

SARTOMER

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June 26, 1995

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Attention: Section 8(e) Coordinator
Office of Toxic Substances
US Environmental Protection Agency
401M Street, SW
Washington, DC 20460



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ORIGINAL

Dear Sir or Madam:

Sartomer Co., Inc. is submitting the enclosed report for your consideration under section 8(e) of the Toxic Substances Control Act (TSCA), *Triethylene Glycol Dimethacrylate (TREGDMA): Carcinogenesis Skin Painting Study in C3H/HeNHsd Male Mice*. (Draft Project Report 92N1168B. May 4, 1995.) Sartomer became aware of the information contained in this report on June 9, 1995.

As the report notes, there was no indication of carcinogenicity of TREGDMA at any dose level; however, there was a slight increase in mortality in the high dose group mice relative to the control groups that was statistically significant. This increase in mortality was unexpected and caused the study to be terminated early, at seventy-eight weeks. It is for this reason that Sartomer Co., Inc., a manufacturer of TREGDMA, feels that this study may meet the criteria of TSCA 8(e).

There was also an increase in mortality among the mid dose mice relative to the control groups that was not statistically significant. The cause or causes of the increased mortality in the high and mid dose groups is unclear. During the course of the study, ingestion of TREGDMA by the test animals was noted and was documented through photographs and recorded in the raw data.

This study was sponsored by the Specialty Acrylates and Methacrylates (SAM) Panel of the Chemical Manufacturer's Association (CMA). It was conducted as part of the joint research program between the EPA and SAM to develop data to support the needs identified by the EPA for the acrylate and methacrylate chemical category. The study protocol was reviewed by the EPA prior to commencement of the study. The results of the study will be presented by SAM to the Agency upon completion.

For your information, Sartomer Co., Inc. sells TREGDMA to industrial users who typically either formulate products for the radiation curing industry or react TREGDMA in place through radiation curing. We do not consider chronic oral consumption of this material to be a likely route of industrial exposure. We will continue to recommend that users of this material utilize personal protective equipment and follow good industrial hygiene practices during use and handling.

Please call me at (610) 344-2133 if you require further information on this subject.

Sincerely,

Joann Cortese
Manager, Environmental, Health and Safety

jc/shs

Enclosure: 1



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DRAFT PROJECT REPORT 92N1168B

**Triethylene Glycol Dimethacrylate (TREGDMA):
Carcinogenesis Skin Painting Study in C3H/HeNHsd
Male Mice**

May 4, 1995

Part 1 of 2

DRAFT



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STUDY TITLE

Triethylene Glycol Dimethacrylate (TREGDMA): Carcinogenesis Skin
Painting Study in C3H/HeNHsd Male Mice

TEST SUBSTANCE

Triethylene Glycol Dimethacrylate (TREGDMA)

DATA REQUIREMENT

Not Applicable

AUTHORS

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DRAFT SUBMISSION DATE

May 4, 1995

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LABORATORY PROJECT ID

92N1168B

SPONSOR

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Chemical Manufacturers Association (CMA)
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CMA REFERENCE NUMBER

SAM-6.0-BIO-BRRC

Page 1 of

UNION CARBIDE CORPORATION

**Triethylene Glycol Dimethacrylate (TREGDMA): Carcinogenesis Skin
Painting Study in C3H/HeNHsd Male Mice**

COMPLIANCE WITH GOOD LABORATORY PRACTICE STANDARDS

The portions of this study conducted by BIRC meet the requirements of Toxic Substances Control Act (TSCA), Good Laboratory Practice Standards, 40 CFR Part 792.

Study Director:

Edward H. Fowler, DVM, Diplomate ACVP

Date

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Triethylene Glycol Dimethacrylate (TREGDMA): Carcinogenesis Skin
Painting Study in C3H/HeNHsd Male Mice

SUMMARY

Concurrent studies were conducted to evaluate the chronic toxicity and carcinogenic potential of triethylene glycol diacrylate (TREGDA, CAS No. 1680-21-3) and triethylene glycol dimethacrylate (TREGDMA, CAS No. 109-16-0). The studies were designed to share the same two control groups and, therefore, all animals for both studies were housed in the same animal room at BRRC. The results and conclusions of the TREGDMA dosing are presented in this report. The results and conclusions of the TREGDA dosing are included in BRRC Report 92N1168A.

This study consisted of 3 TREGDMA treatment groups and 2 control groups. Each group consisted of 70 male mice. The dosing solutions were applied to the dorsal skin of the animals at a constant dose volume of 50 μ l/day for 5 days/week for at least 78 weeks at concentrations of 5, 25, and 50% TREGDMA in acetone. One control group was treated with acetone (vehicle control) and the other control group was maintained and handled the same as all of the other groups, but was not treated throughout the study (untreated control). Epidermal cell proliferation evaluations were performed on 4-5 mice/group after at least 4, 13, 52, and 78 weeks on study. The remaining animals were administered the test substance for 78 weeks and constituted the core group for the evaluation of chronic toxicity/oncogenicity. Monitors for toxicity included clinical signs, including examination for palpable masses, body weight and weight gain, hematology, clinical chemistry, organ weights, gross pathology, and histopathology.

