)
Adjusted rate	6.4%	0.0%	2.3%	0.0%
Terminal rate	2/39 (5%)	0/31 (0%)	0/30 (0%)	0/30 (0%)
First incidence (days)	593	—	698	—
Poly-3 test	P=0.152N	P=0.134N	P=0.338N	P=0.131N

TABLE D2
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Dermal Study of Trimethylolpropane Triacrylate

	Vehicle Control	0.3 mg/kg	1.0 mg/kg	3.0 mg/kg
Skin: Fibrosarcoma or Sarcoma				
Overall rate	4/50 (8%)	1/50 (2%)	2/50 (4%)	1/50 (2%)
Adjusted rate	8.5%	2.3%	4.7%	2.3%
Terminal rate	2/39 (5%)	1/31 (3%)	1/30 (3%)	1/30 (3%)
First incidence (days)	593	729 (T)	698	729 (T)
Poly-3 test	P=0.239N	P=0.206N	P=0.382N	P=0.201N
Skin: Fibroma, Fibrosarcoma, or Sarcoma				
Overall rate	4/50 (8%)	1/50 (2%)	2/50 (4%)	2/50 (4%)
Adjusted rate	8.5%	2.3%	4.7%	4.5%
Terminal rate	2/39 (5%)	1/31 (3%)	1/30 (3%)	2/30 (7%)
First incidence (days)	593	729 (T)	698	729 (T)
Poly-3 test	P=0.458N	P=0.206N	P=0.382N	P=0.370N
Uterus: Stromal Polyp				
Overall rate	0/50 (0%)	1/50 (2%)	2/50 (4%)	5/50 (10%)
Adjusted rate	0.0%	2.3%	4.7%	11.1%
Terminal rate	0/39 (0%)	1/31 (3%)	2/30 (7%)	4/30 (13%)
First incidence (days)	—	729 (T)	729 (T)	409
Poly-3 test	P=0.008	P=0.486	P=0.219	P=0.027
Uterus: Stromal Polyp or Stromal Sarcoma				
Overall rate	0/50 (0%)	1/50 (2%)	2/50 (4%)	6/50 (12%)
Adjusted rate	0.0%	2.3%	4.7%	13.3%
Terminal rate	0/39 (0%)	1/31 (3%)	2/30 (7%)	4/30 (13%)
First incidence (days)	—	729 (T)	729 (T)	409
Poly-3 test	P=0.002	P=0.486	P=0.219	P=0.014
All Organs: Hemangiosarcoma				
Overall rate	2/50 (4%)	2/50 (4%)	4/50 (8%)	4/50 (8%)
Adjusted rate	4.3%	4.6%	9.2%	9.0%
Terminal rate	2/39 (5%)	1/31 (3%)	3/30 (10%)	3/30 (10%)
First incidence (days)	729 (T)	598	633	702
Poly-3 test	P=0.232	P=0.672	P=0.303	P=0.313
All Organs: Hemangioma or Hemangiosarcoma				
Overall rate	2/50 (4%)	2/50 (4%)	6/50 (12%)	5/50 (10%)
Adjusted rate	4.3%	4.6%	13.7%	11.3%
Terminal rate	2/39 (5%)	1/31 (3%)	3/30 (10%)	4/30 (13%)
First incidence (days)	729 (T)	598	561	702
Poly-3 test	P=0.138	P=0.672	P=0.114	P=0.195
All Organs: Malignant Lymphoma				
Overall rate	20/50 (40%)	13/50 (26%)	17/50 (34%)	17/50 (34%)
Adjusted rate	41.4%	29.2%	38.4%	37.2%
Terminal rate	16/39 (41%)	9/31 (29%)	13/30 (43%)	12/30 (40%)
First incidence (days)	576	593	571	424
Poly-3 test	P=0.538	P=0.154N	P=0.465N	P=0.416N
All Organs: Benign Neoplasms				
Overall rate	41/50 (82%)	39/50 (78%)	37/50 (74%)	40/50 (80%)
Adjusted rate	82.8%	82.2%	82.6%	84.9%
Terminal rate	31/39 (80%)	25/31 (81%)	29/30 (97%)	28/30 (93%)
First incidence (days)	576	513	561	409
Poly-3 test	P=0.419	P=0.580N	P=0.606N	P=0.495

TABLE D2
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Dermal Study of Trimethylolpropane Triacrylate

	Vehicle Control	0.3 mg/kg	1.0 mg/kg	3.0 mg/kg
All Organs: Malignant Neoplasms				
Overall rate	38/50 (76%)	32/50 (64%)	37/50 (74%)	33/50 (66%)
Adjusted rate	76.2%	67.1%	77.1%	68.1%
Terminal rate	29/39 (74%)	17/31 (55%)	22/30 (73%)	18/30 (60%)
First incidence (days)	576	513	409	424
Poly-3 test	P=0.320N	P=0.218N	P=0.556	P=0.248N
All Organs: Benign or Malignant Neoplasms				
Overall rate	47/50 (94%)	45/50 (90%)	47/50 (94%)	49/50 (98%)
Adjusted rate	94.0%	92.9%	96.4%	98.5%
Terminal rate	36/39 (92%)	28/31 (90%)	30/30 (100%)	30/30 (100%)
First incidence (days)	576	513	409	409
Poly-3 test	P=0.133	P=0.577N	P=0.459	P=0.252

(T) Terminal kill

[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for liver, lung, and pituitary gland; for other tissues, denominator is number of animals necropsied.

[b] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality

[c] Observed incidence at terminal kill

[d] Beneath the vehicle control incidence is the P value associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the vehicle controls and that dosed group. The Poly-3 test accounts for the differential mortality in animals that do not reach terminal kill. 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 D3a
Historical Incidence of Liver Neoplasms in Control Female B6C3F1/N Mice[a]

Study (Study Start)	Hepatocellular Adenoma Carcinoma	Hepatoblastoma	Hepatocholangiocarcinoma
Historical Incidence: Dermal Studies (all vehicles)			
Bis-(2-Chloroethoxy)methane (October 2002)	3/50	0/50	0/50
1,2-Dibromo-2,4-dicyanobutane (June 2002)	8/50	1/50	0/50
Methyl *trans*-styryl ketone (April 2004)	23/50	0/50	0/50
Pyrogallol (September 2004)	17/50	1/50	0/50
Trimethylolpropane triacrylate (December 2004)	12/50	0/50	0/50
Total (%)	63/250 (25.2%)	2/250 (0.8%)	0/250 (0.0%)
Mean ± standard deviation	25.2% ± 15.5%	0.8% ± 1.1%	
Range	6%-46%	0%-2%	
Overall Historical Incidence: All Routes			
Total (%)	144/1,195 (12.1%)	4/1,195 (0.3%)	0/1,195 (0.0%)
Mean ± standard deviation	12.1% ± 10.8%	0.3% ± 0.8%	
Range	0%-46%	0%-2%	

[a] Data as of October 2011

TABLE D3b
Historical Incidence of Uterus Neoplasms in Control Female B6C3F1/N Mice[a]

Study (Study Start)	Stromal Polyp	Stromal Sarcoma	Stromal Polyp or Stromal Sarcoma
Historical Incidence: Dermal Studies			
Bis-(2-Chloroethoxy)methane (October 2002)	0/50	0/50	0/50
1,2-Dibromo-2,4-dicyanobutane (June 2002)	1/50	0/50	1/50
Methyl *trans*-styryl ketone (April 2004)	1/50	0/50	1/50
Pyrogallol (September 2004)	3/50	0/50	3/50
Trimethylolpropane triacrylate (December 2004)	0/50	0/50	0/50
Total (%)	5/250 (2.0%)	0/250 (0.09%)	5/250 (2.0%)
Mean ± standard deviation	2.0% ± 2.5%		2.0% ± 2.5%
Range	0%-6%		0%-6%
Overall Historical Incidence: All Routes			
Total (%)	24/1,198 (2.0%)	2/1,198 (0.2%)	26/1,198 (2.2%)
Mean ± standard deviation	2.0% ± 2.2%	0.2% ± 0.6%	2.2% ± 2.2%
Range	0%-8%	0%-2%	0%-8%

[a] Data as of October 2011

TABLE D4
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Dermal Study of Trimethylolpropane Triacrylate [a]

