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INITIAL SUBMISSION: ACUTE TOXICITY AND IRRITANCY USING THE RAT (PERORAL TOXICITY) AND THE RABBIT (CUTANEOUS AND EYE TESTS) WITH COVER LETTER DATED 093092		
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TRITON X-193 AG EMULSIFIER		



CONTAINS NO CBI

UNION CARBIDE CORPORATION 39 OLD RIDGEBURY ROAD, DANBURY, CT 06817-0001
September 30, 1992

CERTIFIED MAIL
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8EHQ-1092-8525

Document Processing Center (TS-790)
Room L-100
Office of Toxic Substances
U.S. Environmental Protection Agency
401 M Street, SW
Washington, DC 20460

Re: Union Carbide Corporation ("Union Carbide")
TSCA 8(e) Submission of June 22, 1992
Concerning TRITON® X193 AG Emulsifier

Dear Sir or Madam:

As a follow-up to the above-noted submission, Union Carbide Corporation ("Union Carbide") herewith submits the following report for TRITON® X-193 AG Emulsifier.

"TRITON® X-193 AG Emulsifier: Acute Toxicity and Irritancy Using the Rat (Peroral Toxicity) and the Rabbit (Cutaneous and Eye Tests)", Bushy Run Research Center, BRRC Report 91U0068, August 27, 1992.

In the attached report the term "Confidential" may appear. This precautionary statement was for internal use at the time of issuance of this report. Confidentiality is hereby waived for purposes of the needs of the Agency in assessing health and safety information. The Agency is advised, however, that the publication rights to the contained information are the property of Union Carbide.

Please contact the undersigned with questions, if any, at 203/794-5230.



6EHQ-92-8525
INIT 10/07/92



88930000007

WCK/cr
Attachment

Very truly yours,

William C. Kuryla, Ph.D.
Associate Director
Product Safety

trix193

67 pgs



BUSHY RUN RESEARCH CENTER

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STUDY TITLE

TRITON® X-193 AG Emulsifier: Acute Toxicity and Irritancy Testing Using the Rat (Peroral Toxicity) and the Rabbit (Cutaneous and Eye Tests)

TEST SUBSTANCE

TRITON® X-193 AG Emulsifier

DATA REQUIREMENTS

Not Applicable

AUTHORS

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STUDY COMPLETION DATE

August 27, 1992

PERFORMING LABORATORY

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LABORATORY PROJECT ID

91U0062

SPONSOR

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Union Carbide Chemicals and Plastics Company Inc.
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TRITON® X-193 AG Emulsifier: Acute Toxicity and Irritancy Testing Using
the Rat (Peroral Toxicity) and the Rabbit (Cutaneous and Eye Tests)

CONFIDENTIALITY STATEMENT

This report is Union Carbide Corporation Business Confidential and is not to be released outside of the Corporation without the written consent of the Sponsor.

TRITON® X-100 AG Emulsifier: Acute Toxicity and Irritancy Testing Using
the Rat (Peroral Toxicity) and the Rabbit (Cutaneous and Eye Tests)

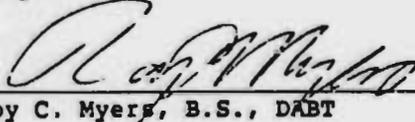
COMPLIANCE WITH GOOD LABORATORY PRACTICE STANDARDS

The portions of this study conducted at BRRC meet the requirements of Toxic Substances Control Act (TSCA) Good Laboratory Practice Standards, 40 CFR Part 792, with exceptions. The exceptions are:

1. The Study Director had no knowledge of the procedures used for chemical analysis for interfering contaminants in the water conducted by the NUS Corporation or procedures used for rat diet analysis by Agway, Inc.
2. Concentrations of test mixtures used for peroral dosing were verified by gravimetric analysis.
3. Analyses for physical and chemical characterization of the test substance or of the homogeneity and stability of the test substance in the carrier used for peroral dosing (distilled water) were not conducted. All doses were given within 30 minutes after test substance preparation.
4. The feed provided to the rabbits used for this study was not analyzed or certified, but was essentially the same as certified feed offered by the same supplier.

These exceptions are not expected to compromise the integrity of the results and conclusions of the study.

Study Director:


Roy C. Myers, B.S., DABT

8-27-92
Date

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TRITON® X-193 AG Emulsifier: Acute Toxicity and Irritancy Testing Using
the Rat (Peroral Toxicity) and the Rabbit (Cutaneous and Eye Tests)

SUMMARY

Rat peroral toxicity, rabbit percutaneous toxicity, rabbit skin irritancy, and rabbit eye irritancy tests were conducted on TRITON® X-193 AG Emulsifier. This test substance is a mixture and, therefore, a specific CAS Number is not available. The procedures followed for these tests were based on current EPA Toxic Substances Control Act (TSCA) Health Effects Test Guidelines. Results from this study, expressed in terms of test substance as received, are as follows:

Peroral, Rat (Fasted)

Males: 1410 mg/kg of body weight (b.w.) killed 0 of 3
Females: LD50 = 1460 (1200 to 1780) mg/kg b.w.

Percutaneous, Rabbit (24-Hour Occluded)

Males: 8.0 g/kg of body weight (b.w.) killed 2 of 3
Females: LD50 = 14.3 (7.4 to 27.4) g/kg b.w.

Skin Irritation, Rabbit (4-Hour Occluded)

Minor erythema on 6 of 6 rabbits, minor edema (transient) on 4 from 0.5 ml. Irritation subsided after 3 to 7 days (edema subsided after 1 day).

Eye Irritation, Rabbit

Minor to moderate corneal injury (opacity) in 4 of 4 eyes (with vascularization), iritis in 4, severe conjunctival irritation in 4 from 0.1 ml; irritation persisted in all eyes through 21 days. Minor to severe corneal injury in 4 of 4 eyes (with vascularization and surface bulging in 1), iritis in 4, severe conjunctival irritation in 4 from 0.01 ml; irritation persisted in 3 eyes through 21 days.

OBJECTIVE

The objective of this study was to assess the acute peroral toxicity, acute percutaneous toxicity, cutaneous irritancy, and ocular irritancy of TRITON® X-193 AG Emulsifier. For all procedures, testing was conducted in accordance with EPA (TSCA) Test Guidelines (Federal Register Vol. 50, No. 188) and 1987 OECD Guidelines for Testing of Chemicals (Section 4: Health Effects).

MATERIALS AND METHODS

The protocol (BPRC Project No. 91-22-11366) and 1 protocol amendment detailing the design and conduct of this study are presented in Appendix 3.

Test Substance

One 1-quart container of TRITON® X-193 AG Emulsifier; Spec # 1-40F.X193-1 Lot No. 25142 was received on October 7, 1991, from Union Carbide Chemicals and Plastics Company Inc., South Charleston, WV (manufactured by Rohm and Haas Company, Philadelphia, PA) and assigned BPRC Sample No. 54-344. The test substance was a brown, translucent, very viscous liquid. The test substance was stored at room temperature. Related correspondence and the Sponsor-supplied Material Safety Data Sheet indicated that the test substance was a blend of nonionic surfactants and organic sulfonates surfactant totaling approximately 89%. Pertinent chemical and physical properties of TRITON® X-193 AG Emulsifier are found in the Material Safety Data Sheet attached to the study protocol (Appendix 3).

Animals and Husbandry

Rats

Male and female Sprague Dawley® albino rats were received from Harlan Sprague Dawley, Inc. (Indianapolis, IN). The strain and species were selected because of their availability and existing historical data. Male rats were ordered to be approximately 195 to 215 g (designated by the supplier to be approximately 7 to 8 weeks of age). Female rats were ordered to be approximately 220 to 240 g (approximately 11 to 12 weeks of age). Occasionally male and female rats that were ordered in at 6 weeks of age (initially received for other acute testing) were used as long as weight requirements were met on the day of dosing. The females were nulliparous and nonpregnant.

Animals were housed in Room 109 from arrival to termination of the study. Once each month, 5 rats/sex received for acute testing and housed in Room 109 were subjected to a quality control evaluation, including gross pathology, parasitology, and viral serology testing. Periodically, a Clinical Veterinarian examined the rats housed in Room 109 for any signs of health deficiencies. All animals were assigned a unique number and identified by cage cards. Animals were also identified by an ear tagging procedure during the week of receipt.

The animals were separated by sex and group housed (up to 5/cage) in stainless steel, wire mesh cages (approximately 16 x 9 x 7 in.). Deotized Animal Cage Board® (Shepherd Specialty Papers, Inc., Kalamazoo, MI) was placed under each cage and changed regularly. 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 continuously (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 during the test period; 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 and the NUS Corporation 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 until the day before dosing. The feed was removed for approximately 18 hours before dose administration. After dosing, feed was again made available ad libitum. Analyses for chemical composition and possible contaminants of each feed lot were performed by Agway Inc., and the results are included in BRRC files.

Rabbits

Male and female New Zealand White rabbits were received from Hazleton Research Products, Inc. (Denver, PA). The strain and species were selected because of their availability and existing historical data. Rabbits were ordered to be between 2.0 and 2.3 kg (designated by the supplier to be approximately 12 to 14 weeks of age). The females were nulliparous and nonpregnant.

Animals were housed in Room 122 from arrival to termination of the study. Periodically, a Clinical Veterinarian examined rabbits housed in Room 122 for any signs of health deficiencies. Within 1 or 2 days of receipt, all animals were assigned a unique number which was marked on the animal cage card. The rabbit number was also marked in indelible ink on 1 ear at the time of dosing.

The rabbits were housed individually in cages with wire floors (approximately 18 x 24 x 15 in.). Deotized Animal Cage Board® (Shepherd Specialty Papers, Inc., Kalamazoo, MI) was placed under each cage and changed regularly. 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 continuously (Cole-Parmer Hygrothermograph® Seven-Day Continuous Recorder, Model No. 8368-00, Cole-Parmer Instrument Co., Chicago, IL). Temperature was routinely maintained at 61-71°F during the test period; relative humidity was routinely maintained at 40-60%. 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 (except during the 4-hour contact period in the irritation test) and was delivered by an automatic watering system with demand control valves mounted on each rack. Water analyses were provided by the supplier and the NUS Corporation at regular intervals. EPA standards for maximum levels of contaminants were not exceeded. Agway® PROLAB® Animal Diet

High Fiber Rabbit (Agway, Inc.) was available ad libitum except during the 4-hour contact period in the irritation test. No analyses of chemical composition or possible contaminants of the feed were conducted by the supplier.

Animal Acclimation

The animals were acclimated for at least 5 days before dosing. Detailed clinical observations were conducted twice, at the time of receipt and during animal identification and/or dosing. In addition, rabbits were examined and weighed twice prior to dosing. Cage-side observations and mortality checks were conducted at least once daily. Animals considered unacceptable for the study, based on the clinical signs or body weights (rabbits), were rejected for use on this study.

Study Organization

The animals were weighed and inspected for health on the day of the test. Only those exhibiting a healthy state were used. Healthy animals appeared alert, active, and well-groomed, with no evidence of discharge, diarrhea, breathing difficulties or locomotor abnormalities. A BRRC veterinarian was available for consultation regarding any animal health concerns. Animals were randomly assigned to cages and were designated for dosing according to need and availability.

Rats

Rat body weights were within $\pm 20\%$ of the group mean for each sex. The body weight range on the day of dosing was 242 to 260 g for males (including those males used for preliminary testing) and 208 to 248 g for females. Totals of 3 male rats and 20 female rats were used for the definitive peroral test. Three male rats were also used for preliminary testing. Available rats not assigned to this study were used as needed for other toxicity testing.

Rabbits

Only rabbits demonstrating weight gain were used. Rabbits weighing between 2.0 and 3.0 kg (approximately 12 to 18 weeks of age) were selected for the definitive tests. If necessary, rabbits weighing up to 3.5 kilograms were used for irritancy testing. The body weight range (on the day of dosing) for males was 2.5 to 3.1 kg. For females, the range was 2.3 to 3.3 kg. A total of 12 males (including 1 preliminary test animal) and 17 females were used for the rabbit tests. Available rabbits not assigned to this study were used as needed for other toxicity testing.