Cutaneous treatment of male mice with TREGDMA did not result in any treatment-related changes in hematology, clinical chemistry, mean absolute body weights, or body weight gain. [The mid and high dose groups had slightly decreased survival as compared to both control groups but only the mean survival time of the high dose group was statistically significantly different from the control groups.] Clinical signs of irritation, consisting primarily of exfoliation (dandruff-like scale), were observed in all dose groups. The time of onset, incidence, and severity of exfoliation were related to dose. Similar observations at the site of treatment were made at necropsy. Both epidermal basal cell proliferation and microscopic diagnoses of the treated skin confirmed the presence of cutaneous irritation in the mid and high dose groups. Epidermal basal cell proliferation at the site of treatment indicated an increased cell turnover rate that was very similar in the mid and high dose groups. The increase was greatest at the 4 and 13 Week measurement intervals and tended to be less pronounced at the 52 and 78 Week measurement intervals. Microscopic examination at 78 Weeks again indicated very similar chronic cutaneous irritation changes at the site of treatment in the mid and high dose groups. There were no biologically significant differences in the rate of epidermal basal cell proliferation or incidence of microscopic lesions observed in the low dose group. Therefore, the biological significance of the increased incidence of clinically observed exfoliation was considered to be equivocal.

While high dose group mice that died or were sacrificed moribund had an increased incidence of hepatocellular adenomas and carcinomas, the overall

incidence of these tumors was similar across all dose groups. There were no other microscopic lesions in the mid and/or high dose groups that were considered to result in an increased incidence of mortality. Therefore, the statistically significantly increased size of the kidneys (observed both at necropsy and as increased mean absolute and relative organ weight) in the mid and high dose groups at the terminal sacrifice was the only lesion in these groups, other than the chronic skin irritation, that was considered to be biologically significant. However, microscopic diagnoses of the kidneys did not reveal a cause of the increased size of the kidneys. The chronic cutaneous irritation observed in this study was not considered to be sufficiently severe to result in increased mortality in these groups. Therefore, while a cause for the increased mortality in the mid and high dose groups was not identified, the increased kidney weights may have been related to the mortality observed in this study.

Based upon observations made during the in-life phase of the study that were recorded in the raw data as well as in photographs taken of some animals on this study, oral consumption of the TREGDMA was likely to have occurred in, at least, the high dose group. The effect of this inadvertent route of exposure on the kidney weights and decreased survival is unknown but must be considered.

Under the conditions of this study, the No-Observed-Effect Level for TREGDMA was considered to be 5%. Furthermore, under the conditions of this study, there was no indication of carcinogenicity of TREGDMA at any dose level.

OBJECTIVE

The objective of this study was to evaluate the chronic toxicity and carcinogenic potential of triethylene glycol dimethacrylate (TREGDMA) when applied to the skin of male mice over a period of at least 78 weeks.

BACKGROUND INFORMATION

A bioassay program was designed to evaluate the chronic toxicity and carcinogenic potential of the test substances. The overall bioassay program and individual study designs were based on the proposed guidelines developed at and modified by the U.S. Environmental Protection Agency (EPA) Dermal Bioassay Workshops (April 28-29, 1987 and May 18-19, 1988). The results and conclusions of the preliminary studies are summarized below.

Two 14-day skin painting studies (BRRC Report 54-538 and 54-554) were conducted with TREGDA and TREGDMA at BRRC. In both studies, 5 C3H/HeNHsd mice/group were treated topically with solutions at concentrations of 0.5, 1, 2, 5, and 10% of TREGDA or 25, 50, and 100% TREGDMA at a constant dose volume of 50 μ l for 14 consecutive days. An additional 5 mice were treated topically with 50 μ l of acetone (vehicle control). No mortality, treatment-related clinical signs, except findings in the treated skin, or effects on body weight were observed in either study.

The clinical signs observed for the TREGDMA-treated animals included exfoliation (present in all mice), color change and eschar formation (present in 2 mice in the 25% group), ulceration (seen in several mice in the 25% group), and erythema (present in 1 mouse in the 25% group). Some of the skin findings observed in this first 14-day study were considered to have resulted from scratching and rubbing of the treatment area of the mice against the box feeders utilized to measure the food consumption of the individual animals. Based on the results of this study, the 14-day study was repeated using hanging feeders that minimized the potential for the mice to scratch and rub the treatment site.

In the repeated 14-day study, the same study design (including dose levels) were utilized except for the change from box to hanging feeders. TREGDMA-treated animals had exfoliation during the study and at necropsy for the 50 and 100% groups. Microscopic changes primarily consisted of dermatitis, intracorneal pustule formation, acanthosis, and hyperkeratosis. A No-Observed-Effect Level (NOEL) was not established for TREGDMA even though the highest concentration (100%) did not result in epidermal necrosis or ulceration; other microscopic changes (dermatitis and acanthosis) were observed even at the lowest concentration (25%).

A 14-day study of similar design was conducted on TREGDA and TREGDMA by SRI International (SRI Project LSC-2427) to evaluate the effect of the treatment regimen on epidermal cell proliferation. As with the BRRC studies, C3H/HeNHsd male mice were treated topically with solutions at concentrations of 0.5, 1, 2, 5, and 10% of TREGDA or 25, 50, and 100% TREGDMA at a constant dose volume of 50 μ l for 14 consecutive days. Epidermal cell proliferation was measured by determining the labeling index (LI) in basal epithelial cells using nuclear labeling with 3 H-thymidine administered by a 1-day osmotic pump implanted intraperitoneally at the end of the treatment period. Both TREGDA and TREGDMA produced gross and microscopic signs of cutaneous irritation similar to those

observed in the BRRC 14-day studies. Both agents also produced very significant increases in cell proliferation in basal epithelium. TREGDMA produced dose-related increases in the LI that were up to 14-fold higher than the acetone control. The effects were generally more pronounced after 14 days of dosing than after 7 days. Both compounds were considered to be extremely potent inducers of cell proliferation in mouse skin. However, the dose of TREGDMA required to produce this effect was over two orders of magnitude greater than that of TREGDA. The correlation between cell proliferation, gross irritation, and histopathologic examination was consistent in all dose groups. In general, microscopic lesions were observed at doses where gross irritation was not readily detected. The induction of cell proliferation correlates extremely well with acanthosis, and was observed at all doses of TREGDA and TREGDMA. No other microscopic lesions were observed at the lowest dose of each agent. These results indicated that both TREGDA and TREGDMA produced significant irritation of mouse skin when applied topically, and that this irritation results in a very significant increase in DNA replication in the basal epithelium.