	Vehicle Control	0.3 mg/kg	1.0 mg/kg	3.0 mg/kg
Disposition Summary				
Animals initially in study	65	65	65	65
2-Week interim evaluation	5	5	5	5
13-Week interim evaluation	5	5	5	5
12-Month interim evaluation	5	5	5	5
Early deaths				
Accidental death		1		
Moribund	8	7	8	7
Natural deaths	3	11	12	13
Survivors				
Died last week of study			1	
Terminal kill	39	31	29	30
Animals examined microscopically	65	65	65	65
2-Week Interim Evaluation				
Integumentary System				
Skin	(5)	(5)	(5)	(5)
Site of application, hyperplasia	0	0	1 (20%)	4 (80%)
Site of application, inflammation, chronic active	1 (20%)	0	4 (80%)	4 (80%)
13-Week Interim Evaluation				
Integumentary System				
Skin	(5)	(5)	(5)	(5)
Site of application, hyperplasia	0	0	0	5 (100%)
Site of application, inflammation, chronic active	1 (20%)	0	2 (40%)	5 (100%)
Site of application, sebaceous gland, hyperplasia	0	0	0	4 (80%)
12-Month Interim Evaluation				
Integumentary System				
Skin	(5)	(5)	(5)	(5)
Site of application, hyperplasia	0	0	1 (20%)	4 (80%)
Site of application, inflammation	0	2 (40%)	4 (80%)	4 (80%)
2-Year Study				
Alimentary System				
Esophagus	(50)	(50)	(50)	(50)
Hemorrhage			1 (2%)	
Inflammation, chronic active				2 (4%)
Gallbladder	(46)	(41)	(39)	(40)
Cyst				1 (3%)
Pigmentation				1 (3%)
Epithelium, hyperplasia, adenomatous, focal				1 (3%)
Intestine large, cecum	(47)	(42)	(40)	(42)
Edema	1 (2%)			1 (2%)
Hemorrhage				1 (2%)
Hyperplasia, lymphoid		1 (2%)		

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

TABLE D4
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Dermal Study of Trimethylolpropane Triacrylate

	Vehicle Control	0.3 mg/kg	1.0 mg/kg	3.0 mg/kg
Alimentary System (continued)				
Intestine large, colon	(47)	(44)	(41)	(44)
Edema				1 (2%)
Fibrosis				1 (2%)
Hemorrhage				1 (2%)
Intestine large, rectum	(48)	(44)	(40)	(43)
Edema		1 (2%)	1 (3%)	
Hemorrhage				1 (2%)
Inflammation, acute			1 (3%)	
Inflammation, chronic active				1 (2%)
Ulcer			1 (3%)	
Intestine small, duodenum	(47)	(42)	(40)	(39)
Fibrosis				1 (3%)
Necrosis	3 (6%)			
Epithelium, hyperplasia	1 (2%)			
Intestine small, ileum	(48)	(42)	(40)	(40)
Fibrosis				1 (3%)
Hyperplasia, lymphoid			1 (3%)	
Inflammation, acute	1 (2%)	3 (7%)	1 (3%)	1 (3%)
Necrosis	2 (4%)			
Epithelium, hyperplasia			1 (3%)	
Intestine small, jejunum	(47)	(41)	(41)	(40)
Hemorrhage				1 (3%)
Hyperplasia, lymphoid		1 (2%)		
Inflammation, acute				1 (3%)
Inflammation, chronic active	2 (4%)			
Necrosis	3 (6%)	3 (7%)		
Epithelium, hyperplasia	1 (2%)			1 (3%)
Liver	(50)	(50)	(50)	(50)
Angiectasis	2 (4%)	1 (2%)	2 (4%)	
Basophilic focus	1 (2%)	3 (6%)	3 (6%)	
Clear cell focus	3 (6%)	2 (4%)	5 (10%)	6 (12%)
Cytoplasmic alteration, diffuse	1 (2%)			
Eosinophilic focus	15 (30%)	23 (46%)	21 (42%)	21 (42%)
Fibrosis				2 (4%)
Hematopoietic cell proliferation	4 (8%)	4 (8%)	10 (20%)	1 (2%)
Hemorrhage	2 (4%)			2 (4%)
Infarct		1 (2%)		
Inflammation, chronic		1 (2%)		1 (2%)
Inflammation, chronic active	26 (52%)	32 (64%)	24 (48%)	21 (42%)
Mineralization	1 (2%)	2 (4%)		
Mixed cell focus				1 (2%)
Necrosis, focal	10 (20%)	8 (16%)	11 (22%)	7 (14%)
Tension lipidosis	1 (2%)		3 (6%)	
Thrombosis		1 (2%)		1 (2%)
Centrilobular, atrophy, diffuse			1 (2%)	1 (2%)
Centrilobular, cytoplasmic alteration		1 (2%)		
Centrilobular, degeneration, granular, diffuse		1 (2%)		
Centrilobular, necrosis	1 (2%)	2 (4%)	1 (2%)	2 (4%)
Centrilobular, hepatocyte, vacuolization cytoplasmic			1 (2%)	
Hepatocyte, hypertrophy				1 (2%)
Hepatocyte, vacuolization cytoplasmic	1 (2%)	2 (4%)	2 (4%)	1 (2%)
Hepatocyte, periportal, hypertrophy, diffuse				1 (2%)
Kupffer cell, hyperplasia	1 (2%)		1 (2%)	1 (2%)
Kupffer cell, pigmentation	4 (8%)	5 (10%)	10 (20%)	4 (8%)

TABLE D4
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Dermal Study of Trimethylolpropane Triacrylate

	Vehicle Control	0.3 mg/kg	1.0 mg/kg	3.0 mg/kg
Alimentary System (continued)				
Mesentery	(24)	(25)	(25)	(14)
Fibrosis			2 (8%)	1 (7%)
Inflammation, chronic	1 (4%)			
Inflammation, chronic active			1 (4%)	
Thrombosis	1 (4%)	1 (4%)		
Fat, necrosis	20 (83%)	23 (92%)	18 (72%)	9 (64%)
Pancreas	(49)	(50)	(46)	(49)
Atrophy	3 (6%)	3 (6%)	5 (11%)	7 (14%)
Cyst			1 (2%)	1 (2%)
Fibrosis				1 (2%)
Hyperplasia	1 (2%)			
Hyperplasia, lymphoid	27 (55%)	28 (56%)	26 (57%)	25 (51%)
Hyperplasia, melanocyte				1 (2%)
Hypertrophy	3 (6%)	1 (2%)		2 (4%)
Inflammation, acute			1 (2%)	1 (2%)
Inflammation, chronic			1 (2%)	
Salivary glands	(50)	(50)	(50)	(49)
Atrophy	1 (2%)	1 (2%)	1 (2%)	
Hyperplasia, lymphoid	47 (94%)	38 (76%)	39 (78%)	38 (78%)
Infiltration cellular, lymphoid		1 (2%)		
Mineralization	1 (2%)	1 (2%)		
Artery, hypertrophy			1 (2%)	
Stomach, forestomach	(50)	(50)	(47)	(50)
Edema	3 (6%)		1 (2%)	1 (2%)
Erosion	1 (2%)			
Inflammation, acute	1 (2%)			
Inflammation, chronic		1 (2%)		1 (2%)
Mineralization		1 (2%)		
Necrosis				1 (2%)
Ulcer	4 (8%)	2 (4%)	4 (9%)	1 (2%)
Epithelium, hyperplasia	4 (8%)	7 (14%)	9 (19%)	3 (6%)
Stomach, glandular	(49)	(46)	(43)	(47)
Cyst	24 (49%)	24 (52%)	20 (47%)	15 (32%)
Edema	1 (2%)			
Erosion	2 (4%)	1 (2%)		2 (4%)
Fibrosis	1 (2%)			
Hemorrhage			1 (2%)	
Infiltration cellular, lipocyte			1 (2%)	
Inflammation, acute			1 (2%)	
Inflammation, chronic active		2 (4%)		1 (2%)
Metaplasia, squamous		2 (4%)	1 (2%)	
Mineralization	1 (2%)	2 (4%)	3 (7%)	4 (9%)
Necrosis	1 (2%)	1 (2%)		
Pigmentation			1 (2%)	
Ulcer	1 (2%)		1 (2%)	
Epithelium, dysplasia	1 (2%)			
Epithelium, hyperplasia	1 (2%)			
Glands, ectasia	6 (12%)	7 (15%)	6 (14%)	7 (15%)
Cardiovascular System				
Heart	(50)	(50)	(50)	(50)
Cardiomyopathy	31 (62%)	21 (42%)	19 (38%)	19 (38%)
Mineralization		1 (2%)	3 (6%)	1 (2%)
Thrombosis	2 (4%)		2 (4%)	2 (4%)