Study Schedule

Peroral Test:	January 16, 1992 to February 27, 1992
Percutaneous Test:	December 19, 1991 to March 4, 1992
Dermal Irritation Test:	January 14, 1992 to January 21, 1992
Eye Irritation Test:	January 14, 1992 to February 11, 1992

Test Procedures/ObservationsPeroral Intubation

Each dosing dilution was prepared just prior to administration by diluting the appropriate amount of TRITON® X-193 AG Emulsifier with distilled water (prepared at BRRC; CAS No. 7732-18-5). All dilutions were mixed for approximately 10 to 30 minutes on a magnetic stirrer. Doses were administered by stomach intubation through a commercial 16 gauge (3-inch) ball-end stainless steel needle attached to a disposable syringe. The exact amounts of test substance and mixture given to each rat were recorded on the raw data form. Concentrations were not adjusted for percent active ingredient of test substance. Fresh dosing solutions were prepared for each day of test substance administration.

The rats were fasted overnight (approximately 18 hours) before dosing. Three male rats were used for preliminary testing. Five female rats were included in each of several dose groups in order to determine an LD50. Three male rats were included on 1 intermediate dose level for comparison. Doses were varied by changing the concentration of test substance in the dosing emulsions and maintaining a constant dose volume. For individual animals, the dosing volume was adjusted according to body weight (to give 1 ml of dose/100 g of rat body weight). Dosed rats were observed frequently for signs of toxicity on the first day of the test and twice a day thereafter (except on weekends or holidays when they were examined for death alone). Weights were recorded on the day of dosing and at 7 and 14 days after dosing and at death.

After 14 days, all survivors were sacrificed by CO₂ overdose. All rats were necropsied after death or sacrifice. Unless tissues were judged to be excessively autolyzed, the following tissues were collected from selected animals and retained in 10% neutral buffered formalin: kidneys, urinary bladder, liver, sciatic nerve, stomach, intestines, spinal column, and spleen. The lungs were also saved because they were anticipated to be potential target organs.

An LD50 was calculated for female rats, based on the 14-day observation period. It was calculated by the moving average method (Thompson, 1947). An estimate of the slope was made by the formula developed by Weil (1983).

Cutaneous Application (Percutaneous Toxicity)

The fur was removed from the entire trunk of each rabbit using veterinary clippers at least 1 day before application of the test substance. As necessary, the rabbit skin was carefully trimmed (to remove excess regrowth of fur) up to the day before dosing. Only animals with an intact and normal epidermis were used in the study. The undiluted material was applied to the dorsal surface and spread over as large a skin area as possible. The amount of test substance applied was recorded for each animal. For each dose level, the approximate area of skin covered was measured and recorded. A double layer of gauze sheeting was wrapped around the trunk and secured with adhesive tape. Polyethylene sheeting was then wrapped around the trunk over the gauze. To secure the polyethylene, plastic ties or rubber bands were added (at the ends of the trunk). The sheeting was protected from removal or tearing by

wrapping the rabbit trunk with VETRAP® bandaging tape. The ends of the VETRAP® were secured. After the 24-hour contact period, all coverings were removed from the animal and any sample residue was wiped off with a cleansing tissue.

One male and 5 female rabbits with intact skin were dosed at 16.0 g/kg, the maximum required dose (limit test). In addition 3 male and 5 female rabbits with intact skin were dosed at 8.0 g/kg. One male rabbit received 4.0 g/kg in preliminary testing. For individual animals, the dose volume was adjusted according to body weight. Treated rabbits were observed frequently for signs of toxic effect on the first day of the test and twice a day thereafter (except on weekends or holidays when they were examined for death alone). Weights were recorded on the day of dosing and at 7 and 14 days after dosing and at death.

An LD50 was calculated for female rabbits, based on the 14-day observation period. It was calculated by the moving average method (Thompson, 1947). It was not possible to calculate the slope because the highest treatment level killed only 3 out of 5 rabbits.

After 14 days, all survivors were sacrificed by ear vein injection using Euthanasia 6 (Veterinarian Laboratories Inc., Lenexa, KS). Necropsies were performed on all animals that died or were sacrificed. The following tissues (unless excessively autolyzed) were collected from selected animals and retained in 10% neutral buffered formalin: kidneys, urinary bladder, liver, sciatic nerve, and spleen. Lungs were also saved because they were anticipated to be a potential target organ.

Primary Skin Irritation

The fur was removed from the dorsal area of the trunk of each rabbit using veterinary clippers a few days before dosing and the dose area was trimmed carefully (avoiding skin abrasion), as necessary, up to the day before application of the test substance. A volume of 0.5 ml was applied to 1 intact (no shaved) site/rabbit. A 1-inch square gauze patch was placed over the dose site and was secured by adhesive tape. Polyethylene sheeting was placed loosely around the trunk and secured. The animal was placed in a restraining device for the 4-hour contact period after which the coverings and as much excess test substance as possible were removed.

The test substance was applied to each of 6 rabbits (3 males, 3 females). Readings were made at 1, 24, 48, and 72 hours and at 7 days, after the end of the contact period according to the system shown in Appendix 1 (Draize, 1959). All rabbits were sacrificed at 7 days (ear vein injection using Euthanasia 6).

Primary Eye Irritation

Both eyes of each rabbit to be dosed were examined, using fluorescein stain, within 24 hours before application. If any preexisting eye injury was apparent, the rabbit was rejected for use in the test. A volume of 0.1 ml of test substance was placed into the conjunctival sac of 1 eye/rabbit. The other eye of each animal served as the control.

A total of 4 rabbits (2 males, 2 females) were dosed. Eye examinations were made at 1, 24, 48, and 72 hours and at 7, 10, 14, 17, and 21 days following instillation. Fluorescein staining was performed at 1 day and each subsequent examination day. Grading and scoring were performed by the system shown in Appendix 1 (based on Draize, 1959). The rabbits were sacrificed by ear vein injection (Euthanasia 6) at 21 days.

Because of the irritation produced from the instillation of 0.1 ml, an additional 4 rabbits (2/sex) were dosed for comparison using the same procedure as described above, but with 0.01 ml of test substance placed directly on the cornea. Readings were made at 1, 24, 48, and 72 hours and at 7, 10, 14, 17, and 21 days following instillation. Fluorescein staining was performed at 1 day and each subsequent examination day. All 4 rabbits were sacrificed at 21 days.

RETENTION OF RECORDS

All raw data, documentation, records, the protocol and a copy of the final report generated as a result of this study are retained in the BRRC Archives. Approximately 20 ml of the remaining sample will be retained for at least 2 years following issuance of this report (for possible analysis or further testing at the request of the Sponsor).

RESULTS AND DISCUSSION

Peroral Intubation

A summary of results from the peroral study is presented in Table 1. Individual results are included in Tables 1 and 2 of Appendix 2 for male and female rats, respectively.

In preliminary testing, 1 male rat was dosed at 500, 2000, or 8000 mg/kg of TRITON® X-193 AG Emulsifier; the animal dosed at 8000 mg/kg died at 1 day, while the remaining 2 survived until sacrifice at 14 days. For the definitive test, the peroral LD50 for TRITON® X-193 AG Emulsifier, expressed in terms of test substance as received, was 1460 mg/kg b.w. for female rats. Three of 3 male rats survived a dose of 1410 mg/kg (an intermediate dose level that killed 2 out of 5 females). Signs of toxicity included sluggishness, lacrimation, diarrhea, piloerection, slowed breathing, red crust on the perinasal fur, brown stain or wetness on the perineal or perianal fur, unsteady gait, and prostration. Deaths occurred within 1 day after dosing. Survivors recovered at 2.5 hours to 2 days and exhibited consistent weight gain. Necropsy of rats that died revealed light to dark red lungs, a trachea filled with clear foam, discoloration of the glandular portion of the stomach (tan, dark red, brown or red to purple), a transparent nonglandular stomach, discolored intestines (red or tan), stomach, and intestines filled or distended with liquid (clear, red, or brown) or gas, a cecum filled with brown-red liquid, livers with black areas, 2 discolored spleens (dark maroon or black), and a small blackened kidney (in 1). Survivors had no gross lesions apparent at necropsy.

Percutaneous Toxicity

A summary of results from the percutaneous study appears in Table 2 of the report. Individual results are presented in Tables 3 and 4 of Appendix 2 for male and female rabbits, respectively.

Following a 24-hour occluded application of TRITON® X-193 AG Emulsifier to rabbit skin, 1 male rabbit died from 16.0 g/kg (the maximum required dose), and 2 of 3 male rabbits died from 8.0 g/kg. In preliminary testing, 1 male survived a dose of 4.0 g/kg. Three of 5 females died from 16.0 g/kg, while 0 of 5 females died from 8.0 g/kg, giving a percutaneous LD₅₀ (expressed in terms of test substance as received) of 14.3 g/kg b.w. for female rabbits. The amount of sample/area covered ranged from approximately 96 mg/cm² (for the male rabbit at 4.0 g/kg) to 159 mg/cm² (for male rabbits at 8 g/kg).

Dermal reactions included erythema, edema, ecchymoses, fissuring, desquamation, spots of brown discoloration, necrosis, alopecia, and scabs (on 2). Signs of toxicity included oral wetness, sluggishness, labored breathing, prostration (in 1), emaciation (in 1), and weight loss. Six rabbits died at 2 to 5 days. Some survivors recovered at 2 to 6 days, although several animals still exhibited some weight depression through 14 days. Necropsy of the rabbits that died revealed lungs with red areas or red foci and a soft texture (in 1), mottled tan livers (1 smaller than normal), a moderate amount of blood in the urine of 1, and tan kidneys. Gross pathologic evaluation of survivors revealed lungs with red foci or consolidated areas and tan kidneys in some of the rabbits.

Primary Skin Irritation

Results of the skin irritation test are presented in Table 3 of the report.

Application of 0.5 ml of TRITON® X-193 AG Emulsifier to covered rabbit skin for a 4-hour contact period produced minor, relatively transient, erythema on 6 of 6 rabbits and minor transient edema on 4 of 6 rabbits. There was no other irritation on any of the 6 rabbits. Within 2 days, the edema was no longer present on any of the rabbits; erythema persisted on 3 animals to 3 days. All animals were normal by 7 days.

Primary Eye Irritation

A summary of results from the eye irritation study appears in Table 4 of the report. Individual results are presented in Table 5 and Table 6 of Appendix 2.

A volume of 0.1 ml of test substance instilled into rabbit eyes produced minor to moderate corneal injury, with vascularization, in 4 of 4 rabbits. Iritis and severe conjunctival irritation were also apparent in all 4 rabbit eyes. Most eyes developed a red or pus-like discharge. Minor to severe ocular irritation persisted in all 4 rabbits (with corneal vascularization in 3) through 21 days.

Following the instillation of 0.01 ml into rabbit eyes, there was minor to severe corneal injury in 4 of 4 rabbits (with vascularization and an irregular corneal shape in 1). Transient iritis was apparent in all 4 eyes. Severe

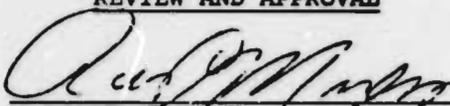
conjunctival irritation was also observed in each rabbit. Two developed a pus-like discharge. Although 1 eye healed by 21 days, irritation persisted in 3 of 4 eyes through 21 days.

CONCLUSIONS

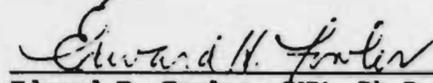
TRITON® X-193 AG Emulsifier was considered to be slightly toxic following single peroral doses to rats and was slightly toxic (with moderate to severe irritation) following single 24-hour occluded contact with rabbit skin. Application of 0.5 ml of TRITON® X-193 AG Emulsifier for 4 hours to occluded rabbit skin resulted in minor (transient) irritation. Instillation of 0.1 ml of TRITON® X-193 AG Emulsifier into rabbit eyes produced severe irritation which persisted in some animals to 21 days. A lower ocular dose (0.01 ml) produced minor to severe reaction which persisted in some animals through 21 days.

REVIEW AND APPROVAL

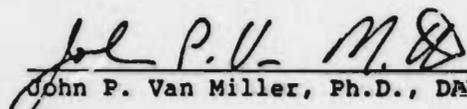
Study Director:


 Roy C. Myers, B.S., DABT 8-27-92
Date

Associate Director:


 Edward H. Fowler, DVM, Ph.D., Diplomate ACVP 8/27/92
Date

Director:


 John P. Van Miller, Ph.D., DABT 8/27/92
Date

KEY PERSONNEL

Study Director: R. C. Myers
 Study Coordinator: S. M. Christopher
 Supervisor: R. C. Myers

Additional personnel are listed in the raw data.