A 90-day dermal dose-finding study (BRRC Report 91N0017) was conducted with TREGDA and TREGDMA at BRRC. In this study, 10 C3H/HeNHsd mice/group were treated topically with solutions at concentrations of 0.05, 0.10, 0.5, and 0.75% of TREGDA or 5, 25, 50, and 100% TREGDMA at a constant dose volume of 50 μ l for 13 weeks (90 days). An additional 10 mice were treated topically with 50 μ l of acetone (vehicle control) while another group was maintained, but not treated throughout the study (untreated control). No mortality occurred. Doses of 0.10, 0.50, and 0.75% of TREGDA or 25, 50, or 75% of TREGDMA resulted in early cutaneous irritation that tended to decrease in severity, but did not entirely resolve, by Day 35. Slight exfoliation/desquamation persisted until the end of the study. Histopathological findings included dermatitis, acanthosis, and hyperkeratosis. Dose-related increases in both absolute and relative weights of livers of mice treated with 50 or 100% TREGDMA were observed. There were no confirmatory microscopic diagnoses; therefore, the etiology and biological significance, if any, is unknown. The persistence of exfoliation/desquamation and the histopathological findings of acanthosis and hyperkeratosis in the majority of animals in the 0.5 and 0.75% dose groups of TREGDA indicated that the maximum tolerate dose (MTD; as defined by the EPA Dermal Bioassay Workshops) was achieved for these groups. The MTD was not exceeded for any of the TREGDMA-treated groups.

Sections of treated skin obtained from animals of all dose groups of the 90-day study were sent to SRI International for evaluation of epidermal cell proliferation using the proliferating cell nuclear antigen (PCNA) technique (SRI Project LSC-2427). SRI also utilized the PCNA technique to evaluate cell proliferation using sections of the skin obtained from the 14-day study conducted at that facility. The PCNA technique confirmed the significant increase in epidermal basal cell proliferation in the 14-day study. Results obtained using the skin sections from the 90-day study indicated that an increased rate of basal cell proliferation continued even after 90 days of treatment. However, the level of PCNA labeling in controls was much higher after 90 days than after 14 days. Because of the elevated levels of PCNA labeling in the controls, the relative increase in the TREGDA and TREGDMA groups was modest, approximately 3-fold higher in the top dose groups than in the controls. These increases were statistically significant only in the 100% TREGDMA and 0.5% TREGDA groups.

DOSE SELECTION

The doses were selected by the Sponsor based upon the results of the 14-day and 90-day dose-finding studies with the test substances.

MATERIALS AND METHODS

The protocol and any protocol amendments detailing the design and conduct of this study are included in Appendix 11. Protocol deviations will also be included in Appendix 11 of the final report.

Test Substance

Two 1-gallon bottles of TREGDMA (CAS Registry No. 109-16-0), Lot No. 85674, were received on February 21, 1991 from Polysciences Inc., Warrington, PA, and assigned BRRC Sample Number 54-43 A and B. The test substance was a clear liquid and was stored refrigerated at approximately 5°C. Related correspondence from the supplier stated the purity of the test substance to be approximately 95%. Samples of the test substance were periodically shipped to the GLP Analytical Skill Center at the UCC South Charleston, WV, Technical Center for compositional analysis which included analysis of the hydroquinone (polymerization inhibitor) concentration. Analyses of these samples by the Skill Center indicated that the concentration of inhibitor or composition of the test substance did not change over the course of the study. The report issued by the Technical Center will be included as Attachment 1 to Appendix 1 in the final report. No corrections for purity were made in any of the calculations. A reserve sample was not retained.

Animals and Husbandry

Seven hundred and fourteen male C3H/HeNHsd mice arrived on October 20, 1992, from Harlan Sprague Dawley, Inc. (Indianapolis, IN). They were designated by the supplier to be approximately 4-5 weeks old (the birth date was recorded as September 18, 1992) upon arrival.

Animals were housed in Room 106 from arrival to termination of the study except for 2 days when the animals were housed in Room 101. The animals were moved to Room 101 due to anticipated noise in Room 106 that was related to maintenance activity in an adjacent room.

Within 2 days of receipt, the animals were examined by a clinical veterinarian and a pretest health screen for representative animals was initiated. The health screen included full necropsy, histologic examination of selected tissues, serum viral antibody analyses, and examinations for fecal parasites. Based on the results of these data, the clinical veterinarian indicated that these animals were in good health and suitable for use.

All animals were assigned unique numbers and identified by cage tags. Animals considered available for the study were also identified by a toe-clipping and ear-notching procedure.