TABLE D4
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Dermal Study of Trimethylolpropane Triacrylate

	Vehicle Control	0.3 mg/kg	1.0 mg/kg	3.0 mg/kg
Endocrine System				
Adrenal cortex	(50)	(50)	(46)	(50)
Accessory adrenal cortical nodule	4 (8%)	3 (6%)	3 (7%)	5 (10%)
Degeneration, fatty	3 (6%)		2 (4%)	
Fibrosis				1 (2%)
Hematopoietic cell proliferation	1 (2%)	2 (4%)	2 (4%)	3 (6%)
Hyperplasia, focal		2 (4%)	2 (4%)	2 (4%)
Hypertrophy, focal	1 (2%)	1 (2%)		1 (2%)
Infiltration cellular, lymphoid		1 (2%)		
Inflammation, acute		1 (2%)	1 (2%)	
Capsule, hyperplasia	49 (98%)	48 (96%)	45 (98%)	49 (98%)
Adrenal medulla	(50)	(48)	(45)	(50)
Hyperplasia	7 (14%)	2 (4%)	6 (13%)	
Islets, pancreatic	(49)	(50)	(46)	(49)
Hyperplasia	6 (12%)	2 (4%)	2 (4%)	6 (12%)
Parathyroid gland	(47)	(47)	(44)	(48)
Pituitary gland	(49)	(47)	(49)	(50)
Thrombosis			1 (2%)	
Pars distalis, angiectasis		3 (6%)	5 (10%)	
Pars distalis, cyst	1 (2%)	1 (2%)	2 (4%)	
Pars distalis, hyperplasia	2 (4%)	1 (2%)	1 (2%)	1 (2%)
Pars distalis, hyperplasia, focal	7 (14%)	5 (11%)	9 (18%)	5 (10%)
Pars intermedia, hyperplasia			1 (2%)	
Pars intermedia, hyperplasia, focal				1 (2%)
Pars intermedia, vacuolization cytoplasmic, focal	1 (2%)			
Rathke's cleft, hemorrhage			1 (2%)	
Thyroid gland	(49)	(49)	(45)	(48)
Hyperplasia, lymphoid				1 (2%)
Inflammation, acute	1 (2%)			
Inflammation, chronic active				1 (2%)
Necrosis				1 (2%)
Follicle, degeneration, focal	29 (59%)	23 (47%)	27 (60%)	20 (42%)
Follicular cell, hyperplasia		1 (2%)		
Follicular cell, hyperplasia, focal	4 (8%)	3 (6%)	5 (11%)	
General Body System				
Tissue NOS	(3)	(2)	(4)	(0)
Fibrosis		1 (50%)	1 (25%)	
Inflammation, suppurative	1 (33%)			
Inflammation, chronic active			2 (50%)	
Genital System				
Clitoral gland	(49)	(48)	(49)	(49)
Inflammation, chronic	3 (6%)	2 (4%)	2 (4%)	3 (6%)
Ovary	(47)	(49)	(45)	(48)
Angiectasis	4 (9%)	3 (6%)	2 (4%)	
Cyst	4 (9%)	10 (20%)	4 (9%)	10 (21%)
Hemorrhage	12 (26%)	15 (31%)	16 (36%)	11 (23%)
Mineralization		1 (2%)		
Necrosis		1 (2%)		
Thrombosis	3 (6%)	1 (2%)	1 (2%)	1 (2%)
Bilateral, cyst		1 (2%)		

TABLE D4
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Dermal Study of Trimethylolpropane Triacrylate

	Vehicle Control	0.3 mg/kg	1.0 mg/kg	3.0 mg/kg
Genital System (continued)				
Uterus	(50)	(50)	(50)	(50)
Angiectasis	1 (2%)	3 (6%)		
Cyst			1 (2%)	
Decidual reaction		1 (2%)		
Edema		2 (4%)	1 (2%)	
Hyperplasia, cystic	48 (96%)	45 (90%)	46 (92%)	46 (92%)
Hyperplasia, lymphoid			1 (2%)	
Inflammation, suppurative	1 (2%)		9 (18%)	1 (2%)
Inflammation, histiocytic, focal			1 (2%)	
Inflammation, acute		1 (2%)		
Inflammation, chronic active			2 (4%)	
Metaplasia, osseous	2 (4%)			
Necrosis	2 (4%)	3 (6%)	3 (6%)	
Thrombosis		1 (2%)		
Myometrium, hypertrophy	1 (2%)			
Vagina	(0)	(1)	(1)	(1)
Hematopoietic System				
Bone marrow	(50)	(50)	(49)	(50)
Hyperplasia	4 (8%)	1 (2%)	2 (4%)	3 (6%)
Infiltration cellular, histiocyte	2 (4%)		2 (4%)	1 (2%)
Lymph node	(10)	(7)	(16)	(10)
Ectasia		2 (29%)	6 (38%)	2 (20%)
Hematopoietic cell proliferation	1 (10%)			
Hemorrhage		1 (14%)		2 (20%)
Iliac, ectasia	2 (20%)			1 (10%)
Iliac, hemorrhage	1 (10%)			
Iliac, hyperplasia, lymphoid	4 (40%)			1 (10%)
Mediastinal, hemorrhage		1 (14%)		
Mediastinal, hyperplasia, lymphoid		1 (14%)		
Pancreatic, hyperplasia	1 (10%)			
Renal, hyperplasia, lymphoid	1 (10%)			
Lymph node, mandibular	(50)	(48)	(48)	(48)
Atrophy				2 (4%)
Hematopoietic cell proliferation	1 (2%)			
Hemorrhage	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Hyperplasia, lymphoid	22 (44%)	14 (29%)	9 (19%)	23 (48%)
Lymph node, mesenteric	(45)	(46)	(42)	(49)
Atrophy	2 (4%)	1 (2%)	3 (7%)	1 (2%)
Ectasia	1 (2%)	2 (4%)	3 (7%)	1 (2%)
Fibrosis		1 (2%)		
Hematopoietic cell proliferation	3 (7%)			1 (2%)
Hemorrhage	4 (9%)	1 (2%)	2 (5%)	1 (2%)
Hyperplasia, histiocytic		1 (2%)		
Hyperplasia, lymphoid	29 (64%)	20 (43%)	21 (50%)	32 (65%)
Necrosis		1 (2%)		
Pigmentation		1 (2%)		
Spleen	(49)	(48)	(44)	(48)
Fibrosis	1 (2%)			1 (2%)
Hematopoietic cell proliferation	27 (55%)	31 (65%)	27 (61%)	29 (60%)
Hyperplasia, lymphoid		3 (6%)	2 (5%)	4 (8%)
Infiltration cellular, lymphoid		1 (2%)		
Necrosis			1 (2%)	
Pigmentation	17 (35%)	22 (46%)	19 (43%)	19 (40%)
Lymphoid follicle, atrophy		1 (2%)		
Lymphoid follicle, hyperplasia	24 (49%)	22 (46%)	18 (41%)	19 (40%)

TABLE D4
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Dermal Study of Trimethylolpropane Triacrylate