REFERENCES

Draize, J. H. (1959) The Appraisal of Chemicals in Foods, Drugs and Cosmetics. *The Association of Food and Drug Officials of the United States.*

Thompson, W. R. (1947) Use of moving averages and interpolation to estimate medium-effective dose. *Bacteriological Rev.*, 11:115-145

Weil, C. S. (1983) Economical LD50 and slope determination, *Drug and Chemical Toxicology*, 6(6), 595-603.

TABLE 1
 TRITON® X-193 AG EMULSIFIER: ACUTE TOXICITY AND IRRITANCY TESTING USING THE RAT (PERORAL TOXICITY) AND THE RABBIT (CUTANEOUS AND EYE TESTS)

SUMMARY OF RESULTS FROM SINGLE PERORAL DOSES - RATS

Material: TRITON® X-193 AG Emulsifier			Sample No.: 54-344		
Dose, mg/kg b.w.	Dead/ Dosed	Days to Death	Mean Weight, g ± S.D.		
			0 Days	7 Days	14 Days
MALES					
1410	0/3	—	255 ±5.8	318 ±2.1	346 ±4.6
FEMALES					
4000	5/5	1,1,1,1,1	224 ±14.9	—	—
2000	5/5	1,1,1,1,1	228 ±9.3	—	—
1410	2/5	1,1	234 ±7.5	258 ±6.2	264 ±5.7
1000	0/5	—	225 ±11.5	253 ±13.3	261 ±13.0

LD50s, expressed in terms of
 mg of TRITON® X-193 AG Emulsifier/kg of body weight:
 Male: 1410 mg/kg killed 0 of 3
 Female: 1460 (1200 to 1780) mg/kg

Estimated LD50 Slopes:
 Male: Not applicable
 Female: 9.95

TABLE 2
TRITON® X-193 AG EMULSIFIER: ACUTE TOXICITY AND IRRITANCY TESTING USING THE RAT (PERORAL TOXICITY) AND THE RABBIT (CUTANEOUS AND EYE TESTS)

SUMMARY OF RESULTS FROM SINGLE PERCUTANEOUS DOSES - RABBITS

Material: TRITON® X-193 AG Emulsifier		Sample No.: 54-344			
Dose, g/kg b.w.	Dead/ Dosed	Days to Death	Mean Weight, g ± S.D.		
			0 Days	7 Days	14 Days
MALES					
16.0	1/1	5	2805	—	—
8.0	2/3	4,4	2843 ±50.2	2573	2732
FEMALES					
16.0	3/5	2,2,3	2414 ±56.5	2128 ±107	2338 ±186
8.0	0/5	—	2635 ±186	2377 ±75.7	2691 ±111

LD50s with 95% confidence limits, expressed in terms of
 g of TRITON® X-193 AG Emulsifier/kg of body weight:
 Male: 8.0 g/kg killed 2 of 3
 Female: 14.3 (7.4 to 27.4) g/kg

LD50 Slopes:
 Male: Not applicable
 Female: Not calculable

TABLE 3
 TRITON® X-192 AG EMULSIFIER: ACUTE TOXICITY AND IRRITANCY TESTING USING THE RAT (PERORAL TOXICITY) AND THE RABBIT (CUTANEOUS AND EYE TESTS)

PRIMARY SKIN IRRITATION RESULTS - RABBITS

Material: TRITON® X-192 AG Emulsifier Sample No.: 54-344 Conditions: 0.5 ml dosed
 4 hour contact

DATE:	01-14-92	01-14-92	01-14-92	01-14-92	01-14-92	01-14-92
RABBIT NO.	91-27086	91-27089	91-27210	91-26918	91-27216	91-28323
SEX:	Male	Male	Male	Female	Female	Female

Erythema & Eschar Formation

Time (After Initiation of Contact)	Score	Score	Score	Score	Score	Score	Mean Score
5 hours	1	1	1	1	1	1	1.0
1 day	1	1	1	1	1	1	1.0
2 days	1	1	1	1	1	1	1.0
3 days	0	0	0	1	1	1	0.5
7 days	0	0	0	0	0	0	0.0

Edema Formation

Time	Score	Score	Score	Score	Score	Score	Mean Score
5 hours	0	0	0	1	1	0	0.3
1 day	0	0	1	0	0	1	0.3
2 days	0	0	0	0	0	0	0.0
3 days	0	0	0	0	0	0	0.0
7 days	0	0	0	0	0	0	0.0

Other Irritation or Effects

Time	Effect	Effect	Effect	Effect	Effect	Effect
5 hours	None	None	None	None	None	None
1 day	None	None	None	None	None	None
2 days	None	None	None	None	None	None
3 days	None	None	None	None	None	None
7 days	None	None	None	None	None	None

TABLE 4
 TRITON® X-193 AG EMULSIFIER: ACUTE TOXICITY AND IRRITANCY TESTING USING THE RAT (PERCUTANEOUS TOXICITY) AND THE RABBIT (CUTANEOUS AND EYE TESTS)

SUMMARY OF PRIMARY EYE IRRITATION RESULTS - RABBITS

Material: TRITON® X-193 AG Emulsifier

Sample No.: 54-344

		OBSERVATION TIMES								
OBSERVATION		1 Hr	24 Hr	48 Hr	72 Hr	7 Days	10 Days	14 Days	17 Days	21 Days
		Volume Instilled: 0.1 ml								
CORNEA										
Opacity:	Range	1	1	1	1	1-2	1-2	0-2	0-2	0-3
	Mean	1.0	1.0	1.0	1.0	1.2	1.2	1.5	1.2	1.8
Area:	Range	1	1	1-2	1-3	1-2	1-2	0-1	0-1	0-1
	Mean	1.0	1.0	1.2	2.0	1.8	1.2	0.8	0.8	0.8
IRIS										
Injury:	Range	0-1	1	1	1	0-1	0-1	0-1	0-1	0-1
	Mean	0.8	1.0	1.0	1.0	0.5	0.2	0.5	0.2	0.2
CONJUNCTIVAE										
Redness:	Range	1	2	3	2-3	1-3	1-3	1-2	1-2	1-3
	Mean	1.0	2.0	3.0	2.8	2.0	2.2	1.5	1.5	2.2
Chemosis:	Range	1-2	1-2	1-2	1-2	1	1-2	1-2	1-2	0-1
	Mean	1.8	1.8	1.5	1.5	1.0	1.5	1.2	1.2	0.8
Discharge:	Range	2-3	2-3	2-3	2-3	1-2	1-2	1-2	1-2	1-2
	Mean	2.8	2.8	2.2	2.5	1.5	1.5	1.2	1.2	1.8

(Continued)

TABLE 4 (Continued)

TRITON® X-193 AG EMULSIFIER: ACUTE TOXICITY AND IRRITANCY TESTING USING THE RAT (PERCUTANEOUS TOXICITY) AND THE RABBIT (CUTANEOUS AND EYE TESTS)

SUMMARY OF PRIMARY EYE IRRITATION RESULTS - RABBITS

Material: TRITON® X-193 AG Emulsifier

Sample No.: 54-344

		OBSERVATION TIMES								
OBSERVATION		1 Hr	24 Hr	48 Hr	72 Hr	7 Days	10 Days	14 Days	17 Days	21 Days
		Volume Instilled: 0.01 ml								
CORNEA										
Opacity:	Range	1	1	1	0-1	0-1	0-4	0-4	0-4	0-4
	Mean	1.0	1.0	1.0	0.8	0.8	1.2	1.0	1.0	1.0
Area:	Range	1	1-2	1-2	0-2	0-1	0-1	0-1	0-1	0-1
	Mean	1.0	1.2	1.5	1.0	0.8	0.5	0.2	0.2	0.2
IRIS										
Injury:	Range	1	0-1	0-1	0-1	0-1	0-1	0-1	0	0
	Mean	1.0	0.8	0.5	0.5	0.5	0.8	0.3	0	0.0
CONJUNCTIVAE										
Redness:	Range	1	2-3	2-3	2-3	1-3	1-3	1-3	0-1	0-2
	Mean	1.0	2.5	2.8	2.8	2.0	1.8	1.8	0.8	1.0
Chemosis:	Range	1	1-2	1	1	1-2	1-2	0-1	0-1	0-1
	Mean	1.0	1.2	1.0	1.0	1.2	1.2	0.8	0.2	0.2
Discharge:	Range	2	2-3	1-3	1-3	1-3	1-3	0-3	0-3	0-2
	Mean	2.0	2.2	1.8	1.8	1.5	1.8	1.5	1.2	0.8



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Quality Assurance Unit Study Inspection Summary

Test Substance: TRITON® X-193 AG Emulsifier

Study: Acute Toxicity and Irritancy Testing Using the Rat
(Peroral Toxicity) and the Rabbit (Cutaneous and Eye
Tests)

Study Director: Roy C. Myers, B.S., DABT

The Quality Assurance Unit of BRRC conducted the inspections listed below and reported the results to the study director and to management on the dates indicated. It is the practice of this Quality Assurance Unit to report the results of each inspection to both the study director and management.

<u>Date</u>	<u>Inspection Type</u>	<u>Date QAU Report Issued</u>	
		<u>To Study Director</u>	<u>To Management</u>
10-23-91	Protocol	10-23-91	11-5-91
12-26-91	Event-7 Day Weight	12-30-91	2-12-92
1-15-92	Event-24 Hour Eye Reading	1-17-92	2-12-92
1-15-92	Event-4 Hour Contact 1 Day Reading	1-17-92	2-12-92
1-20-92	Protocol Amendment #1	1-20-92	1-22-92
1-22-92	Event-Peroral Dosing	1-22-92	2-12-92
6-16-92 to 7-20-92	Raw Data and Report	7-30-92	8-27-92
8-27-92	Archives	8-27-92	8-27-92

Linda J. Calisti 8/27/92
Linda J. Calisti, Manager Date
Good Laboratory Practices/Quality Assurance

TRITON® X-193 AG Emulsifier: Acute Toxicity and Irritancy Testing Using the
Rat (Peroral Toxicity) and the Rabbit (Cutaneous and Eye Tests)

Scoring System for Skin and Eye Irritation

(3 Pages)

Scoring System for Skin Irritation Test

<u>Erythema and Eschar Formation</u>	<u>Value</u>
No erythema.....	0
Very slight erythema (barely perceptible).....	1
Well-defined erythema.....	2
Moderate to severe erythema.....	3
Severe erythema (beet redness) to slight eschar formation (injuries in depth).....	4
Maximum possible.....	4

<u>Edema Formation</u>	<u>Value</u>
No edema.....	0
Very slight edema (barely perceptible).....	1
Slight edema (edges of area well defined by definite raising).....	2
Moderate edema (raised approximately 1 millimeter).....	3
Severe edema (raised more than 1 millimeter and extending beyond area of exposure).....	4
Maximum possible.....	4

Scoring System for Eye Irritation Test (Draize)

CORNEA

Opacity: degree of density (area most dense taken for reading).

No ulceration or opacity.....	0
Scattered or diffuse areas of opacity (other than slight dulling of normal luster), details of iris clearly visible.....	1*
Easily discernible translucent area, details of iris slightly obscured.....	2*
Nacreous (opalescent) area, no details of iris visible, size of pupil barely discernible.....	3*
Opaque cornea, iris not discernible through the opacity.....	4*

Area of Cornea Involved

- One quarter (or less) but not 0.....	1
- Greater than one-quarter, less than one-half.....	2
- Greater than one-half, less than three-quarters.....	3
- Greater than three-quarters up to whole area.....	4

IRIS

Normal.....	0
Markedly deepened rugae (folds), congestion, swelling, moderate circumcorneal hyperemia, or injection, any of these or combination of any thereof, iris still reacting to light (sluggish reaction is positive).....	1*
No reaction to light, hemorrhage, gross destruction (any or all of these).....	2*

CONJUNCTIVAE

Redness: (refers to palpebral and bulbar conjunctivae, cornea, and iris)

Blood vessels normal.....	0
Some blood vessels definitely hyperemic (injected).....	1
Diffuse, crimson color, individual vessels not easily discernible.....	2*
Diffuse, beefy red.....	3*

Chemosis: Lids and/or nictitating membranes

No swelling.....	0
Any swelling above normal (includes nictitating membranes).....	1
Obvious swelling with partial eversion of lids.....	2*
Swelling with lids about half closed.....	3*
Swelling with lids more than half closed.....	4*

Discharge:

No discharge.....	0
Any amount of discharge different from normal.....	1
Discharge with moistening of the lids and hairs adjacent to lids.....	2
Discharge with considerable moistening around the eyes.....	3

*Starred figures indicate positive effect.