The animals were housed 2/cage for approximately 6 days in stainless steel, wire mesh cages (22.5 x 10.0 x 12.5 cm). The purpose of the double housing was to help acclimate the animals to their new surroundings. DACB® (Deotized Animal Cage Board; Shepherd Specialty Papers, Inc.) was placed under each cage

and changed regularly. Cages were changed and sanitized at least once every 2 weeks. The cages and racks were rotated at least once every 2 weeks according to a predetermined schedule in order to better ensure equivalent environmental conditions for all animals. An automatic timer was set to provide fluorescent lighting for a 12-hour photoperiod (approximately 0500 to 1700 hours for the light phase). Temperature and relative humidity were recorded (Cole-Parmer Hygrothermograph® Seven-Day Continuous Recorder, Model No. 8368-00, Cole-Parmer Instrument Co., Chicago, IL). Temperature was routinely maintained at 65-77°F; relative humidity was routinely maintained at 40-70%. Any minor exceptions to these specified ranges were noted in the raw data.

Tap water (Municipal Authority of Westmoreland County, Greensburg, PA) was available ad libitum and was delivered by an automatic watering system with demand control valves mounted on each rack. Water analyses were provided by the supplier, Halliburton NUS Environmental Laboratories, Professional Service Industries, Inc., and Lancaster Laboratories, Inc. at regular intervals. EPA standards for maximum levels of contaminants were not exceeded. Pelleted, certified AGWAY® PROLAB® Animal Diet Rat, Mouse, Hamster 3000 (Agway Inc.) was available ad libitum. Analyses for chemical composition and possible contaminants of each feed lot were performed by Agway Inc., and the results were included in the raw data.

Animal Acclimation

The acclimation period was approximately 3 weeks. During this period, the animals were weighed 2 times at scheduled intervals. Detailed clinical observations were conducted weekly. Animals were observed once daily for any overt clinical signs of disease or abnormality. The animals were examined just prior to the end of the acclimation period by a clinical veterinarian. Animals considered unacceptable for the study, based on the clinical signs, body weight, or body weight gain, were rejected. The fate of rejected animals and the reasons for rejection were documented in the raw data.

Study Organization

Following the second pretest body weight, the animals were assigned to 6 treatment groups (3 TREGDA and 3 TREGDMA) and 2 control groups using a nonstratified randomization procedure based on body weight. At the time of group assignment, only animals with body weight within $\pm 20\%$ of the population mean for each sex were included. The body weight range on the day of first treatment was 22.3 to 28.0 g for TREGDMA males.

The first 50 animals/group were designated as core animals. The last 20 animals/group were designated as satellite animals to be utilized for cell proliferation evaluations performed at 4, 13, 52, and 78 weeks. An additional 30 animals not selected for use on the study were designated as sentinel animals. For the week 78 cell proliferation evaluation, animals designated as core animals were used as replacements for satellite animals which died during the study to maintain a satellite group size of 5 animals/group.

The treatment began on November 9, 1992 (Study Day 0). Animals were treated 5 days/week (Monday through Friday) for 78 weeks. Five animals/group were sacrificed for cell proliferation evaluations on December 8, 1992, February 9, 1993, November 9, 1993 (4/group for groups 2-7), and May 10, 1994. All

surviving animals were sacrificed between May 12, 1994 and May 19, 1994 after at least 78 weeks of treatment.

The following table summarizes the organization of the study.

Group	Number of Animals	Test Substance	Concentration ¹ (%)
Untreated Control	70	None	None
Vehicle Control	70	Acetone	100.00
Low	70	TREGDA	0.05
Mid	70	TREGDA	0.10
High	70	TREGDA	0.50
Low	70	TREGDMA	5.00
Mid	70	TREGDMA	25.00
High	70	TREGDMA	50.00

¹Based on test substances as received.

Administration of Test Substance

Preparation of Skin

During the week prior to the initial dose administration, the fur was clipped from the dorsal area of the trunk with veterinary clippers. One day prior to the first dose, the fur was clipped again in preparation of dosing.

During the study, animals were clipped as needed in the afternoons (generally more than 3 hours after the completion of dosing). Clipping was generally completed on Monday or Tuesday of each week. The animals from both control groups were clipped before clipping the chemical-treated animals. Clipping of treated animals was completed according to test substance (that is, all of the animals treated with one chemical were clipped before any of the animals treated with the other chemical). The clipping of the treated animals proceeded in a low to high dose group order. The first treated animals to be clipped (TREGDA or TREGDMA) generally rotated from week to week. The clipper blades were cleaned with acetone between clipping animals treated with different chemicals and at the end of each day of clipping.

Dosing Solution Preparation

Dosing solutions were prepared by adding the appropriate amount of TREGDMA (ml) to a 25 ml volumetric flask, then diluting to volume with acetone. Each solution was mixed manually by inversion. After mixing, the solutions were transferred to amber glass dosing bottles equipped with teflon-lined lids. The solutions were stored refrigerated at approximately 4°C between use.

Dosing

The test substance, dissolved in acetone, was applied topically to the clipped interscapular region of the back by an automatic pipette. The pipette was

calibrated at least once a month throughout the study. Mice were treated 5 days/week for at least 78 weeks with a single dose of 50 μ l/animal/day. Vehicle control animals were similarly treated with acetone only. The untreated control group was not treated with either test substance or acetone. However, animals from the untreated control group were picked up on each dose day and the interscapular region of the back of the animals from this group was clipped on the same schedule as the other animals.

Dosing Solution Analysis

Before initiating dosing, the test solutions were prepared to assess the homogeneity and stability. Homogeneity (duplicate samples each from the top, middle, and bottom of the mixing vessel) was determined for the 5, 25, and 50% solutions. Stability was evaluated by determining the test substance concentration in triplicate samples from the 5 and 50% solution concentrations used for the stability study. Stability of the test substance in the solutions was determined for Day 0 (directly after preparation), Day 7, and Day 14 under storage conditions identical to those used during dosing.