	Vehicle Control	0.3 mg/kg	1.0 mg/kg	3.0 mg/kg
Hematopoietic System (continued)				
Thymus	(47)	(49)	(44)	(44)
Cyst	10 (21%)	11 (22%)	12 (27%)	7 (16%)
Hemorrhage	9 (19%)	15 (31%)	13 (30%)	10 (23%)
Hyperplasia, lymphoid	15 (32%)	19 (39%)	13 (30%)	22 (50%)
Hyperplasia, reticulum cell			1 (2%)	
Integumentary System				
Mammary gland	(50)	(50)	(50)	(50)
Hyperplasia	11 (22%)	8 (16%)	8 (16%)	11 (22%)
Inflammation, chronic			1 (2%)	
Skin	(50)	(50)	(50)	(50)
Cyst epithelial inclusion				1 (2%)
Edema			1 (2%)	1 (2%)
Hyperkeratosis		1 (2%)		3 (6%)
Hyperplasia, melanocyte			2 (4%)	2 (4%)
Inflammation, acute		1 (2%)		
Inflammation, chronic			1 (2%)	3 (6%)
Inflammation, chronic active			1 (2%)	1 (2%)
Ulcer				4 (8%)
Control, edema	1 (2%)		3 (6%)	
Control, hyperkeratosis	40 (80%)	40 (80%)	39 (78%)	35 (70%)
Control, hyperplasia, melanocyte			1 (2%)	
Control, inflammation, acute	1 (2%)		1 (2%)	
Control, inflammation, chronic	28 (56%)	19 (38%)	26 (52%)	27 (54%)
Control, necrosis			1 (2%)	
Control, epidermis, hyperplasia	1 (2%)		1 (2%)	
Control, epidermis, subcutaneous tissue, hyperplasia	1 (2%)			
Epidermis, hyperplasia		1 (2%)	3 (6%)	4 (8%)
Epidermis, site of application, hyperplasia	7 (14%)	7 (14%)	15 (30%)	34 (68%)
Hair follicle, dilatation				1 (2%)
Hair follicle, site of application, dilatation			1 (2%)	1 (2%)
Lip, inflammation, chronic				1 (2%)
Site of application, erosion	1 (2%)			
Site of application, fibrosis		1 (2%)		1 (2%)
Site of application, hyperkeratosis	50 (100%)	49 (98%)	50 (100%)	50 (100%)
Site of application, hyperplasia, melanocyte	1 (2%)	1 (2%)	3 (6%)	33 (66%)
Site of application, inflammation, acute	1 (2%)	1 (2%)	2 (4%)	4 (8%)
Site of application, inflammation, chronic	37 (74%)	36 (72%)	43 (86%)	48 (96%)
Site of application, necrosis				1 (2%)
Site of application, ulcer			3 (6%)	3 (6%)
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Fibrosis	8 (16%)	9 (18%)	13 (26%)	11 (22%)
Fibrous osteodystrophy	1 (2%)			
Fracture				1 (2%)
Cranium, fibrosis	1 (2%)	2 (4%)		
Femur, fibrosis		3 (6%)	1 (2%)	
Vertebra, arthrosis			1 (2%)	
Skeletal muscle	(8)	(3)	(4)	(3)
Degeneration	4 (50%)			1 (33%)
Hemorrhage		1 (33%)		

TABLE D4
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Dermal Study of Trimethylolpropane Triacrylate

	Vehicle Control	0.3 mg/kg	1.0 mg/kg	3.0 mg/kg
Nervous System				
Brain	(50)	(50)	(50)	(50)
Compression	4 (8%)	2 (4%)	3 (6%)	
Cyst epithelial inclusion				1 (2%)
Degeneration	1 (2%)			
Developmental malformation			1 (2%)	
Gliosis	4 (8%)			1 (2%)
Hemorrhage	2 (4%)	1 (2%)	2 (4%)	1 (2%)
Hyperplasia, lymphoid	1 (2%)		3 (6%)	1 (2%)
Inflammation, chronic				1 (2%)
Necrosis	6 (12%)	2 (4%)	4 (8%)	2 (4%)
Thrombosis	1 (2%)			
Meninges, fibrosis			1 (2%)	
Meninges, inflammation, chronic		1 (2%)		
Peripheral nerve	(3)	(2)	(0)	(1)
Degeneration	3 (100%)	1 (50%)		1 (100%)
Spinal cord	(3)	(2)	(0)	(1)
Degeneration				1 (100%)
Hemorrhage		1 (50%)		
Inflammation, chronic	1 (33%)			
Necrosis	1 (33%)	1 (50%)		
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Fibrosis	1 (2%)			2 (4%)
Hemorrhage	4 (8%)	4 (8%)	4 (8%)	2 (4%)
Hyperplasia, lymphoid	1 (2%)			
Infiltration cellular, histiocyte	6 (12%)	9 (18%)	6 (12%)	2 (4%)
Inflammation, suppurative				1 (2%)
Inflammation, chronic	1 (2%)			
Metaplasia, osseous		1 (2%)	2 (4%)	
Mineralization	1 (2%)		2 (4%)	1 (2%)
Pigmentation			1 (2%)	
Proteinosis	1 (2%)			
Thrombosis			2 (4%)	1 (2%)
Alveolar epithelium, hyperplasia	7 (14%)	2 (4%)	1 (2%)	4 (8%)
Nose	(50)	(50)	(50)	(50)
Cyst			1 (2%)	
Hemorrhage	1 (2%)	1 (2%)		1 (2%)
Inflammation, chronic	6 (12%)	5 (10%)	6 (12%)	5 (10%)
Special Senses System				
Eye	(48)	(45)	(43)	(45)
Cataract	1 (2%)			
Inflammation, acute	1 (2%)			1 (2%)
Inflammation, chronic	2 (4%)	1 (2%)		
Inflammation, chronic active			1 (2%)	
Necrosis	1 (2%)			
Capillary, hyperplasia	1 (2%)			
Capillary, cornea, hyperplasia			1 (2%)	
Cornea, hyperplasia	1 (2%)	2 (4%)	1 (2%)	
Retina, degeneration	1 (2%)			

TABLE D4
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Dermal Study of Trimethylolpropane Triacrylate

	Vehicle Control	0.3 mg/kg	1.0 mg/kg	3.0 mg/kg
Special Senses System (continued)				
Harderian gland	(50)	(50)	(48)	(49)
Hyperplasia				1 (2%)
Hyperplasia, focal	3 (6%)	4 (8%)	3 (6%)	
Inflammation, acute			1 (2%)	
Inflammation, chronic	36 (72%)	39 (78%)	34 (71%)	32 (65%)
Necrosis				1 (2%)
Urinary System				
Kidney	(49)	(46)	(43)	(47)
Casts protein	4 (8%)		2 (5%)	1 (2%)
Cyst	2 (4%)	1 (2%)	1 (2%)	
Glomerulosclerosis				1 (2%)
Hyperplasia, lymphoid	43 (88%)	38 (83%)	34 (79%)	38 (81%)
Infarct	5 (10%)	4 (9%)	6 (14%)	3 (6%)
Infiltration cellular, lymphoid		2 (4%)		
Metaplasia, osseous	4 (8%)		2 (5%)	3 (6%)
Mineralization	7 (14%)	6 (13%)	6 (14%)	5 (11%)
Nephropathy	34 (69%)	29 (63%)	28 (65%)	36 (77%)
Papilla, necrosis				1 (2%)
Pelvis, degeneration	1 (2%)			
Pelvis, dilatation	1 (2%)		1 (2%)	1 (2%)
Renal tubule, accumulation, hyaline droplet	4 (8%)		1 (2%)	2 (4%)
Renal tubule, dilatation, focal	28 (57%)	20 (43%)	19 (44%)	15 (32%)
Renal tubule, dilatation, diffuse		1 (2%)		2 (4%)
Renal tubule, hyperplasia	1 (2%)			
Renal tubule, necrosis	1 (2%)		1 (2%)	
Renal tubule, pigmentation	1 (2%)	2 (4%)		
Transitional epithelium, hyperplasia	1 (2%)			
Urinary bladder	(48)	(48)	(46)	(48)
Hyperplasia, lymphoid	40 (83%)	29 (60%)	24 (52%)	31 (65%)
Inflammation, chronic active		1 (2%)		
Transitional epithelium, hyperplasia			1 (2%)	

APPENDIX E
GENETIC TOXICOLOGY

GENETIC TOXICOLOGY

BACTERIAL MUTAGENICITY TEST PROTOCOL

Testing procedures used by SITEK Research Laboratories (Rockville, MD) were modified from those reported by Zeiger *et al*. (1992). Coded samples of trimethylolpropane triacrylate (the same chemical lot that was used in the 2-year studies) were incubated with the *Salmonella typhimurium* (TA98 and TA100) or *Escherichia coli* (WP2 *uvrA*/pKM101) tester strains either in buffer or S9 mix (metabolic activation enzymes and cofactors from Aroclor 1254-induced male Sprague-Dawley rat liver) for 20 minutes at 37º 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 37º C.