TRITON® X-193 AG Emulsifier: Acute Toxicity and Irritancy Testing Using the
Rat (Peroral Toxicity) and the Rabbit (Cutaneous and Eye Tests)

Individual Animal Data

(18 Pages)

TABLE 1

TRITON® X-193 AG EMULSIFIER: ACUTE TOXICITY AND IRRITANCY TESTING USING THE RAT (PERORAL TOXICITY) AND THE RABBIT (CUTANEOUS AND EYE TESTS)

INDIVIDUAL RESULTS FROM SINGLE PERORAL DOSES - RATS
MALES

Material: TRITON® X-193 AG Emulsifier					Sample No.: 54-344			
Rat Number	Dose, mg/kg b.w. ^a	Amt. of Sample, mg	Conc.	Dose Vol., ml	Rat Weight (g) at Day			Time to Death
					Init.	7	14	
92-01215	1410	360	14.14	2.6	255	320	350	—
<u>Signs of Toxicity:</u> None noted.								
<u>Gross Pathology:</u> No gross lesions.								
92-01216	1410	361	14.14	2.6	256	316	341	—
<u>Signs of Toxicity:</u> None noted.								
<u>Gross Pathology:</u> No gross lesions.								
92-01217	1410	360	14.14	2.6	255	317	347	—
<u>Signs of Toxicity:</u> None noted.								
<u>Gross Pathology:</u> No gross lesions.								

^a Dose given as mg of TRITON® X-193 AG Emulsifier/kg of body weight; sample dosed as received.

TABLE 2
TRITON® X-193 AG EMULSIFIER: ACUTE TOXICITY AND IRRITANCY TESTING USING THE RAT (PERORAL TOXICITY) AND THE RABBIT (CUTANEOUS AND EYE TESTS)

INDIVIDUAL RESULTS FROM SINGLE PERORAL DOSES - RATS
FEMALES

Material: TRITON® X-193 AG Emulsifier				Sample No.: 54-314				
Rat Number	Dose, mg/kg b.w. ^a	Amt. of Sample, mg	Conc.	Dose Vol., ml	Rat Weight (g) at Day			Time to Death
					Init.	7	14	
92-00272	4000	888	40%	2.2	222	—	—	1 day
<u>Signs of Toxicity:</u> Marked diarrhea at 1 hr; marked sluggishness, marked diarrhea, lacrimation at 2.5 hr.								
<u>Gross Pathology:</u> Lungs light red (all lobes); trachea filled with clear foam; glandular portion of stomach tan; intestines tan and red, gas and liquid filled; spleen dark maroon.								
92-00270	4000	992	40%	2.5	248	—	—	1 day
<u>Signs of Toxicity:</u> Marked sluggishness, marked diarrhea, lacrimation at 2.5 hr.								
<u>Gross Pathology:</u> Glandular portion of stomach dark red; intestines dark red; stomach and intestines distended with brown to clear liquid and gas.								
92-00269	4000	832	40%	2.1	208	—	—	1 day
<u>Signs of Toxicity:</u> Marked diarrhea at 1 hr; marked sluggishness, marked diarrhea, lacrimation at 2.5 hr.								
<u>Gross Pathology:</u> Lungs light red (all lobes); stomach and intestines distended with gas; liver with black areas on lower lobes.								
92-00268	4000	868	40%	2.2	217	—	—	1 day
<u>Signs of Toxicity:</u> Marked sluggishness, marked diarrhea, lacrimation at 2.5 hr.								
<u>Gross Pathology:</u> Lungs mottled red; stomach tan; intestines red and tan; liver mottled black on lower lobes; spleen black.								
92-00271	4000	904	40%	2.3	226	—	—	1 day
<u>Signs of Toxicity:</u> Marked diarrhea at 1 hr; marked sluggishness, marked diarrhea, lacrimation at 2.5 hr.								
<u>Gross Pathology:</u> Stomach and intestines tan, severely distended with clear liquid.								

^a Dose given as mg of TRITON® X-193 AG Emulsifier/kg of body weight; sample dosed as received.

(Continued)

TABLE 2 (Continued)
 TRITON® X-193 AG EMULSIFIER: ACUTE TOXICITY AND IRRITANCY TESTING USING THE RAT (PERORAL TOXICITY) AND THE RABBIT (CUTANEOUS AND EYE TESTS)

INDIVIDUAL RESULTS FROM SINGLE PERORAL DOSES - RATS
 FEMALES

Material: TRITON® X-193 AG Emulsifier				Sample No.: 54-344				
Rat Number	Dose, mg/kg b.w. ^a	Amt. of Sample, mg	Conc.	Dose Vol., ml	Rat Weight (g) at Day			Time to Death
					Init.	7	14	
92-00763	2000	436	20%	2.2	218	—	—	1 day
<p><u>Signs of Toxicity:</u> Marked diarrhea at 1.5 hr; marked sluggishness, lacrimation, piloerection, slow breathing at 2.5 hr.</p> <p><u>Gross Pathology:</u> Lungs mottled dark red (all lobes); glandular portion of stomach brown; stomach and intestines filled with red liquid; intestines dark red.</p>								
92-00761	2000	474	20%	2.4	237	—	—	1 day
<p><u>Signs of Toxicity:</u> Marked diarrhea at 1.5 hr; sluggishness at 2.5 hr.</p> <p><u>Gross Pathology:</u> Lungs bright red (all lobes); stomach and intestines distended with gas; liver black on lower lobes; glandular portion of stomach tan; intestines red.</p>								
92-00762	2000	464	20%	2.3	232	—	—	1 day
<p><u>Signs of Toxicity:</u> Marked diarrhea at 1.5 hr; sluggishness at 2.5 hr.</p> <p><u>Gross Pathology:</u> Lungs red (all lobes); stomach filled with red liquid; intestines red; liver black on lower lobes.</p>								
92-00754	2000	470	20%	2.4	235	—	—	1 day
<p><u>Signs of Toxicity:</u> Marked diarrhea at 1.5 hr; sluggishness at 2.5 hr.</p> <p><u>Gross Pathology:</u> Glandular portion of stomach brown; intestines filled with red liquid, intestines red and brown; lower lobes of liver black.</p>								
92-00760	2000	436	20%	2.2	218	—	—	1 day
<p><u>Signs of Toxicity:</u> Marked diarrhea at 1.5 hr; marked sluggishness, lacrimation, piloerection, slow breathing at 2.5 hr.</p> <p><u>Gross Pathology:</u> Lungs mottled dark red (all lobes); glandular portion of stomach tan, filled with red liquid; intestines and cecum filled with brownish-red liquid; lower lobes of liver black.</p>								

^a Dose given as mg of TRITON® X-193 AG Emulsifier/kg of body weight; sample dosed as received.

(Continued)

TABLE 2 (Continued)

TRITON® X-193 AG EMULSIFIER: ACUTE TOXICITY AND IRRITANCY TESTING USING THE RAT (PERORAL TOXICITY) AND THE RABBIT (CUTANEOUS AND EYE TESTS)

INDIVIDUAL RESULTS FROM SINGLE PERORAL DOSES - RATS
FEMALES

Material: TRITON® X-193 AG Emulsifier		Sample No.: 54-344						
Rat Number	Dose, mg/kg b.w. ^a	Amt. of Sample, mg	Conc.	Dose Vol., ml	Rat Weight (g) at Day			Time to Death
					Init.	7	14	
92-01274	1410	333	14.10	2.4	236	—	—	1 day
<p><u>Signs of Toxicity:</u> Sluggishness, marked diarrhea at 1.5 hr; marked sluggishness, lacrimation, unsteady gait 3 hr.; prostration, slow breathing (marked), piloerection at 6 hr.</p> <p><u>Gross Pathology:</u> Lungs mottled red and dark red (all lobes); glandular portion of stomach red, non-glandular portion of stomach transparent; intestines red; liver black on underside of lobes at point of contact with the stomach (possible chemical permeation, black areas possibly necrotic).</p>								
92-01275	1410	347	14.10	2.5	246	263	269	—
<p><u>Signs of Toxicity:</u> Sluggishness, marked diarrhea at 1.5 hr; sluggishness, lacrimation, piloerection at 6 hr; red perinasal crust, dry brown stain on perineal fur at 1 day. Recovery at 2 days.</p> <p><u>Gross Pathology:</u> No gross lesions.</p>								
92-01277	1410	327	14.10	2.3	232	251	258	—
<p><u>Signs of Toxicity:</u> Sluggishness at 1.5 hr; sluggishness, lacrimation, piloerection at 6 hr; red perinasal crust, dry brown stain on perineal fur at 1 day. Recovery at 2 days.</p> <p><u>Gross Pathology:</u> No gross lesions.</p>								
92-01273	1410	326	14.10	2.3	231	260	266	—
<p><u>Signs of Toxicity:</u> Marked diarrhea at 45 min.; sluggishness, marked diarrhea at 1.5 hr.; sluggishness, lacrimation, piloerection at 6 hr.; red perinasal crust, dry brown stain on perineal fur at 1 day. Recovery at 2 days.</p> <p><u>Gross Pathology:</u> No gross lesions.</p>								

(Continued)

TABLE 2 (Continued)

TRITON® X-193 AG EMULSIFIER: ACUTE TOXICITY AND IRRITANCY TESTING USING THE RAT (PERORAL TOXICITY) AND THE RABBIT (CUTANEOUS AND EYE TESTS)

INDIVIDUAL RESULTS FROM SINGLE PERORAL DOSES - RATS
FEMALES

Material: TRITON® X-193 AG Emulsifier Sample No.: 54-344

Rat Number	Dose, m./kg b.w. ^a	Amt. of Sample, mg	Conc.	Dose Vol., ml	Rat Weight (g) at Day			Time to Death
					Init.	7	14	
92-01276	1410	319	14.14	2.3	226	—	—	1 day

Signs of Toxicity: Sluggishness, marked diarrhea at 1.5 hr; sluggishness, unsteady gait, lacrimation at 3 hr.; marked sluggishness, unsteady gait, lacrimation, piloerection at 6 hr.

Gross Pathology: Lungs mottled red and dark red with dark red multiple foci (all lobes); glandular portion of stomach red; intestines red, liver black on underside of lobes at point of contact with the stomach (possible chemical permeation, black areas possibly necrotic); left kidney small; right kidney with black discoloration throughout 50% of the tissue.