Dosing solutions were prepared weekly during the study and analyzed for concentration of TREGDMA prior to the first day of dosing and at 1, 3, 6, 12, and 18 months after initiation of the study.

Standards for acceptable accuracy of mixing were: the mean of the analyzed samples were within $\pm 10\%$ of nominal; the difference between duplicate analyses did not exceed 15%; and individual analyses were within $\pm 15\%$ of nominal.

Observations and Measurements

In-life Evaluations

All animals were observed for mortality and overt signs of toxicity twice daily and once each day on the weekends until December 18, 1993. After that date, observations for mortality and overt signs of toxicity were conducted twice daily, seven days/week. Detailed examinations for clinical signs of disease or abnormality, which involve animal handling, were conducted once weekly. All external structures were examined and each mouse was thoroughly palpated for external masses.

Individual body weights were measured weekly for the first 13 weeks of the study and every fourth week thereafter through termination.

Photography

Five surviving animals/group were photographed (treated skin) after 2, 4, 6, 13, 26, 52, and 78 weeks of treatment. The photographs were retained in the raw data. Furthermore, late in the study, photographs of several mice were taken on a Friday followed by photographs of the same mice on the following Monday.

Clinical Pathology Evaluations

Clinical investigations (hematology) were conducted on 10 core animals/group at 12 (Week 52) and 18 (Week 79) months. Blood was obtained from 5

animals/group for hematology and 5 animals/group for clinical chemistry. All blood samples were obtained from methoxyflurane or halothane anesthetized animals via puncture of the retroorbital sinus.

The following were measured or calculated:

Hematology

hematocrit	mean corpuscular hemoglobin
hemoglobin	concentration (MCHC)
erythrocyte count	total leukocyte count
mean corpuscular volume (MCV)	differential leukocyte count ¹
mean corpuscular hemoglobin (MCH)	platelet count

¹Differential leukocyte counts were performed on high dose groups (Groups 5 and 8) and control groups (Groups 1 and 2).

Clinical Chemistry

glucose (nonfasting)	chloride
urea nitrogen	aspartate aminotransferase (AST)
creatinine	alanine aminotransferase (ALT)
total protein	creatine kinase (CK)
total bilirubin	gamma-glutamyl transferase (GGT)
calcium	alkaline phosphatase (ALK)
phosphorus	albumin
sodium	cholesterol
potassium	

Details of the clinical pathology procedures are included in Appendix 3.

Anatomic Pathology Evaluations

Cell Proliferation - Necropsy

Cutaneous cell proliferation evaluations were performed on 5 mice/group at 4 evaluation periods during the study. Alzet® Osmotic Pumps (Model 1003D; 1 µl/hour) were implanted on Monday morning following the completion of 4, 13, 52, and 78 weeks on study for infusion of bromodeoxyuridine (BrdU; 20 mg/ml in Dulbecco's Phosphate Buffered Saline). Animals were euthanized 24 hours after implanting the pumps for subsequent evaluations of BrdU uptake by epidermal basal cells in the treated skin. Animals were anesthetized by methoxyflurane and killed by severing the brachial vessels to permit exsanguination 24 hours after the implantation of the pump. All animals received a completed necropsy. All tissues listed in the core animal necropsy section were removed and fixed in 10% neutral buffered formalin (NBF). Selected organs were also weighed for animals sacrificed at Week 78.

Cell Proliferation - Histology

Skins were processed to blocks using xylene substitute and tissue sections were cut at 5µ, mounted on Fisher Plus Slides (Fisher Scientific, Pittsburgh, PA), and stained using routine immunohistochemical procedures for nuclear incorporation of BrdU. Additional tissues for animals sacrificed at Week 78

were processed and evaluated microscopically as described in the core animal - histology section.

Cell Proliferation - Counting Procedure

Two skin sections/animal were evaluated at 40X magnification. Each section was arbitrarily assigned as section 1 or section 2. The stained duodenum (internal control) and skin sections were scanned (at low magnification) for proper and even staining.

Only clearly identified cells in the plane of section were used in the evaluation. Necrotic or pyknotic nuclei or cells not in the plane of section were not counted. To evaluate sections that contained hair follicles, two imaginary lines were drawn on either side of the base of the follicle and no cells in between those 2 imaginary lines were used in the evaluation.

Beginning at one end of each skin section and moving field by field (to avoid overlapping and re-counting cells), labeled and unlabeled cells were identified until 500 cells/skin section were counted. The total number of labeled and unlabeled cells/field were entered into a computer program designed to calculate the percent of labeled cells/animal.

Core Animals - Necropsy

At the end of treatment, all surviving animals were anesthetized with halothane and killed by severing the brachial vessels to permit exsanguination. On the day of sacrifice, body weights were obtained to allow expression of relative organ weights. A complete necropsy was performed on all animals. The liver, kidneys, brain, testes, and spleen were weighed for all sacrificed animals. The following tissues were collected for all animals and retained in 10% neutral buffered formalin:

gross lesions	aorta
lungs	skin
brain	esophagus
pituitary	stomach
thyroid/parathyroid	duodenum
thymic region	jejunum
trachea	ileum
heart	cecum
bone, sternum	colon
salivary gland	rectum
liver	urinary bladder
spleen	lymph node, mesenteric
kidneys	lymph node, other
adrenal gland	thigh musculature
pancreas	nerve, sciatic
testes	eyes and harderian gland
epididymis	femur
prostate	spinal cord
seminal vesicles	gall bladder
	bone marrow smear (femur)

Animals found dead or sacrificed in a moribund condition (including satellite animals) were handled as described above, except no body or organ weights were recorded.