Each trial consisted of triplicate plates of concurrent positive and negative controls and five doses of trimethylolpropane triacrylate. The high dose was limited by experimental design to 10,000 µg per plate. 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.

RESULTS

Trimethylolpropane triacrylate (1,500 to 10,000 µg per plate; lot no. 08409HI) did not induce mutations in *S. typhimurium* strains TA98 or TA100 or in *E. coli* strain WP2 *uvrA*/pKM101, with or without 10% rat liver S9 mix (Table E1).

TABLE E1
Mutagenicity of Trimethylolpropane Triacrylate in Bacterial Tester Strains[a]

Strain	Dose (µg/plate)	Without S9	Without S9	With 10% rat S9	With 10% rat S9
TA100					
	0	111 ± 9	81 ± 5	67 ± 2	77 ± 2
	1,500	111 ± 1	75 ± 2	66 ± 5	81 ± 2
	3,000	72 ± 7	62 ± 4	60 ± 4	74 ± 7
	5,000	44 ± 2	55 ± 2	44 ± 2	83 ± 3
	7,500	32 ± 3	40 ± 4	51 ± 7	64 ± 1
	10,000	20 ± 2	35 ± 4	33 ± 2	30 ± 3
Trial summary		Negative	Negative	Negative	Negative
Positive control[b]		687 ± 13	581 ± 19	997 ± 100	740 ± 3
TA98					
	0	27 ± 3	17 ± 3	21 ± 3	27 ± 3
	1,500	22 ± 2	16 ± 2	16 ± 2	19 ± 3
	3,000	17 ± 3	17 ± 1	16 ± 2	8 ± 1
	5,000	9 ± 1[c]	12 ± 1	16 ± 1	7 ± 1
	7,500	9 ± 2[c]	7 ± 0	11 ± 1	5 ± 1
	10,000	7 ± 2[c]	3 ± 0	6 ± 1[c]	3 ± 1
Trial summary		Negative	Negative	Negative	Negative
Positive control		463 ± 19	290 ± 20	728 ± 19	624 ± 51
***Escherichia coli* WP2 *uvrA*/pKM101 (analogous to TA102)**					
	0	135 ± 4	199 ± 17	159 ± 7	129 ± 4
	1,500	110 ± 10	138 ± 4	187 ± 6	96 ± 2
	3,000	101 ± 4	115 ± 8	158 ± 10	82 ± 1
	5,000	126 ± 3	115 ± 5	160 ± 5	199 ± 9
	7,500	120 ± 3	114 ± 4	142 ± 19	118 ± 10
	10,000	121 ± 4	105 ± 6	131 ± 8	110 ± 16
Trial summary		Negative	Negative	Negative	Negative
Positive control		1,585 ± 6	1,886 ± 128	972 ± 90	912 ± 18

[a] Study was performed at SITEK Research Laboratories using the same lot (08409HI) of chemical that was used in the 2-year studies. Data are presented as revertants/plate (mean ± standard error) from three plates. 0 µg/plate was the solvent control.

[b] The positive controls in the absence of metabolic activation were sodium azide (TA100), 4-nitro-*o*-phenylenediamine (TA98), and methyl methanesulfonate (*E. coli*). The positive control for metabolic activation with all strains was 2-aminoanthracene.

[c] Slight toxicity

APPENDIX F
CHEMICAL CHARACTERIZATION AND DOSE FORMULATION STUDIES

CHEMICAL CHARACTERIZATION AND DOSE FORMULATION STUDIES

PROCUREMENT AND CHARACTERIZATION

Trimethylolpropane Triacrylate

Trimethylolpropane triacrylate was obtained from Aldrich Chemical Company (Milwaukee, WI) in one lot (08409HI) which was used for the 2-year studies. Identity and purity analyses were conducted by the analytical chemistry laboratory at Battelle Columbus Laboratories (Columbus, OH) and by the study laboratory at Southern Research Institute (Birmingham, AL). Karl Fischer titration and elemental analysis were performed by Prevalere Life Sciences, Inc. (Whitesboro, NY). One additional lot (01031AW) was obtained from Aldrich Chemical Company and was used by the analytical chemistry laboratory for dose formulation stability studies but not used in the 2-year animal studies. Reports on analyses performed in support of the trimethylolpropane triacrylate studies are on file at the National Institute of Environmental Health Sciences.

The chemical, a colorless to yellow viscous liquid, was identified as trimethylolpropane triacrylate by the analytical chemistry laboratory using infrared (IR), and proton and carbon-13 nuclear magnetic resonance (NMR) spectroscopy, and was confirmed by the study laboratory using IR spectroscopy. All spectra were consistent with the literature spectra (*Aldrich*, 1985; *Sadtler*, IR1116) and spectra of a previously analyzed lot used in another study (NTP, 2005a). A representative infrared spectrum is presented in Figure F1.

For lot 08409HI, Karl Fischer titration was used to determine the water content and elemental analysis was used to determine the carbon and hydrogen content. The purity was determined by the analytical chemistry laboratory using gas chromatography (GC) with flame ionization detection (FID) by system A (Table F1) and high-performance liquid chromatography (HPLC) with ultraviolet detection (UV) by system A (Table F2). HPLC coupled with mass spectrometry (MS) by system B (Table F2) was used to determine whether hydroquinone and/or methyl hydroquinone (potential reported stabilizers) were present in the bulk chemical.

For lot 08409HI, Karl Fischer titration indicated an average water content of 0.10%; elemental analyses for carbon and hydrogen were in agreement with the theoretical values for trimethylolpropane triacrylate. GC analysis indicated one major peak consisting of 87.4% of the total peak area and five impurities, each with 0.1% or greater of the total peak area (0.1%, 0.1%, 9.9%, 0.2%, and 2.3%). HPLC/UV analysis indicated one major peak (78.2%) and four impurities, each greater than 0.1% of the total peak area (7.1%, 2.3%, 10.8%, and 1.5%). In an attempt to identify these impurities, the analytical laboratory used GC with mass spectrometry (MS) by system B (Table F1) and HPLC/MS by system C (Table F2). GC/MS analysis was inconclusive due to the absence of molecular ions or their fragments in the spectrum. HPLC/MS analysis made it possible to tentatively identify three of the four impurities as structurally related compounds; trimethylolpropane diacrylate (7.1%), trimethylolpropane triacrylate-trimethylolpropane monoacrylate adduct (2.3%), and trimethylolpropane triacrylate-trimethylolpropane diacrylate adduct (10.8%); the impurity comprising 1.5% of the total peak area was not specifically identified; however, the fragment ions were consistent with that of a trimethylolpropane triacrylate adduct. HPLC/MS analysis indicated that neither hydroquinone nor methyl hydroquinone was detected above 0.1% of the total peak area in the bulk chemical. The overall purity of lot 08409HI was determined to be greater than 78%, which was comparable to that of a different lot (80%) previously used in another study (NTP, 2005a).

To ensure stability, the bulk chemical was stored at room temperature protected from light in amber glass containers sealed with Teflon®-lined lids. Periodic reanalyses of the bulk chemical were performed at least every 6 months by the study laboratory using GC/FID by system C (Table F1), and no degradation of the bulk chemical was detected.

Acetone

Acetone was obtained from Sigma-Aldrich, Inc. (Milwaukee, WI), in two lots (00557CC and 01039LD) for use during the 2-year studies. The chemical, a clear liquid, was identified as acetone by the study laboratory using IR spectroscopy; the sample spectra were consistent with the reference spectrum of acetone (*Sadtler,* 1972). The purity of each lot was determined using GC/FID by system D (Table F1). No impurities were detected that exceeded a relative concentration of 0.1% of the total peak area in either lot.

To ensure stability, the bulk chemical was stored at room temperature. Periodic reanalyses were performed by the study laboratory approximately every 6 months during the 2-year studies using GC/FID by system D (Table F1); no degradation of the acetone was detected.