(Continued)

TABLE 2 (Continued)

TRITON® X-193 AG EMULSIFIER: ACUTE TOXICITY AND IRRITANCY TESTING USING THE RAT (PERORAL TOXICITY) AND THE RABBIT (CUTANEOUS AND EYE TESTS)

INDIVIDUAL RESULTS FROM SINGLE PERORAL DOSES - RATS
FEMALES

Material: TRITON® X-193 AG Emulsifier					Sample No.: 54-344			
Rat Number	Dose, mg/kg b.w. ^a	Amt. of Sample, mg	Conc.	Dose Vol., ml	Rat Weight (g) at Day			Time to Death
					Init.	7	14	
92-00774	1000	229	100	2.3	229	255	260	—
<p><u>Signs of Toxicity:</u> Sluggishness, marked unsteady gait at 2 hr; red perinasal crust, wet brown stain on perineal fur at 1 day. Recovery at 2 days.</p> <p><u>Gross Pathology:</u> No gross lesions.</p>								
92-00771	1000	228	100	2.3	228	240	247	—
<p><u>Signs of Toxicity:</u> Diarrhea at 2 hr; mild red perinasal crust and dry brown stain on perianal fur at 1 day. Recovery at 2 days.</p> <p><u>Gross Pathology:</u> No gross lesions.</p>								
92-00773	1000	211	100	2.1	211	239	246	—
<p><u>Signs of Toxicity:</u> None noted.</p> <p><u>Gross Pathology:</u> No gross lesions.</p>								
92-00772	1000	216	100	2.2	216	270	269	—
<p><u>Signs of Toxicity:</u> Diarrhea at 2 hr; mild red perinasal crust and dry brown stain on perianal fur at 1 day. Recovery at 2 days.</p> <p><u>Gross Pathology:</u> No gross lesions.</p>								
92-00770	1000	240	100	2.4	240	260	273	—
<p><u>Signs of Toxicity:</u> None noted.</p> <p><u>Gross Pathology:</u> No gross lesions.</p>								

TABLE 3
TRITON® X-193 AG EMULSIFIER: ACUTE TOXICITY AND IRRITANCY TESTING USING THE RAT (PERCUTANEOUS TOXICITY) AND THE RABBIT (CUTANEOUS AND EYE TESTS)

INDIVIDUAL RESULTS FROM SINGLE DOSES TO INTACT SKIN - RABBITS
MALES

Material: TRITON® X-193 AG Emulsifier		Sample No.: 54-344				
Rabbit Number	Dose, g/kg b.w. ^a	Total Dose, ml ^b	Rabbit Weight (g) at Day			Time to Death
			Initial	7 Days	14 Days	
91-26908	16.0	43.2	2805	—	—	5 days
<u>Skin Irritation:</u> Erythema, edema at 1 day and death.						
<u>Signs of Toxicity:</u> Sluggishness at 1 day; wetness (green) under the chin at 4 days; emaciation at death. Death at 5 days.						
<u>Gross Pathology:</u> Liver appears small.						
92-0090	8.0	22.1	2872	—	—	4 days
<u>Skin Irritation:</u> Erythema, edema, "spotty" brown discoloration at 1 day; erythema, edema, necrosis (mainly on ventral surface) at death.						
<u>Signs of Toxicity:</u> Sluggishness at 2 days. Death at 4 days.						
<u>Gross Pathology:</u> Lungs small dark red to light red consolidated areas, with very soft texture.						
92-0092	8.0	22.1	2872	—	—	4 days
<u>Skin Irritation:</u> Erythema, edema, "spotty" brown discoloration at 1 day; erythema, edema, ecchymoses, "spotty" necrosis at death.						
<u>Signs of Toxicity:</u> Sluggishness 2 days. Death at 4 days.						
<u>Gross Pathology:</u> Liver mottled light tan.						
92-0685	8.0	21.4	2785	2573	2732	—
<u>Skin Irritation:</u> Erythema, edema at 1 day; fissuring, "spotty" brown discoloration with desquamation at 7 days; desquamation at 14 days.						
<u>Signs of Toxicity:</u> Audible and labored breathing at 1 day.						
<u>Gross Pathology:</u> Lungs light red with moderate red foci.						

^a Dose given as g of TRITON® X-193 AG Emulsifier/kg of body weight; sample dosed as received.

^b Dose converted to dose volumes using a density of 1.04 g/ml (determined at BRRC).

TABLE 4
 TRITON® X-193 AG EMULSIFIER: ACUTE TOXICITY AND IRRITANCY TESTING USING THE RAT (PERIORAL TOXICITY) AND THE RABBIT (CUTANEOUS AND EYE TESTS)

INDIVIDUAL RESULTS FROM SINGLE DOSES TO INTACT SKIN - RABBITS
 FEMALES

Material: TRITON® X-193 AG Emulsifier Sample No.: 54-344

Rabbit Number	Dose, g/kg b.w. ^a	Total Dose, ml ^b	Rabbit Weight (g) at Day			Time to Death
			Initial	7 Days	14 Days	
92-953	16.0	37.0	2400	—	—	2 days
<u>Skin Irritation:</u> Erythema, edema at 1 day; erythema at death.						
<u>Signs of Toxicity:</u> Sluggishness, slightly audible breathing at 1 day; excessive perioral wetness at death. Death at 2 days.						
<u>Gross Pathology:</u> Lungs with dark red consolidated areas (small area); liver mottled light tan; kidneys tan.						
92-954	16.0	38.1	2476	—	—	2 days
<u>Skin Irritation:</u> Erythema, edema at 1 day; erythema at death.						
<u>Signs of Toxicity:</u> Perioral wetness (possibly from grooming), mild sluggishness at 1 day; marked sluggishness, prostration, moribund appearance at 2 days. Death at 2 days.						
<u>Gross Pathology:</u> Lungs with light red "patchy" areas; liver mottled tan; kidneys tan, vessels visible; moderate amount of blood in urine (positive by HEMASTIX®).						
92-955	16.0	36.9	2396	2204	2469	—
<u>Skin Irritation:</u> Erythema, edema, ecchymoses on hind legs at 1 day; fissuring, desquamation, alopecia, necrosis on sides at 7 days; desquamation, alopecia at 14 days.						
<u>Signs of Toxicity:</u> Excessive perioral wetness at 2 days. Recovery at 7 days.						
<u>Gross Pathology:</u> Liver mottled tan.						

(Continued)

TABLE 4 (Continued)

TRITON® X-193 AG EMULSIFIER: ACUTE TOXICITY AND IRRITANCY TESTING USING THE RAT (PERCUTANEOUS TOXICITY) AND THE RABBIT (CUTANEOUS AND EYE TESTS)

INDIVIDUAL RESULTS FROM SINGLE DOSES TO INTACT SKIN - RABBITS
FEMALES

Material: TRITON® X-193 AG Emulsifier			Sample No.: 54-344			
Rabbit Number	Dose, g/kg b.w. ^a	Total Dose, ml ^b	Rabbit Weight (g) at Day			Time to Death
			Initial	7 Days	14 Days	
92-957	16.0	36.0	2336	2052	2206	—
<p><u>Skin Irritation:</u> Erythema, edema at 1 day; fissuring, desquamation, alopecia, necrosis on sides at 7 days; desquamation, alopecia at 14 days.</p> <p><u>Signs of Toxicity:</u> Sluggishness (mild) at 1 day. Recovery at 2 days.</p> <p><u>Gross Pathology:</u> Lungs light red to moderate red consolidated areas, moderate red foci.</p>						
92-958	16.0	37.9	2462	—	—	3 days
<p><u>Skin Irritation:</u> Erythema, edema, necrosis near hind leg at 1 day; erythema, ecchymoses on ventral surface at death.</p> <p><u>Signs of Toxicity:</u> Sluggishness at 1 day; perioral wetness, sluggishness at 2 days. Death at 3 days.</p> <p><u>Gross Pathology:</u> Lungs light to dark red consolidated areas.</p>						

(Continued)

TABLE 4 (Continued)

TRITON® X-193 AG EMULSIFIER: ACUTE TOXICITY AND IRRITANCY TESTING USING THE RAT (PERIORAL TOXICITY) AND THE RABBIT (CUTANEOUS AND EYE TESTS)

INDIVIDUAL RESULTS FROM SINGLE DOSES TO INTACT SKIN - RABBITS
FEMALES

Material: TRITON® X-193 AG Emulsifier Sample No.: 54-344

Rabbit Number	Dose, g/kg b.w. ^a	Total Dose, ml ^b	Rabbit Weight (g) at Day			Time to Death
			Initial	7 Days	14 Days	
92-231	8.0	21.9	2844	2349	2804	—

Skin Irritation: Erythema, edema at 1 day; fissuring, "leathery" skin texture (on sides of rabbit) at 7 days; desquamation, alopecia at 14 days.

Signs of Toxicity: Perioral wetness at 3 and 6 days (mild at 6 days); rapid breathing at 14 days.

Gross Pathology: Lungs with small dark red consolidated areas.

92-232	8.0	21.8	2825	2403	2719	—
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Skin Irritation: Erythema, edema, "spotty" necrosis at 1 day; fissuring, desquamation at 7 days; desquamation, alopecia at 14 days.

Signs of Toxicity: Excessive perioral wetness at 2 days. Recovery at 6 days.

Gross Pathology: Lungs with light red foci.

92-706	8.0	19.6	2542	2478	2784	—
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Skin Irritation: Erythema, edema at 1 day; fissuring, scabs, desquamation at 7 days; desquamation, alopecia at 14 days.

Signs of Toxicity: None noted.

Gross Pathology: No gross lesions.

(Continued)

TABLE 4 (Continued)

TRITON® X-193 AG EMULSIFIER: ACUTE TOXICITY AND IRRITANCY TESTING USING THE RAT (PERORAL TOXICITY) AND THE RABBIT (CUTANEOUS AND EYE TESTS)

INDIVIDUAL RESULTS FROM SINGLE DOSES TO INTACT SKIN - RABBITS
FEMALES

Material: TRITON® X-193 AG Emulsifier		Sample No.: 54-344				
Rabbit Number	Dose, g/kg b.v. ^a	Total Dose, ml ^b	Rabbit Weight (g) at Day			Time to Death
			Initial	7 Days	14 Days	
92-707	8.0	19.5	2528	2384	2584	—
<u>Skin Irritation:</u> Erythema, edema at 1 day; fissuring, scabs, desquamation, alopecia at 7 days; desquamation, alopecia at 14 days.						
<u>Signs of Toxicity:</u> Audible breathing at 1 day. Recovery at 2 days.						
<u>Gross Pathology:</u> No gross lesions.						
92-708	8.0	18.8	2438	2271	2565	—
<u>Skin Irritation:</u> Erythema, edema at 1 day; fissuring, desquamation, alopecia at 7 days; desquamation, alopecia at 14 days.						
<u>Signs of Toxicity:</u> None noted.						
<u>Gross Pathology:</u> Kidney tan.						

^a Dose given as g of TRITON® X-193 AG Emulsifier/kg of body weight; sample dosed as received.^b Dose converted to dose volumes using a density of 1.04 g/ml (determined at BRRC).

TABLE 5

TRITON® X-193 AG EMULSIFIER: ACUTE TOXICITY AND IRRITANCY TESTING USING THE RAT (PERORAL TOXICITY) AND THE RABBIT (CUTANEOUS AND EYE TESTS)

PRIMARY EYE IRRITATION - RABBIT

Material: TRITON® X-193 AG Emulsifier Sample No.: 54-344 Amount: 0.1 ml

Animal No.:	91-28295	91-28296	91-27105	91-27108
Sex/Eye Dosed:	Male/R	Male/L	Female/R	Female/L
Date Dosed:	01-14-92	01-14-92	01-14-92	01-14-92

Scores and Effects at 1 Hour

					Mean	
Cornea:	Opacity	1	1	1	1	1.0
	Area	1	1	1	1	1.0
Iris:	Inflam.	1	1	1	0	0.8
Conjunct:	Redness	1	1	1	1	1.0
	Chemosis	2	2	2	1	1.8
	Discharge	3	2	3	3	2.8

Scores and Effects at 24 Hours

					Mean	
Cornea:	Opacity	1	1	1	1	1.0
	Area	1	1	1	1	1.0
Iris:	Inflam.	1	1	1	1	1.0
Conjunct:	Redness	2	2	2	2	2.0
	Chemosis	1	2	2	2	1.8
	Discharge	2	3	3	3	2.8
Fluorescein Exam.	100%	100%	100%	85%	96%	

Other Effects/Remarks: Rabbit 28295 with a reddish ocular discharge.

Scores and Effects at 48 Hours

					Mean	
Cornea:	Opacity	1	1	1	1	1.0
	Area	1	2	1	1	1.2
Iris:	Inflam.	1	1	1	1	1.0
Conjunct:	Redness	3	3	3	3	3.0
	Chemosis	1	2	1	2	1.5
	Discharge	2	2	2	3	2.2
Fluorescein Exam.	90%	80%	80%	75%	81%	

Other Effects/Remarks: Rabbit 28295 with a pus-like, reddish ocular discharge.

(Continued)

TABLE 5 (Continued)

TRITON® X-193 AG EMULSIFIER: ACUTE TOXICITY AND IRRITANCY TESTING USING THE RAT (PERCUTANEOUS TOXICITY) AND THE RABBIT (CORNEAL AND EYE TESTS)

PRIMARY EYE IRRITATION - RABBIT

Material:	TRITON® X-193 AG Emulsifier				Sample No.:	54-344				Amount:	0.1 ml					
Animal No.:	91-28295				91-28296				91-27105				91-27108			
Sex/Eye Dosed:	Male/R				Male/L				Female/R				Female/L			
Date Dosed:	01-14-92				01-14-92				01-14-92				01-14-92			

Scores and Effects at 72 Hours

						Mean
Cornea:	Opacity	1	1	1	1	1.0
	Area	3	3	1	1	2.0
Iris:	Inflam.	1	1	1	1	1.0
	Conjunct:	3	2	3	3	2.6
	Redness	1	2	1	2	1.5
	Chemosis	3	2	2	3	2.5
	Discharge	85%	50%	80%	75%	72%

Other Effects/Remarks: Rabbits 28295 and 27105 with a pus-like ocular discharge.