Ears and toe-clipped feet were saved for identification purposes.

Core Animals - Histology

Microscopic examinations were performed on the above listed tissues for all animals from both control and high dose groups. In addition, the lungs, liver, kidneys, spleen, treated skin, untreated skin, stomach, and grossly lesioned tissues were examined from those animals assigned to the mid and low dose groups. All tissues to be examined were paraffin-embedded, sectioned at approximately 5 micrometers, and stained with hematoxylin and eosin. Animals either found dead or sacrificed moribund (including satellite animals) were handled in a similar manner, according to their respective dose groups.

Details of the anatomic pathology procedures are included in Appendix 2.

Data Analyses

The data for quantitative continuous variables and cell proliferation data were intercompared for the 3 treatment groups and the control groups by use of Levene's test for equality of variances, analysis of variance (ANOVA), and t-tests. The t-tests were used when the F value from the ANOVA was significant. When Levene's test indicated similar variances, and the ANOVA was significant, a pooled t-test was used for pairwise comparisons. When Levene's test indicated heterogeneous variances, all groups were compared by an ANOVA for unequal variances followed, when necessary, by a separate variance t-test for pairwise comparisons.

Nonparametric data were statistically evaluated using the Kruskal-Wallis test followed by the Mann-Whitney U-test. Incidence data were compared using Fisher's Exact Test. Other analyses used included life-table analysis. For all statistical tests, except life-table analyses, the probability value of < 0.05 (two-tailed) was used as the critical level of significance. The probability value of < 0.05 (one-tailed) was used for life-table tumor analyses.

Various models of calculators, computers, and computer programs may have been used to analyze data for this study. Since various models round or truncate numbers differently, values in some tables may differ slightly from those in other tables or from independently calculated data. The integrity of the study and interpretation of the data were unaffected by these differences.

RETENTION OF RECORDS

All raw data, documentation, photographs of animals, paraffin blocks and tissue slides, the protocol and any amendments, and a copy of the final report generated as a result of this study and as a result of the concurrent study with TREGDA will be retained together in the BRRRC Archives for at least 10 years. Due to the nature of the test substance, a reserve sample was not retained.

RESULTS AND DISCUSSION

All references of differences in group mean values in the following text refer to comparisons of statistically significant differences between the treatment group and the control groups unless otherwise noted. Repeated reference to the control and the statistical significance will not be made in order to simplify the text.

Analytical Chemistry

The report and summary tables for analytical chemistry are included in Appendix 1.

For the stability analyses, the mean measured concentrations of the 5 and 50% solutions ranged from 100.9 to 105.7 and 100.1 to 105.9% of nominal, respectively. These results indicated that TREGDMA in acetone remained stable at the specified concentrations for at least 14 days when stored refrigerated.

For the homogeneity analyses, the mean measured concentrations (\pm SD) of TREGDMA in the 5, 25, and 50% solutions were 105.7 (\pm 0.7), 100.4 (\pm 0.9), and 101.6 (\pm 0.6)% of nominal, respectively. The coefficients of variation of the percent of nominal for the 5, 25, and 50% solutions were 0.7, 0.9, and 0.6%, respectively. These results show that the solutions were uniformly prepared.

The mean measured concentrations of the 5, 25, and 50% solutions ranged from 94.4 to 106.2% of nominal for the 6 periods of analysis. TREGDMA was not detected in the control dosing solutions.

Clinical Observations, Mortality, and Palpable Masses

A summary of mortality is presented in Table 1. A summary of the clinical observations is presented in Table 2. Individual animal fate data are included in Appendix 4. Individual animal clinical observation data are included in Appendix 5. Individual palpable mass data are included in Appendix 6.

There were no biologically significant differences in the survival or incidence of clinical observations between the vehicle and untreated control groups. The survival rates over the study period (including those sacrificed moribund but excluding accidental and procedural deaths) were 74, 71, 73, 63, and 49% for the untreated control, vehicle treated control, low, mid, and high dose groups, respectively. Life-table analyses (Kaplan-Meier, 1958) indicated that the survival of the high dose group was statistically significantly decreased as compared to both control groups. While both the survival rate and the mean survival time for the mid dose group was lower than either control group, the mean survival time was not statistically significantly different from either control group.

Treatment-related clinical signs of toxicity were generally limited to local signs of irritation at the site of treatment. Exfoliation (dandruff like scale) was observed in all dose groups including the controls and, therefore, was considered to be at least partially related to the manipulative procedures such as clipping. The slight increase in incidence of exfoliation between the untreated controls (19/70) and vehicle treated controls (25/70) was not considered to be biologically significant. An increased incidence of

exfoliation was observed in all TREGDMA-treatment groups as compared to both control groups. Exfoliation was first observed on Day 8 in the high dose group and by Day 29 was observed in all TREGDMA-treated groups (exfoliation was not observed in either control group until Day 127). Exfoliation was observed in all but 3 animals from the mid dose group and all animals from the high dose group. While the summary table (Table 2) suggests that the number of animals observed with exfoliation was increased in the low dose group as well as the mid and high dose groups, the incidence of this finding in the low dose group was not considered to be biologically significant as indicated by the following table of randomly selected study periods:

<u>Study Days</u>	<u>Number of animals with Exfoliation</u>				
	<u>Untreated</u>	<u>Vehicle</u>	<u>5%</u>	<u>25%</u>	<u>50%</u>
35-42	0	0	1	22	49
210-215	0	0	2	6	17
350-355	2	2	7	4	10
440-445	0	1	7	13	17
546-550	3	4	21	24	25

Two animals from the mid dose group and 7 animals from the high dose group were observed with exfoliation of a grade of 1 (compared to "P" for present) while none of the low dose group or control animals were observed with this greater severity of exfoliation. An exfoliation grade of 1 was subjectively assigned to an animal based upon both the apparent size of the dandruff like flakes as well as the overall amount of flaking. No animals in the study were assigned exfoliation grades of 2 or 3 that were indicative of large areas of the skin peeling away from the treatment area.