PREPARATION AND ANALYSIS OF DOSE FORMULATIONS

The dose formulations were prepared by mixing the appropriate amount of trimethylolpropane triacrylate with acetone to achieve the required concentration (Table F3). The dose formulations were prepared approximately every 4 weeks and stored protected from light in amber glass containers sealed with Teflon®-lined lids at room temperature for up to 35 days.

Stability studies of 50 and 400 µg/mL formulations were performed by the analytical chemistry laboratory using GC/FID by system E (Table F1). The formulation stability samples were sealed with butyl rubber septa. When analyzed, an additional peak was present in the formulations that increased with storage time and temperature, but did not seem related to trimethylolpropane triacrylate. An experiment was performed using containers filled with acetone only and sealed with either butyl rubber or Teflon®septa. Results indicated the presence of a peak in the butyl rubber capped samples, and none in the Teflon®-lined samples. Stability was confirmed for up to 35 days for formulations stored in amber glass containers sealed with Teflon®-lined lids at temperatures up to room temperature and for up to 3 hours under simulated animal room conditions, with the condition that animal room samples be covered with a watch glass between dosing to prevent evaporation of the acetone, which loss could be up to 5% during a 3-hour period. During the study, fresh bottles of dose formulations were provided each day for each concentration for both rats and mice.

Periodic analyses of the dose formulations of trimethylolpropane triacrylate were conducted by the study laboratory using GC/FID by system E (Table F1). Dose formulations were analyzed approximately every 3 months during the 2-year studies; animal room samples were also analyzed. Of the dose formulations analyzed and used for rats, all 35 were within 10% of the target concentrations; two of 12 animal room samples were within 10% of the target concentrations (Table F4). Of the dose formulations analyzed and used for mice, all 37 were within 10% of the target concentrations; eight of 15 animal room samples were within 10% of the target concentrations (Table F4). The animal room sample concentrations were generally higher than the target due to the evaporation of acetone during dosing.

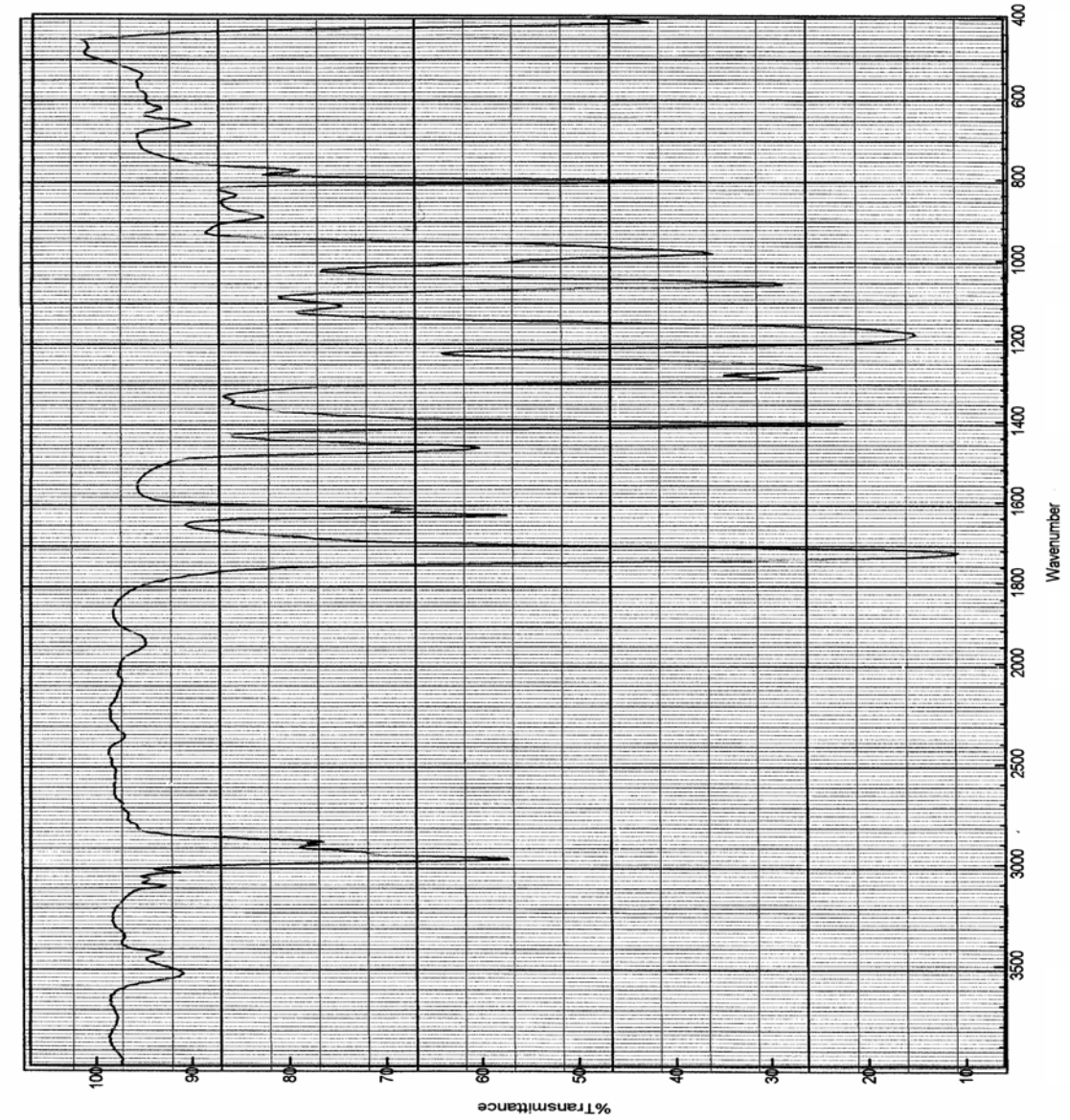

FIGURE F1
Infrared Absorption Spectrum of Trimethylolpropane Triacrylate

TABLE F1
Gas Chromatography Systems Used in the 2-Year the Dermal Studies of Trimethylolpropane Triacrylate[a]

Detection System	Column	Carrier Gas	Oven Temperature Program
System A			
Flame ionization	RTX®-5, 30 m × 0.32 mm, 0.25 µm film (Restek, Bellefonte, PA)	Helium at 3 to 5 mL/minute	70° C for 2.5 minutes, then 9° C/minute to 210° C, held for 10 minutes
System B			
Mass spectrometry	RTX®-5, 30 m × 0.32 mm, 0.25 µm film (Restek)	Helium at ~3.1 mL/minute	70° C for 2.5 minutes, then 9° C/minute to 210° C, held for 10 minutes
System C			
Flame ionization	RTX®-5, 30 m × 0.32 mm, 0.25 µm film (Restek)	Helium at ~3.1 mL/minute	70° C for 2.5 minutes, then 9° C/minute to 210° C, held for 10 minutes
System D			
Flame ionization	RTX®-5, 30 m × 0.25 mm, 0.25 µm film (Restek)	Helium at ~3 mL/minute	70° C for 2.5 minutes, then 9° C/minute to 210° C, held for 10 minutes
System E			
Flame ionization	DB™-WAX, 30 m × 0.53 mm, 1.0 µm film (Agilent Technologies, Inc., Santa Clara, CA)	Helium at 10 mL/minute	40° C for 5 minutes, then 10° C/minute to 220° C, held for 5 minutes

[a] The gas chromatographs were manufactured by Agilent Technologies, Inc. (Santa Clara, CA) (Systems A, B, and E), or Hewlett Packard (Palo Alto, CA) (Systems C and D).