Scores and Effects at 7 Days

						Mean
Cornea:	Opacity	1	1	2	1	1.2
	Area	2	2	1	2	1.8
Iris:	Inflam.	0	1	1	0	0.5
	Conjunct:	2	1	3	2	2.0
	Redness	1	1	1	1	1.0
	Chemosis	1	1	2	2	1.5
	Discharge	50%	10%	25%	25%	28%

Other Effects/Remarks: All rabbits with corneal vascularization.

Scores and Effects at 10 Days

						Mean
Cornea:	Opacity	1	1	1	2	1.2
	Area	2	1	1	1	1.2
Iris:	Inflam.	0	0	1	0	0.2
	Conjunct:	2	1	3	3	2.2
	Redness	1	1	2	2	1.5
	Chemosis	1	1	2	2	1.5
	Discharge	50%	0%	20%	25%	24%

Other Effects/Remarks: Rabbit 27108 with a pus-like ocular discharge; Rabbits 28295, 27105 and 27108 with corneal vascularization.

(Continued)

TABLE 6 (Continued)

TRITON® X-193 AG EMULSIFIER: ACUTE TOXICITY AND IRRITANCY TESTING USING THE RAT (PERORAL TOXICITY) AND THE RABBIT (CUTANEOUS AND EYE TESTS)

PRIMARY EYE IRRITATION - RABBIT

Material:	TRITON® X-193 AG Emulsifier			
	Sample No.:		54-344	
	Amount: 0.01 ml			
Animal No.:	91-28309	91-28310	91-27220	91-27221
Sex/Eye Dosed:	Male/R	Male/L	Female/R	Female/L
Date Dosed:	01-21-92	01-21-92	01-21-92	01-21-92

Scores and Effects at 72 Hours

					Mean	
Cornea:	Opacity	1	1	1	0	0.8
	Area	1	2	1	0	1.0
Iris:	Inflam.	1	1	0	0	0.5
Conjunct:	Redness	3	3	3	2	2.8
	Chemosis	1	1	1	1	1.0
	Discharge	3	2	1	1	1.8
Fluorescein Exam.		25%	30%	10%	0%	16%

Other Effects/Remarks: Rabbits 28309 and 28310 with a pus-like ocular discharge.

Scores and Effects at 7 Days

					Mean	
Cornea:	Opacity	1	1	1	0	0.8
	Area	1	1	1	0	0.8
Iris:	Inflam.	1	1	0	0	0.5
Conjunct:	Redness	3	3	1	1	2.0
	Chemosis	2	1	1	1	1.2
	Discharge	3	1	1	1	1.5
Fluorescein Exam.		20%	10%	10%	0%	10%

Other Effects/Remarks: Rabbit 28309 with pus-like ocular discharge.

Scores and Effects at 10 Days

					Mean	
Cornea:	Opacity	4	1	0	0	1.2
	Area	1	1	0	0	0.5
Iris:	Inflam.	1	1	1	0	0.8
Conjunct:	Redness	3	1	2	1	1.8
	Chemosis	2	1	1	1	1.2
	Discharge	3	1	2	1	1.8
Fluorescein Exam.		20%	5%	0%	0%	6%

Other Effects/Remarks: Rabbit 28309 with corneal vascularization and pus-like ocular discharge.

(Continued)

TABLE 6 (Continued)
 TRITON® X-193 AG EMULSIFIER: ACUTE TOXICITY AND IRRITANCY TESTING USING THE RAT (PEROSAL TOXICITY) AND THE RABBIT (CUTANEOUS AND EYE TESTS)

PRIMARY EYE IRRITATION - RABBIT

Material: TRITON® X-193 AG Emulsifier Sample No.: 54-344 Amount: 0.01 ml

Animal No.:	91-28309	91-28310	91-27220	91-27221
Sex/Eye Dosed:	Male/R	Male/L	Female/R	Female/L
Date Dosed:	01-21-92	01-21-92	01-21-92	01-21-92

Scores and Effects at 14 Days

					Mean	
Cornea:	Opacity	4	0	0	0	1.0
	Area	1	0	0	0	0.2
Iris:	Inflam.	*	0	1	0	0.3
Conjunct:	Redness	2	1	3	1	1.0
	Chemosis	1	1	1	0	0.8
	Discharge	3	1	2	0	1.5
Fluorescein Exam.		10%	0%	0%	0%	2%

Other Effects/Remarks: Rabbit 28309 with corneal vascularization and pus-like ocular discharge.
 * Iris could not be scored because of corneal injury.

Scores and Effects at 17 Days

					Mean	
Cornea:	Opacity	4	0	0	0	1.0
	Area	1	0	0	0	0.2
Iris:	Inflam.	0	0	0	0	0.0
Conjunct:	Redness	1	0	1	1	0.8
	Chemosis	1	0	0	0	0.2
	Discharge	3	1	1	0	1.2
Fluorescein Exam.		5%	0%	0%	0%	1%

Other Effects/Remarks: Rabbit 28309 with corneal vascularization and pus-like ocular discharge.

Scores and Effects at 21 Days

					Mean	
Cornea:	Opacity	4	0	0	0	1.0
	Area	1	0	0	0	0.2
Iris:	Inflam.	0	0	0	0	0.0
Conjunct:	Redness	2	0	1	1	1.0
	Chemosis	1	0	0	0	0.2
	Discharge	2	0	1	0	0.8
Fluorescein Exam.		15%	0%	0%	0%	4%

Other Effects/Remarks: Rabbits 28309 with corneal vascularization and corneal bulging (irregular surface).

TRITON® X-193 AG Emulsifier: Acute Toxicity and Irritancy Testing Using the
Rat (Peroral Toxicity) and the Rabbit (Cutaneous and Eye Tests)

Protocol and Protocol Amendment

(25 Pages)



BUSHY RUN RESEARCH CENTER

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PROTOCOL

TITLE: TRITON® X-193 AC Emulsifier: Acute Toxicity and Irritancy Testing Using the Rat (Peroral Toxicity) and the Rabbit (Cutaneous and Eye Tests)

BRRC PROJECT NUMBER: 91-22-21366

SPONSOR: Industrial Chemicals Division
Union Carbide Chemicals
and Plastics Company Inc.
39 Old Ridgebury Road
Danbury, CT 06817-0001

TESTING FACILITY: Bushy Run Research Center (BRRC)
Union Carbide Chemicals and
Plastics Company Inc.
6702 Mellon Road
Export, PA 15632-8902

Reviewed and Approved by:

Bushy Run Research Center:

Roy C. Myers 10-22-91
Roy C. Myers, B.S., DABT Date
Study Director

Edward H. Fowler 11/2/91
Edward H. Fowler, DVM, Ph.D., DACVP Date
Associate Director

Linda J. Calisti 10/23/91
Linda J. Calisti, B.S. Date
Manager, Good Laboratory
Practices/Quality Assurance

John P. Van Miller 10/23/91
John P. Van Miller, Ph.D., DABT Date
Director

Union Carbide Chemicals
and Plastics Company Inc.:

Hon-Wing Leung 10/30/91
Hon-Wing Leung, Ph.D., DABT, CIH Date
Associate Director of Applied Toxicology

Division: *William M. Snellings* 11/4/91
William M. Snellings, Ph.D. Date
Manager of Occupational Health
and Product Safety

Union Carbide Chemicals and Plastics Company Inc.
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OBJECTIVE

The objective of this study will be to determine and evaluate the potential for the test substance to produce acute toxic effects by the following tests: peroral intubation in the rat; cutaneous application in the rabbit; skin irritation in the rabbit; and eye irritation in the rabbit.

GENERAL INFORMATION

Sponsor Industrial Chemicals Division
Union Carbide Chemicals
and Plastics Company Inc.
39 Old Ridgebury Road
Danbury, CT 06817-0001

Testing Facility Bushy Run Research Center, Export, PA 15632-8902

Personnel

Acute Toxicology P. E. Biondo, A.S., AALAS Cert. II
M. G. Brawley, HT(ASCP)
S. M. Christopher, B.S.
T. A. Christopher, AALAS Cert. II

Anatomic Pathology (if required) E. H. Fowler, DVM, Ph.D., DACVP
P. E. Losco, VMD, DACVP

Clinical Veterinarian M. K. Walter, DVM, DACVP

Additional personnel will be noted in the raw data.

Proposed Date for Initiation of Testing November 4, 1991

Proposed Date for Completion of Testing January 17, 1992

Proposed Date for Submission of the Draft Final Report February 17, 1992

Basis for the Study

Procedures followed for the study are based on 1985 EPA (TSCA) Test Guidelines (Federal Register Vol 50, No. 188) and on 1987 OECD Guidelines for Testing of Chemicals (Section 4: Health Effects).

The portions of this study conducted at the Bushy Run Research Center (BRRC) will be performed in compliance with Good Laboratory Practice Regulations, TSCA, 40 CFR Part 792.

Alteration of Design

Alterations to this protocol may be made as the study progresses. No changes in the protocol will be made without the specific written request or consent of the Sponsor. In the event that the Sponsor authorizes a protocol change verbally, such change will be honored. However, it then becomes the responsibility of the Sponsor to follow such verbal change with a written

verification. BRRC reserves the right to revise the protocol or deviate therefrom solely at the discretion of the Study Director if prior approval of the Sponsor cannot be obtained and the integrity of the study is considered to be in jeopardy. In this event, the Sponsor shall be notified of the alteration as soon as possible, and written verification of the change will be the responsibility of the Study Director. All protocol modifications will be signed by the Study Director and a representative of the Sponsor.

METHODS

Test Substance

Chemical Name	TRITON® X-193 AC Emulsifier
Source	Rohm and Haas Company, Philadelphia, PA
CAS Registry Number	Not applicable (mixture)
Sponsor Identification Number	Product Code: 89558 Specification Number: 1-40F.X193-1 Lot Number: 25142
BRRC Sample Number	54-344
Description	Brown, translucent, very viscous liquid
Percent Active Material	An approximate 89% blend of nonionic surfactants and organic sulfonates surfactant
Storage Conditions	The test substance will be stored at room temperature in well-ventilated conditions in an appropriate storage area.
Quantity Received	One quart
Test Substance Preparation	As necessary, the density may be determined by BRRC. Dilutions of the test substance will be prepared as necessary using vehicles of low toxicity for which BRRC has extensive experience (including water, CAS No. 7732-18-5; aqueous methyl cellulose, CAS No. 9004-67-5; saline, CAS No. for NaCl: 7647-14-5; corn oil, CAS No. 8001-30-7; mineral oil, CAS No. 8012-95-1; agar, CAS No. 9002-18-0; propylene glycol, CAS No. 57-50-6; and polyethylene glycol, CAS No. 25322-68-3). The stability and homogeneity of sample in the vehicle will not be determined by BRRC. The content of the dosing mixtures will be documented by gravimetric analysis. BRRC will retain the remaining

test substance for approximately a 3-month period following report issuance. If possible, approximately 20 ml (or 20 g) of test substance will be saved for at least 2 years. The dosing mixtures will not be saved.

Safety

A Material Safety Data Sheet (MSDS) supplied by the Sponsor will be reviewed by all personnel prior to the initiation of the study (Attachment 1). This review will be documented. Precautions will include the use of disposable paper or plastic coats or jumpsuits, hats, booties or shoe covers, and appropriate gloves while in the animal rooms. Eye protection will include the use of safety glasses at all times. In addition, monogoggles and plastic or rubber sleeves will be used when handling the test substance. Transfer and preparation of the test substance and its dilutions will be done carefully in a fume hood or downdraft table to avoid exposure.