The number of animals observed with one or several non-specific signs including emaciated body, dehydration, abdominal distention, cold extremities, or labored respiration was generally increased in the high dose group. These findings are frequently observed in animals prior to death and, therefore, the increased incidence of these findings was attributed to the increased mortality in this dose group.

In addition to routine observations for clinical signs of toxicity, observations made by study personnel during the in-life portion of this study suggested that oral consumption of the TREGDMA was likely to have occurred in the high dose group and possibly in the mid and low dose groups because the fur surrounding the treatment site became contaminated with the test substance. These observations were recorded in the raw data and photographs of representative animals taken periodically throughout the study. The contamination gradually became more noticeable from Monday to Friday (days of dosing) and improved over the weekend (animals were not dosed over the weekend). Therefore, it is assumed that the normal preening behavior of the animals resulted in oral consumption of the test substance (an examination of the inside of the caging for some of these animals did not indicate that the test substance was rubbing off onto the cage). The possible effects of this inadvertent route of exposure must be taken into account in the evaluation of the results of this study.

There were no other clinical signs of toxicity (including palpable masses) that were considered to be related to treatment.

Body Weights

Summaries of absolute body weight and body weight gain are presented in Tables 3 and 4. A graph of body weight (grams) versus time (weeks) is presented in Figure 1. Individual animal body weight data are included in Appendix 7.

There were no biologically significant effects on absolute body weights or body weight gains observed in the study. Occasional statistically significant differences in the mean body weight or body weight gain values were considered to be spurious.

Clinical Pathology Evaluations

Summaries of the hematology measurements are presented in Tables 5 and 6. Summaries of the clinical chemistry measurements are presented in Tables 7 and 8. Individual clinical pathology data are included in Appendix 10. Detailed results and discussion of the clinical pathology measurements are included in Appendix 3.

There were no treatment-related effects on hematology or clinical chemistry measurements observed in any group. Furthermore, there were no biologically significant differences in any clinical pathology parameter between the untreated and vehicle treated control groups.

Cell Proliferation

The summary data are presented in Table 9. Individual cell proliferation data are included in Appendix 8.

There were no biologically significant differences in the mean rate of epidermal basal cell proliferation between the untreated and vehicle treated control groups. The mean measured rate of epidermal basal cell proliferation in the control groups tended to slightly increase after one year on study. This is opposite of what has generally been observed in human skin where the rate of epidermal cell proliferation tends to decrease with age (Lamminuusta and Maibach, 1988; Roberts and Marks, 1980). However, the increased mean rate of basal cell proliferation observed in this study may have been secondary to greater variability in the animals as they aged (the standard deviations of the control groups tended to gradually increase with age). Therefore, the biological significance of the increased rate of epidermal basal cell proliferation in the older animals from the control groups was not known.

The mean measured rate of epidermal basal cell proliferation of the mid and high dose groups was consistently increased as compared to both control groups throughout the study. While the rate of epidermal cell proliferation was slightly higher in the high dose group than the mid dose group at all measurement intervals except at Week 4, the differences between these dose groups were most likely not biologically significant. At the Week 4 and 13 measurement intervals, the rate of cell proliferation for both of these groups was approximately 65 to 125% increased over the control groups. However, at the Week 52 and 78 measurement intervals the rate of cell proliferation for these groups was approximately 25 to 60% increased over the control groups. Therefore, the proliferative response of the skin to TREGDMA decreased as the animals aged. The cause or biological significance of this change in

proliferative response was unknown. There were no biologically significant differences in the rate of epidermal basal cell proliferation between the control groups and the low dose group of TREGDMA-treated mice.

Organ Weights, Necropsy Observations, and Microscopic Diagnoses

Summary results of organ weights, organ weights relative to final body weight, and organ weights relative to brain weight are presented in Tables 10 to 12. Summary results of necropsy observations are presented in Tables 13 and 18. Summary results of microscopic diagnoses are presented in Tables 19 and 26. Individual anatomic pathology data are included on Appendix 9. Detailed results and discussion of the anatomic pathology results are included in Appendix 2.

A significant increase in both the mean absolute liver weights of the vehicle treated control group as compared to the untreated control and low and high dose groups was attributed to a few animals in the vehicle treated control group with relatively large liver masses. The overall incidence of tumor masses and nodules was generally similar in all groups and, therefore, the increased liver weight of this dose group was not considered to be biologically significant.

Both the mean absolute and relative weight of the kidneys were statistically significantly increased in the mid (8 to 12%) and high (14 to 19%) dose groups as compared to both control groups.

There were no biologically significant differences in the incidence of necropsy findings between the untreated and vehicle treated control groups. As observed during the in-life phase of the study, there was a dose-related increased incidence of exfoliation observed at necropsy in all groups of mice treated with TREGDMA. At Week 52 and 78, there was also a numerical increase in the number of animals with grossly enlarged kidneys. There were no other biologically significant, treatment-related necropsy findings observed in any dose group.