TABLE F2
High-Performance Liquid Chromatography Systems Used in the 2-Year Dermal Studies of Trimethylolpropane Triacrylate[a]

Detection System	Column	Solvent System
System A		
Ultraviolet (220 nm) light	Ultracarb 5 ODS (150 mm × 4.6 mm, 5 µm particle size (Phenomenex, Torrance, CA)	A) Water with methanol 50:50 and B) Water with methanol 10:90; linear gradient of 100% A to 100% B in 30 minutes, held 30 minutes, then 100% B to 100% A in 1 minute, held 10 minutes; flow rate of 0.8 mL/minute
System B		
Ultraviolet (220 nm) light	Ultracarb 5 ODS (250 mm × 4.6 mm, 5 µm particle size (Phenomenex)	A) Water with methanol 50:50 and B) Water with methanol 10:90; linear gradient of 100% A to 100% B in 30 minutes, held 30 minutes, then 100% B to 100% A in 1 minute, held 10 minutes; flow rate of 0.8 mL/minute
System C		
Ultraviolet (220 nm) light coupled with mass spectrometry	Ultracarb 5 ODS (150 mm × 4.6 mm, 5 µm particle size (Phenomenex)	A) Water with methanol 50:50 and B) Water with methanol 10:90; linear gradient of 100% A to 100% B in 30 minutes, held 30 minutes, then 100% B to 100% A in 1 minute, held 10 minutes; flow rate of 0.8 mL/minute

[a] The high-performance liquid chromatographs were manufactured by Waters, Inc. (Milford, MA) (Systems A and B), or Agilent (Palo Alto, CA) (System C). The mass spectrometer was manufactured by Waters-Micromass (Manchester, England).

TABLE F3
Preparation and Storage of Dose Formulations in the 2-Year Dermal Studies of Trimethylolpropane Triacrylate

Preparation
For each concentration, the appropriate amount of trimethylolpropane triacrylate was weighed and placed in a small beaker with a portion of acetone, stirred with a stir bar for approximately 15 minutes or until dissolved, then quantitatively transferred to a volumetric flask with acetone rinses, diluted to volume with acetone, and stirred with a stir bar for 15 minutes. The dose formulations were prepared approximately every 4 weeks or as needed.

Chemical Lot Number
08409HI

Maximum Storage Time
35 days

Storage Conditions
Stored at room temperature, protected from light in sealed amber glass containers.

Study Laboratory
Southern Research Institute (Birmingham, AL)

TABLE F4
Results of Analyses of Dose Formulations Administered to Rats and Mice in the 2-Year Dermal Studies of Trimethylolpropane Triacrylate

Date Prepared	Date Analyzed	Target Concentration (mg/mL)	Determined Concentration[a] (mg/mL)	Difference from Target (%)
Rats				
January 3, 2005	January 4-5, 2005	0.600	0.623	+4
		2.00	2.00	0
		6.00	6.07	+1
	February 7-8, 2005[b]	0.600	0.793	+32
		2.00	2.48	+24
		6.00	8.06	+34
February 28, 2005	March 1-2, 2005	2.00	2.02	+1
		6.00	6.02	0
March 2, 2005	March 3, 2005	0.600	0.597	–1
May 23, 2005	May 24-25, 2005	0.600	0.616	+3
		2.00	2.04	+2
		6.00	6.07	+1
July 18, 2005	July 19-20, 2005	0.600	0.613	+2
		2.00	2.02	+1
		6.00	6.06	+1
	August 23-24, 2005[b]	0.600	0.739	+23
		2.00	2.40	+20
		6.00	6.87	+14
October 10, 2005	October 11-12, 2005	0.600	0.603	+1
		2.00	2.05	+2
		6.00	5.99	0
December 2, 2005	December 5-6, 2005	0.600	0.605	+1
		2.00	2.02	+1
		6.00	5.93	–1
February 27, 2006	February 28-March 1, 2006	0.600	0.613	+2
		2.00	2.06	+3
		6.00	6.04	+1
	April 3-4, 2006[b]	0.600	0.537	–11
		2.00	4.33	+116
		6.00	7.93	+32
April 24, 2006	April 25-26, 2006	0.600	0.630	+5
		0.600	0.609	+2
		2.00	2.02	+1
		2.00	2.00	0
		6.00	5.89	–2
July 17, 2006	July 18-19, 2006	0.600	0.600	0
		2.00	1.98	–1
		6.00	5.98	0

TABLE F4
Results of Analyses of Dose Formulations Administered to Rats and Mice in the 2-Year Dermal Studies of Trimethylolpropane Triacrylate

Date Prepared	Date Analyzed	Target Concentration (mg/mL)	Determined Concentration (mg/mL)	Difference from Target (%)
Rats (continued)				
September 11, 2006	September 12-13, 2006	0.600	0.592	–1
		2.00	2.01	+1
		6.00	6.03	+1
	October 16-17, 2006[b]	0.600	0.652	+9
		2.00	2.66	+33
		6.00	6.59	+10
December 4, 2006	December 5-6, 2006	0.600	0.602	0
		2.00	2.00	0
		6.00	5.92	–1
Mice				
December 7, 2004	December 7-8, 2004	0.150	0.148	–1
		0.500	0.503	+1
		1.50	1.50	0
	January 10-11, 2005[b]	0.150	0.225	+50
		0.500	0.708	+42
		1.50	2.22	+48
January 3, 2005	January 4-5, 2005	0.150	0.152	+1
		0.500	0.489	–2
January 5, 2005	January 5, 2005	1.50	1.53	+2
	February 7-8, 2005[b]	0.150	0.158	+6
		0.500	0.515	+3
		1.50	1.60	+7
February 28, 2005	March 1-2, 2005	0.150	0.152	+1
		0.500	0.498	–1
March 2, 2005	March 3, 2005	1.50	1.52	+1
May 23, 2005	May 24-25, 2005	0.150	0.157	+5
		0.500	0.472	–6
		1.50	1.53	+2
July 18, 2005	July 19-20, 2005	0.150	0.154	+3
		0.500	0.510	+2
		1.50	1.51	0
	August 23-24, 2005[b]	0.150	0.165	+10
		0.500	0.571	+14
		1.50	1.66	+10
October 10, 2005	October 11-12, 2005	0.150	0.152	+1
		0.500	0.472	–6
		1.50	1.53	+2

TABLE F4
Results of Analyses of Dose Formulations Administered to Rats and Mice in the 2-Year Dermal Studies of Trimethylolpropane Triacrylate

Date Prepared	Date Analyzed	Target Concentration (mg/mL)	Determined Concentration (mg/mL)	Difference from Target (%)
Mice (continued)				
December 2, 2005	December 5-6, 2005	0.150	0.153	+2
		0.500	0.532	+6
		1.50	1.52	+1
February 27, 2006	February 28-March 1, 2006	0.150	0.154	+2
		0.500	0.510	+2
		1.50	1.53	+2
	April 3-4, 2006[b]	0.150	0.171	+14
		0.500	0.615	+23
		1.50	1.82	+21
April 24, 2006	April 25-26, 2006	0.150	0.159	+6
		0.500	0.513	+3
		1.50	1.55	+4
		1.50	1.53	+2
July 17, 2006	July 18-19, 2006	0.150	0.151	+1
		0.500	0.501	0
		1.50	1.50	0
September 11, 2006	September 12-13, 2006	0.150	0.147	–2
		0.500	0.500	0
		1.50	1.49	–1
	October 16-17, 2006[b]	0.150	0.156	+4
		0.500	0.527	+5
		1.50	1.60	+7
December 4, 2006	December 5-6, 2006	0.150	0.151	+1
		0.500	0.495	–1
		1.50	1.51	+1

[a] Results of duplicate analyses. For rats, dosing volume=0.5 mL/kg; 0.600 mg/mL=0.3 mg/kg, 2.00 mg/mL=1.0 mg/kg, 6.00 mg/mL=3.0 mg/kg. For mice, dosing volume=2.0 mL/kg; 0.150 mg/mL=0.3 mg/kg, 0.500 mg/mL=1.0 mg/kg, 1.50 mg/mL=3.0 mg/kg.
[b] Animal room samples

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

TABLE G1
Ingredients of NTP-2000 Rat and Mouse Ration

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

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

TABLE G2
Vitamins and Minerals in NTP-2000 Rat and Mouse Ration[a]