Test Animals

Rats

Male and female Sprague-Dawley albino rats, weighing between 200 and 250 grams (approximately 7 to 13 weeks of age), will be used because of this laboratory's extensive experience with this species and strain. Larger animals, up to 300 g, may be used for an oral study provided that the range of weights for each sex is not greater than $\pm 20\%$ of the mean weight. The rats will be obtained from Harlan Sprague-Dawley, Inc. (Indianapolis, IN). The rats will be acclimated for at least 5 days before they are dosed. Upon receipt, they will be housed in Room 109, where they will be subsequently dosed and observed until death or sacrifice. All rats will be assigned unique animal numbers and identified by a system of ear tags.

The rats will be housed (according to USDA specifications) in stainless steel cages, 1 to 5 per cage, with wire-mesh floors under which animal cage board is placed. The animals will be maintained on commercial pelleted rodent diet (Agway RMH 3000 Certified Rodent Pellets). The feed will be available ad libitum until early afternoon of the day before dosing and again following dosing. Water will be supplied by the Municipal Authority of Westmoreland County (Greensburg, PA) and will be available at all times except during the actual dosing period. Periodic water analyses, as they are available, will be reviewed by the Study Director. The feed and water will contain no contaminants which would be expected to interfere with the conduct of this study. The animal room temperature and humidity will be controlled and recorded continuously. Typically, the

room temperatures will be maintained at 71°F ± 6°F, and humidity will be maintained at 40% to 70%. Prolonged deviations from these limits and the causes of the deviations (such as equipment failure or shut down) will be documented. Room lights will be on for 12 hours and off for 12 hours (timed automatically).

The rats will be weighed and inspected for health on the day of the test. Only those exhibiting a healthy state will be used. Such animals will be alert, active and well-groomed, with no evidence of discharge, diarrhea, breathing difficulties or locomotor abnormalities. Once per month, 5 rats per sex received for acute testing and housed in Room 109 are to be subjected to a quality control evaluation, including gross pathology, parasitology and viral serology testing. Animals will be randomly assigned to cages, and they will be designated for dosing according to need and availability. The available rats not assigned to the study will be used for other toxicity testing or will be sacrificed by CO₂ overdose.

Rabbits

Male and female New Zealand White rabbits, weighing between 2.0 and 3.0 kg (approximately 12 to 18 weeks of age) will be used. Larger rabbits (up to 3.5 kg) may be used for irritation testing (if required) if standard-sized rabbits are not available. Rabbits will be received from Hazleton Research Products, Inc. (Denver, PA). These animals will be used because of this laboratory's past experience with this species and strain. The rabbits will be acclimated in a suitable holding area for at least 5 days before they are dosed. Dosing and observation will be conducted in Room 122. Each rabbit will receive a unique identification number which will be marked, in indelible ink, on one ear and on the animal cage card.

The rabbits will be housed individually (according to USDA specifications) in stainless steel cages with wire floors under which animal cage board is placed. They will be maintained on pelleted rabbit diet (Agway PROLAB High Fiber). Water will be provided by an automatic water system and will be supplied by the Municipal Authority of Westmoreland County (Greensburg, PA). Both feed and water will be available ad libitum except during the dosing procedure and contact period in the dermal irritancy test (if conducted). The temperature and humidity will be controlled. Typical room temperatures will be maintained at 66°F ± 5°F, and humidity will be kept at 40% to 60%. Prolonged deviations from these limits

and the causes of the deviations (such as equipment failure or shut down) will be documented and reported. Room lights will be on for 12 hours and off for 12 hours (timed automatically).

The rabbits will be weighed and inspected on the day of the test. Only those exhibiting a healthy state will be used. Healthy animals will be alert, active and well-groomed, with no evidence of discharge, diarrhea, breathing difficulties, locomotor abnormalities or weight depression. Rabbits will be randomly assigned to cages, and they will be designated for dosing according to need and availability. Those available rabbits not assigned to the study will be used for other toxicity testing or sacrificed by lethal injection of euthanasia solution.

Test Procedures

Peroral Intubation Toxicity Test

Using an appropriately-sized syringe, the required amount of test substance or its dilution in a suitable vehicle, will be administered by stomach intubation through a commercial 14 to 18 gauge (3-inch) ball-end stainless steel needle. The exact amounts of sample and dilution dosed for each rat will be recorded. Distilled water or a 0.25% (w/v) methyl cellulose solution in distilled water will be the first choices as vehicles. Other vehicles (especially corn oil) will be considered if a suitable aqueous dilution or suspension cannot be prepared.

All doses will be administered on the basis of weight of material per rat body weight (mg/kg or g/kg). The rats will be fasted overnight (approximately 18 hours) before dosing. For each dose level, a different concentration will be prepared to keep the dose volumes uniform. For individual doses, the volume of sample, suspension or dilution will be adjusted according to individual rat weights. The total volume to be administered should not exceed 1.0 ml/100 g of body weight or 2.0 ml/100 g for aqueous solutions. If a single dose is not possible, the dose may be given in smaller fractions over a period of 1 hour or more, but not exceeding 24 hours.

Preliminary testing may first be performed to determine the approximate LD50 and to aid in establishing suitable dosing concentrations. One or 2 animals may be included in each preliminary dose group. Only limited observations may be made.

Dosed rats will be observed frequently for signs of toxic effect on the first day of the test and twice a day thereafter (except on weekends or holidays, when they will be examined for death alone). Examination

will be made of the skin, fur and eyes, and the rats will be observed for lethargy, tremors, convulsions, salivation, lacrimation, diarrhea and other signs of central nervous system, somatomotor, respiratory, circulatory or behavioral effects. Urine will be tested for the presence of occult blood through the use of HEMASTIX® Reagent Strips (Ames). Weights will be recorded shortly before dosing, weekly thereafter and at sacrifice (or at death if appropriate). After 14 days, all survivors will be sacrificed (by CO₂ overdose). If signs persist at 14 days, the animals may be observed for a longer period according to the needs of the Sponsor. Animals will be observed for shorter periods than 14 days if they appear to be in extreme distress. After death or sacrifice, all rats will be necropsied by qualified personnel. If necropsy is not possible soon after death, rats will be stored in a refrigerator until necropsy can be performed.

Selected tissues will be saved from each test animal, unless tissues are judged to be excessively autolyzed or the Sponsor indicates that tissues need not be saved. At a minimum, tissues will include kidney, urinary bladder, liver, sciatic nerve, central nervous system and spleen. Additional tissues may be saved depending on results of the test (signs or necropsy findings) or Sponsor instructions. Where tissue change is apparent or suspected, all or some of the saved tissues may be subjected to histologic evaluation (at extra cost to the Sponsor). Clinical pathology may also be included, upon Sponsor request. As required, these additions will be documented by protocol amendment.

Limit Test - For materials of suspected low toxicity, 5 males and 5 females will be administered 16 g of sample per kg of body weight. If all (or most) animals survive this "limit test", no further dosing will be required. If a material produces a significant degree of mortality (usually in half or more of the treated animals) at this dose level, a complete LD50 study may be required.

LD50 Determination - For the LD50 test, a minimum of 3 dose levels will be administered, including (if possible) at least one dose level which produces a fractional mortality ratio. Five females will be employed per dose group because experience at BREC has shown that whenever minor sex differences occur, the female is the more sensitive sex. If necessary to achieve a fractional mortality ratio, 1 or 2 intermediate levels may be tested, provided that sufficient sample is available. A few males will be treated for comparison. If there appears to be an

unusually large sex difference or if required to meet certain test guidelines, LD50s may be required in both sexes (and so requested by the Sponsor). Doses will be varied by a constant factor until sufficient mortality data are collected to calculate an LD50 based on the 14-day observation period. Unless otherwise required, the LD50 will be calculated by the moving average method (Thompson, 1947). Estimates of the slope will use the method of Weil (1983).

Cutaneous
Application
Toxicity Test

The entire trunk of each rabbit will be clipped closely at 1 or more days before application of the sample. As necessary, the rabbit skin may be carefully trimmed (to remove excess fur regrowth) up to the day before dosing. If abrasions occur during the trimming process, the rabbit will not be used in the cutaneous test. Liquid samples will be dosed as received, and solids will be moistened with a sufficient volume of distilled water (or 0.25% aqueous methyl cellulose, corn oil or other suitable vehicle) to ensure good contact with the skin. All doses will be administered on the basis of weight of test substance per rabbit body weight (mg/kg or g/kg). Any change in dose will be made through varying dose volume or weight while keeping the concentration of test substance constant.

The test substance or its dilution will be applied to the dorsal surface and spread over as large a skin area as possible. The rabbit may be temporarily restrained (using a flat board and cloth ties) during this process. The amount of test substance applied and, if appropriate, the amount of vehicle used will be recorded for each animal. For each dose, the approximate area of skin covered will be recorded. After sample application, a double layer of gauze sheeting will be wrapped around the trunk and secured with adhesive tape. Polyethylene sheeting will then be wrapped around the trunk over the gauze. To secure the polyethylene, plastic ties or rubber bands will be added (at the ends of the trunk). The sheeting will be protected from removal or tearing by wrapping the rabbit trunk with VETRAP® bandaging tape (Myers et al., 1989). The ends of the VETRAP® will be secured with adhesive tape. At this stage, the rabbit will be removed from any restraining device and returned to its cage (with access to feed and water) for a 24-hour contact period.

After the contact period, all coverings will be removed from the animal, and any residual test substance will be carefully wiped off. Water or other appropriate (relatively non-toxic) solvent will be used to remove the remaining test substance when necessary.

Preliminary testing may be performed first to determine the approximate LD50 and to aid in establishing suitable dosing concentrations. One or 2 animals may be included in each preliminary dose group. Only limited observations may be made.

Dosed rabbits will be observed frequently for signs of toxic effect on the first day of the test and twice a day thereafter (except on weekends or holidays, when they will be examined for death alone). Examination will be made of the skin, fur and eyes, and the rabbits will be observed for lethargy, tremors, convulsions, salivation, lacrimation, diarrhea and other signs of central nervous system, somatomotor, respiratory, circulatory or behavioral effects. Urine will be tested for the presence of occult blood through the use of HEMASTIX® Reagent Strips (Ames). Weights will be recorded shortly before dosing, weekly thereafter and at sacrifice (or at death if appropriate). After 14 days, all survivors will be sacrificed. If signs persist at 14 days, the animals may be observed for a longer period according to the needs of the Sponsor. Animals will be observed for shorter periods than 14 days if they appear to be in extreme distress. After death or sacrifice, all rabbits will be necropsied by qualified personnel. If necropsy is not possible soon after death, rabbits will be stored in a refrigerator until necropsy can be performed.

Selected tissues will be saved from each test animal, unless tissues are judged to be excessively autolyzed or the Sponsor indicates that tissues need not be saved. At a minimum, tissues will include kidney, urinary bladder, liver, sciatic nerve, central nervous system and spleen. Additional tissues may be saved depending on results of the test (signs or necropsy findings) or Sponsor instructions. Where tissue change is apparent or suspected, all or some of the saved tissues may be subjected to histologic evaluation (at extra cost to the Sponsor). Clinical pathology may also be included, upon Sponsor request. As required, these additions will be documented by protocol amendment.

Limit Test - For materials of suspected low toxicity, 5 males and 5 females will be administered 16 g of sample per kg of body weight. If all (or most) animals survive this "limit test", no further dosing will be required. For a material which produces a significant degree of mortality (usually in half or more of treated animals) a complete LD50 study may be performed.

LD50 Determination - For the LD50 test, a minimum of 3 dose levels will be administered, including (if possible) at least 1 dose level which produces a fractional mortality ratio. Five females will be employed per dose group because experience at BRRC has shown that whenever minor sex differences occur, the female is the more sensitive sex. If necessary to achieve a fractional mortality ratio, 1 or 2 intermediate levels may be added, provided that sufficient sample is available. A few males will be treated for comparison. If there appears to be an unusually large sex difference or if required to meet certain test guidelines, LD50s may be required in both sexes (and so requested by the Sponsor). Dose levels will be varied (using different volumes) by a constant factor until sufficient mortality data are collected to calculate an LD50, based on the 14-day observation period. Unless otherwise required, the LD50 will be calculated by the moving average method of Thompson (1947). Estimates of the slope will use the method of Weil (1983).