Upon microscopic examination, there were several statistically significant differences between the untreated and vehicle treated control groups. The incidence of adnexal atrophy was increased in the vehicle treated control group indicating a change in the skin secondary to chronic acetone administration. The incidence of myelin sheath swelling was increased in the vehicle treated control group. However, most of these changes were graded as minimal and, therefore, the biological significance of this change is equivocal. Furthermore, subchronic oral administration of acetone by other researchers did not produce any neuropathological lesions (Spencer *et al.*, 1978). The only other microscopic lesion in the vehicle treated control group that may have been biologically significant was an increase in lung mineralization. The toxicological significance of this lesion was unknown. Other statistically significant differences in the incidence of microscopic lesions between the untreated and vehicle treated control groups were not considered to be related to acetone treatment due to a similarity of the untreated control with the TREGDMA dose groups or overall low incidence of the lesion. These lesions included a decreased incidence of myocardial degeneration/fibrosis, increased incidence of anomalous lobulation of the liver, decreased incidence of thyroglossal duct cyst in the thyroid gland,

clitoral/preputial gland duct ectasia of the skin, and splenic extramedullary hematopoiesis.

Comparison of the incidence of microscopic lesions in the mid and high dose groups with both control groups indicated TREGDMA-related changes only in the skin. The diagnosis and incidence of lesions in the mid and high dose groups were similar and were indicative of chronic cutaneous irritation/inflammation. The lesions, primarily graded as minimal to mild, included acanthosis, hyperkeratosis/parakeratosis, and dermatitis. There were no biologically significant indications of chronic inflammation at the treatment site in the low dose group.

Microscopic diagnoses did not reveal a cause for either the increased kidney weights or decreased survival in the mid and high dose groups. While dilated hyperplastic tubules of the kidney was statistically significantly increased in the high dose group as compared to both control groups, the lesion was graded as minimal for most affected animals and was not, therefore, considered to be biologically significant. High dose group mice that died or were sacrificed moribund had an increased incidence of hepatocellular adenomas and carcinomas. However, the incidence of these lesions was decreased in animals that survived to the terminal sacrifice and the overall incidence of these tumors was similar across all dose groups. In high dose group animals that died or were sacrificed in a moribund condition, there was a slightly increased frequency of mineralization in several organs as well as increased frequency of alveolar histiocytosis as compared to both controls. Neither of these lesions were considered to be responsible for the increased mortality in the high dose group. Finally, there were no biologically significant differences between groups in the frequencies of kidney lesions in animals that died or were sacrificed in a moribund condition. Therefore, a cause for the decreased survival in the high dose group was not identified.

CONCLUSIONS

Cutaneous treatment of C3H/HeNHsd male mice with 50 μ l of 5, 25, or 50% of TREGDMA in acetone 5 days/week for at least 78 weeks did not result in any treatment-related changes in hematology, clinical chemistry, mean absolute body weights, or body weight gain. The mid and high dose groups had slightly decreased survival as compared to both control groups but only the mean survival time of the high dose group was statistically significantly different from the control groups. Clinical signs of irritation, consisting primarily of exfoliation (dandruff-like scale), were observed in all dose groups. The time of onset, incidence, and severity of exfoliation were related to dose. Similar observations at the site of treatment were made at necropsy. Both epidermal basal cell proliferation and microscopic diagnoses of the treated skin confirmed the presence of cutaneous irritation in the mid and high dose groups. Epidermal basal cell proliferation at the site of treatment indicated an increased cell turnover rate that was very similar in the mid and high dose groups. The increase was greatest at the 4 and 13 Week measurement intervals and tended to be less pronounced at the 52 and 78 Week measurement intervals. Microscopic examination at 78 Weeks again indicated very similar chronic cutaneous irritation changes at the site of treatment in the mid and high dose groups. There were no biologically significant differences in the rate of epidermal basal cell proliferation or incidence of microscopic lesions

observed in the low dose group. Therefore, the biological significance of the increased incidence of clinically observed exfoliation was considered to be equivocal.

While high dose group mice that died or were sacrificed moribund had an increased incidence of hepatocellular adenomas and carcinomas, the overall incidence of these tumors was similar across all dose groups. There were no other microscopic lesions in the mid and/or high dose groups that were considered to result in an increased incidence of mortality. Therefore, the statistically significantly increased size of the kidneys (observed both at necropsy and as increased mean absolute and relative organ weight) in the mid and high dose groups at the terminal sacrifice was the only lesion in these groups, other than the chronic skin irritation, that was considered to be biologically significant. However, microscopic diagnoses of the kidneys did not reveal a cause of the increased size of the kidneys. An increased incidence of dilated hyperplastic tubules of the kidney in animals sacrificed at Week 78 was not considered to be biologically significant. The chronic cutaneous irritation observed in this study was not considered to be sufficiently severe to result in increased mortality in these groups. Therefore, while a cause for the increased mortality in the mid and high dose groups was not identified, the increased kidney weights may have been related to the mortality observed in this study.

Based upon observations made during the in-life phase of the study that were recorded in the raw data as well as in photographs taken of some animals on this study, oral consumption of the TREGDMA was likely to have occurred in, at least, the high dose group. The effect of this inadvertent route of exposure on the kidney weights and decreased survival is unknown but must be considered.

Under the conditions of this study, the No-Observed-Effect Level for TREGDMA was considered to be 5%. Furthermore, under the conditions of this study, there was no indication of carcinogenicity of TREGDMA at any dose level.

REVIEW AND APPROVAL

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Date

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