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

[a] Per kg of finished product

TABLE G3
Nutrient Composition of NTP-2000 Rat and Mouse Ration

Nutrient	Mean ± Standard Deviation	Range	Number of Samples
Protein (% by weight)	14.6 ± 0.68	13.5 – 16.3	25
Crude fat (% by weight)	8.2 ± 0.36	7.6 – 9.3	25
Crude fiber (% by weight)	9.2 ± 0.46	8.4 – 10.0	25
Ash (% by weight)	4.9 ± 0.27	4.6 – 5.4	25
Amino Acids (% of total diet)			
Arginine	0.778 ± 0.068	0.670 – 0.970	21
Cystine	0.220 ± 0.025	0.150 – 0.250	21
Glycine	0.701 ± 0.042	0.620 – 0.800	21
Histidine	0.354 ± 0.079	0.270 – 0.680	21
Isoleucine	0.544 ± 0.045	0.430 – 0.660	21
Leucine	1.092 ± 0.068	0.960 – 1.240	21
Lysine	0.704 ± 0.112	0.310 – 0.840	21
Methionine	0.409 ± 0.047	0.260 – 0.490	21
Phenylalanine	0.626 ± 0.040	0.540 – 0.720	21
Threonine	0.503 ± 0.043	0.430 – 0.610	21
Tryptophan	0.148 ± 0.027	0.110 – 0.200	21
Tyrosine	0.397 ± 0.058	0.280 – 0.540	21
Valine	0.666 ± 0.044	0.550 – 0.730	21
Essential Fatty Acids (% of total diet)			
Linoleic	3.92 ± 0.227	3.49 – 4.54	21
Linolenic	0.30 ± 0.030	0.21 – 0.35	21
Vitamins			
Vitamin A (IU/kg)	3,891 ± 742	2,340 – 5,590	25
Vitamin D (IU/kg)	1,000[a]		
α-Tocopherol (ppm)	80.1 ± 22.48	27.0 – 124.0	21
Thiamine (ppm)[b]	7.7 ± 1.17	6.3 – 10.5	25
Riboflavin (ppm)	7.1 ± 1.91	4.20 – 11.20	21
Niacin (ppm)	78.6 ± 9.16	66.4 – 98.2	21
Pantothenic acid (ppm)	27.1 ± 12.89	17.4 – 81.0	21
Pyridoxine (ppm)[b]	9.47 ± 2.01	6.4 – 13.7	21
Folic acid (ppm)	1.63 ± 0.49	1.15 – 3.27	21
Biotin (ppm)	0.319 ± 0.10	0.200 – 0.704	21
Vitamin B_{12} (ppb)	53.8 ± 40.6	18.3 – 174.0	21
Choline (ppm)[b]	2,885 ± 459	1,820 – 3,790	21
Minerals			
Calcium (%)	0.972 ± 0.051	0.879 – 1.080	25
Phosphorus (%)	0.563 ± 0.033	0.499 – 0.623	25
Potassium (%)	0.663 ± 0.027	0.626 – 0.732	21
Chloride (%)	0.387 ± 0.039	0.300 – 0.474	21
Sodium (%)	0.190 ± 0.016	0.160 – 0.222	21
Magnesium (%)	0.216 ± 0.063	0.185 – 0.490	21
Sulfur (%)	0.170 ± 0.029	0.116 – 0.209	14
Iron (ppm)	185 ± 40.1	135 – 311	21
Manganese (ppm)	51.6 ± 10.49	21.0 – 73.1	21
Zinc (ppm)	53.6 ± 8.62	43.3 – 78.5	21
Copper (ppm)	7.07 ± 2.611	3.21 – 16.30	21
Iodine (ppm)	0.497 ± 0.209	0.158 – 0.972	21
Chromium (ppm)	0.684 ± 0.279	0.330 – 1.380	20
Cobalt (ppm)	0.26 ± 0.164	0.11 – 0.86	19

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

TABLE G4
Contaminant Levels in NTP-2000 Rat and Mouse Ration[a]

	Mean ± Standard Deviation[b]	Range	Number of Samples
Contaminants			
Arsenic (ppm)	0.23 ± 0.058	0.15 – 0.39	25
Cadmium (ppm)	0.05 ± 0.006	0.04 – 0.07	25
Lead (ppm)	0.09 ± 0.014	0.07 – 0.13	25
Mercury (ppm)	<0.02		25
Selenium (ppm)	0.29 ± 0.099	0.18 – 0.49	25
Aflatoxins (ppb)	<5.00		25
Nitrate nitrogen (ppm)[c]	13.8 ± 7.31	4.76 – 36.8	25
Nitrite nitrogen (ppm)[c]	<0.61		25
BHA (ppm)[d]	<1.0		25
BHT (ppm)[d]	<1.0		25
Aerobic plate count (CFU/g)	10 ± 0.0	10.0	25
Coliform (MPN/g)	3.0 ± 0.0	3.0	25
Escherichia coli (MPN/g)	<10		25
Salmonella (MPN/g)	Negative		25
Total nitrosoamines (ppb)[e]	5.2 ± 1.76	2.2 – 9.9	25
N-Nitrosodimethylamine (ppb)[e]	2.9 ± 1.19	1.0 – 6.3	25
N-Nitrosopyrrolidine (ppb)[e]	2.3 ± 1.07	1.1 – 6.1	25
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	<0.10		25
Estimated PCBs	<0.20		25
Ronnel	<0.01		25
Ethion	<0.02		25
Trithion	<0.05		25
Diazinon	<0.10		25
Methyl chlorpyrifos	0.140 ± 0.126	0.020 – 0.415	25
Methyl parathion	<0.02		25
Ethyl parathion	<0.02		25
Malathion	0.245 ± 0.243	0.020 – 0.997	25
Endosulfan I	<0.01		25
Endosulfan II	<0.01		25
Endosulfan sulfate	<0.03		25

[a] All samples were irradiated. CFU=colony-forming units; MPN=most probable number; BHC=hexachlorocyclohexane or benzene hexachloride

[b] For values less than the limit of detection, the detection limit is given as the mean.

[c] Sources of contamination: alfalfa, grains, and fish meal

[d] Sources of contamination: soy oil and fish meal

[e] All values were corrected for percent recovery.

APPENDIX H
SENTINEL ANIMAL PROGRAM

SENTINEL ANIMAL PROGRAM

METHODS

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

Serum samples were collected from five sentinel rats and five sentinel mice per sex at 1, 6, 12, and 18 months and from five randomly selected rats and mice per sex in the 3.0 mg/kg groups at the end of the studies. Blood from rats and mice was collected and allowed to clot, and the serum was separated; fecal samples were collected from five male and five female sentinel mice at 18 months and tested for *Helicobacter* species by polymerase chain reaction. The samples were processed appropriately and sent to BioReliance Corporation (Rockville, MD) for determination of antibody titers. The laboratory methods and agents for which testing was performed are tabulated below; the times at which samples were collected during the studies are also listed.

Method and Test	Time of Collection
RATS	
ELISA	
PVM (pneumonia virus of mice)	1, 6, 12, and 18 months, study termination
RCV/SDA	
(rat coronavirus/sialodacryoadenitis virus)	1, 6, 12, and 18 months, study termination
Sendai	1, 6, 12, and 18 months, study termination
Immunofluorescence Assay	
Parvovirus	1, 6, 12, and 18 months, study termination
RCV/SDA	1 and 6 months
Sendai	6 months
Western Blot	
PVM	6 months

MICE

ELISA	
Ectromelia virus	1, 6, 12, and 18 months, study termination
EDIM (epizootic diarrhea of infant mice)	1, 6, 12, and 18 months, study termination
GDVII (mouse encephalomyelitis virus)	1, 6, 12, and 18 months, study termination
LCM (lymphocytic choriomeningitis virus)	1, 6, 12, and 18 months, study termination
Mouse adenoma virus-1	12 and 18 months, study termination
Mouse adenoma virus-FL	1 and 6 months
MHV (mouse hepatitis virus)	1, 6, 12, and 18 months, study termination
MMV VP2 (mouse minute virus)	1, 6, 12, and 18 months, study termination
MPV VP2 (mouse parvovirus)	1, 6, 12, and 18 months, study termination
Mycoplasma arthritidis	Study termination
Mycoplasma pulmonis	Study termination
PVM	1, 6, 12, and 18 months, study termination
Reovirus 3	1, 6, 12, and 18 months, study termination
Sendai	1, 6, 12, and 18 months, study termination
Immunofluorescence Assay	
Ectromelia virus	6 months, study termination
Mouse adenoma virus-1	12 months
MCMV (mouse cytomegalovirus)	Study termination
MMV	Study termination
PVM	12 and 18 months, study termination
Reovirus 3	12 months
Polymerase Chain Reaction	
Helicobacter species	18 months

RESULTS

All test results were negative.