Primary Skin
Irritation Test

For the primary skin irritation test, the dorsal area of the trunk of each rabbit will be clipped closely 1 or more days before dosing and trimmed carefully, as necessary, up to the day preceding application of the test substance. Any abrasion of the skin during trimming will render the animal unsuitable for the skin test. A dose of 0.5 ml (liquid) or 0.5 g (solid moistened with water or other vehicle) will be applied to 1 dorsal site on each of 6 rabbits. Fewer animals may be used if requested by the Sponsor. If the amount of test substance that can be applied is restricted by its percutaneous toxicity, primary irritancy or physical properties, doses of 0.1 ml (0.1 g) or 0.05 ml (0.05 g) may be administered. A 1-inch square (6 cm²) gauze patch will be placed over the dose site and secured by adhesive tape. It may be more suitable to place the sample onto the gauze and then apply the gauze to the skin. Plastic sheeting will be attached loosely around the trunk and secured. The animal will be placed in a restraining device for the 4-hour contact period, after which the coverings and excess sample will be removed. If necessary, water or other appropriate solvent may be used to remove excess test substance.

Readings will be made at 60 minutes and at 24, 48 and 72 hours and at 7 days after the end of the contact period according to the system shown in Attachment 2. If irritation persists at 7 days, additional readings will be made at 14 days after the dose. Any local or systemic effects not included in the scoring system will also be recorded.

If any rabbit exhibits dermal corrosion (full-thickness necrosis or ulceration), it may be necessary to apply the sample for shorter time periods (1 hour and/or 3 minutes) for satisfaction of shipping regulations. If high corrosivity is anticipated, it may be necessary to dose only 1 or 2 rabbits for 4 hours or to start directly with the shorter time periods.

With Sponsor approval, fewer than 6 rabbits (per contact time) may be sufficient to fulfill the objectives of the study. Moreover, any rabbit that appears to be in extreme distress (from severe irritation) will be sacrificed before the scheduled date for humane reasons.

**Primary Eye
Irritation Test**

Eyes to be dosed will be examined using fluorescein stain within 24 hours before application. If any pre-existing eye injury is apparent, the eye will be rejected for use in the test. A dose of 0.1 ml (liquid) or a volume equivalent to 0.1 ml of a finely-ground solid (up to 100 mg) will be instilled. For solids, the weight will be recorded. If the amount of sample that can be given is restricted by toxicity (based on preliminary eye tests), primary irritancy or physical properties, a dose of 0.01 ml will be used. It may be necessary to dose only 1 or 2 eyes with 0.1 ml or to start directly with the smaller dose. The 0.1 ml volume will be placed into the lower conjunctival sac of the eye. Smaller volumes will be placed directly on the cornea. The lids will be held together for about 1 second. A total of 4 eyes will be dosed using 1 eye per rabbit. The remaining eye of each animal will serve as a control. Eyes may be washed with lukewarm water at 24 hours, if necessary, to assist in examinations, e.g., when excessive discharge obscures the conjunctivae.

Readings will be made at 1, 24, 48 and 72 hours and at 7 days following instillation of the test substance. Fluorescein staining will be included at 1 day and subsequent days. If injury persists, additional readings will be made twice a week up to 21 days after dose. Grading will be performed by the system shown in Attachment 3. Any effects not included in the scoring scheme will also be noted.

With Sponsor approval, fewer than 4 rabbits may be sufficient to fulfill the objectives of the study. Moreover, any rabbit that appears to be in extreme distress (from severe irritation) will be sacrificed before the scheduled date for humane reasons.

RECORDS

All raw data, correspondence and reports from this study will be stored in the BRRC Archives after completion of the study. Data may later be stored offsite in a secure archival facility.

REPORTS

Draft Final Report

A draft final report will be submitted to the Sponsor approximately 1 month following completion of the in-life phase of the study unless additional work is requested, e.g., additional histopathologic evaluations. This report will be a comprehensive report which will include all information necessary to provide a complete and accurate description and evaluation of the test procedures and results. It will include a summary, appropriate text discussions of the experimental design, materials and methods, results and interpretations of the results, and summary and individual data tables.

Final Report

The final report will be audited by the BRRC Quality Assurance Unit. Quality Assurance and Sponsor comments will be considered in preparing a final report. An appropriate Quality Assurance Statement will be added to the report at the time of final issuance.

ANIMAL USE POLICY

It is the goal of BRRC, through the establishment and activities of the Institutional Animal Care and Use Committee (IACUC), to comply with the U.S. Animal Welfare Act and the subsequent rules promulgated by the U.S. Department of Agriculture and in effect on the date of this protocol. It has been determined that the work described herein minimizes the number of animals used, is necessary, and uses the most appropriate species and strain in order to provide meaningful results and the most useful information for comparative purposes relative to previous studies. Furthermore, this study will be conducted humanely and, to the best of our knowledge, neither unnecessarily duplicates any previous work, nor can it be accomplished using currently available, validated non-animal models.

GOOD LABORATORY PRACTICES

The Bushy Run Research Center, through the administration of a quality assurance program by the Good Laboratory Practices Committee and Quality Assurance Unit, assures compliance of all phases of toxicological studies conducted at the Bushy Run Research Center with existing regulations and generally accepted good laboratory practices.

The study will be subjected to periodic inspections, and the final report will be reviewed by the BRRC Quality Assurance Unit.

REFERENCES

- Myers, R. C., Hufford, K. R., and Bellich, W. S., Using Vetrap[®] bandaging during rabbit dermal toxicity testing, Lab. Animal, 18(7):44-45, 1989.
- Thompson, W. R., Use of moving averages and interpolation to estimate median effective dose, Bacterial. Rev., 11:113-145, 1947.
- Weil, C. S., Economical LD50 and slope determination, Drug Chem. Toxicol., 6(6):595-603, 1983.

ATTACHMENT 1



UNION CARBIDE CHEMICALS AND PLASTICS COMPANY INC.
Industrial Chemicals Division



**MATERIAL SAFETY DATA SHEET
ADVANCE INFORMATION**

**CAUTION!! This is a newly introduced product.
Complete safety information is not available.**

Union Carbide urges each customer or recipient of this MSDS to study it carefully to become aware of and understand the hazards associated with the product. The reader should consider consulting reference works or individuals who are experts in ventilation, toxicology, and fire prevention, or necessary or appropriate to him and understand the data contained in this MSDS.

To promote safe handling, each customer or recipient should (1) notify its employees, agents, contractors and others whom it knows or believes will see this material of the information in this MSDS and any other information regarding hazards or safety, (2) furnish this same information to each of its customers for the product; and (3) request its customers to notify their employees, customers, and other users of the product of this information.

EFFECTIVE DATE: 05/01/91

OBSOLETE DATE 05/01/92

I. IDENTIFICATION

PRODUCT NAME TRITON X-103 Ag Emulsifier

CHEMICAL NAME Blend of nonionic surfactants and organic sulfonates surfactant.

CHEMICAL FAMILY Surfactant

FORMULA Not Applicable (mixture)

MOLECULAR WEIGHT Not Applicable (mixture)

SYNONYMS Not Applicable

CAS # and Not Applicable

CAS NAME Not Applicable (mixture)

II. PHYSICAL DATA (Determined on typical material)

BOILING POINT, 760 mm Hg 88C/155F (METHANOL)

FREEZING POINT, 18C/63F POIN POINT

SPECIFIC GRAVITY(H₂O = 1):
1.04

VAPOR PRESSURE AT 20C:
96 @ 25C/77F (METHANOL)

VAPOR DENSITY (air = 1):
> 1

SOLUBILITY IN WATER by wt:
Dispersible

EVAPORATION RATE
(Butyl Acetate = 1): > 1

APPEARANCE AND ODOR. Milky amber liquid, mild odor.

Copyright 1991, Union Carbide Chemicals & Plastics Technology Corp.
TRITON is a Trademark of Union Carbide Chemicals & Plastics Technology Corp.
EMERGENCY PHONE NUMBER: 1-800-UCC-HELP (Number available at all times) or 304-744-3497

UNION CARBIDE CHEMICALS AND PLASTICS COMPANY INC.
Industrial Chemicals Division
39 Old Ridgebury Road, Danbury, CT. 06817-0001

ATTACHMENT 1 (Continued)

PRODUCT NAME: TRITON X-193 Ag Emulsifier

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III. INGREDIENTS

<u>MATERIAL</u>	<u>%</u>	<u>TLV (Units)</u>	<u>HAZARD</u>
Octylphenoxypolyethoxy-methanol (CAS # 9036-18-8)	~28	None established	See Section V
Calcium dodecylbenzene sulfonate (CAS # 26264-08-2)	~21	None established	See Section V
Methanol (CAS# 67-56-1)	~ 8	200 ppm TWA, 260 ppm STEL, ACGIH and OSHA (ppm)	See Section V
Xylenes (CAS# 1330-20-7)	~1.5	100ppm TWA, 150ppm STEL, ACGIH & OSHA	See Section V
Solvent Naphtha (CAS # 64742-85-8)	~ 5	None established	See Section V
Butoxypropylpropylene glycol polyethylene glycol (CAS # 6038-85-3)	~40	None established	See Section V

IV. FIRE AND EXPLOSION HAZARD DATA

FLASH POINT 31C/87F Closed Cup
 (test method(s))

FLAMMABLE LIMITS IN AIR, % by volume
 LOWER 57 (Methanol)
 UPPER 36 (Methanol)

EXTINGUISHING MEDIA: Apply alcohol-type or all-purpose-type foams applied by manufacturer's recommended techniques for large fires. Use CO2 or dry chemical media for small fires

SPECIAL FIRE FIGHTING PROCEDURES: Use water spray to disperse vapors, re-ignition is possible. Use water spray to cool fire-exposed containers and structures. Approach methanol fire with caution, methanol burns with an almost invisible flame in daylight. Use self-contained breathing apparatus and protective clothing

UNUSUAL FIRE AND EXPLOSION HAZARDS: Vapors form from this product and may travel or be moved by air currents and ignited by pilot lights, other flames, sparks, heaters, electrical equipment, static discharges or other ignition sources at locations distant from product handling point. Vapors may settle in low or confined areas, or travel a long distance to an ignition source and flash back explosively. This material may produce a floating fire hazard

V. HEALTH HAZARD DATA

EXPOSURE LIMIT(S): See Section R

EFFECTS OF SINGLE OVEREXPOSURE:

ATTACHMENT 1 (Continued)

PRODUCT NAME: TRITON X-193 Ag Emulsifier

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SWALLOWING: Nausea, abdominal pain, vomiting, headache, dizziness, dizziness, shortness of breath, weakness, fatigue, leg cramps, restlessness, confusion, drunken behavior, visual disturbances, drowsiness, coma, and death. There may be a delay of several hours between swallowing methanol and the onset of signs and symptoms. The effects observed are in part due to acidosis and peritomy to cerebral edema. Visual effects include blurred vision, diplops, changes in color perception, restriction of visual fields, complete blindness. Ingestion of moderate quantities of methanol also produces metabolic acidosis. Onset of symptoms may be delayed up to 48 hours. 50-200 ml of methanol is a fatal dose for most adults. Ingestion of as little as 10 ml has caused blindness. With massive overdoses, liver, kidney and heart muscle injury have been described. Aspiration into the lungs may occur during ingestion or vomiting resulting in lung injury.

SKIN ABSORPTION: No evidence of adverse effects from available information.

INHALATION: May cause dizziness, drowsiness, disturbances of vision, and tingling, numbness, and shooting pains in the hands and forearms.

SKIN CONTACT: Causes irritation with discomfort, seen as local redness and possible swelling.

EYE CONTACT: Causes irritation experienced as discomfort, with excess blinking and tear production, and seen as excess redness and swelling of the conjunctiva.

EFFECTS OF REPEATED OVEREXPOSURE:

Long-term repeated overexposure to methanol vapor concentrations of 3000 ppm or greater may show a cumulative effect to occur with resulting nausea, vomiting, headache, ringing in the ears, insomnia, trembling, unsteady gait, vertigo, clouded and double vision. Liver and/or kidney injury may occur. Prolonged overexposure at levels of 800-1000 ppm may result in severe eye damage in some persons.

Repeated skin contact may result in the development of a cumulative dermatitis.

MEDICAL CONDITIONS AGGRAVATED BY OVEREXPOSURE:

Due to its liver and kidney-injuring potential, methanol may aggravate existing liver and/or kidney diseases.

Because of its irritating properties, this material may aggravate an existing dermatitis.

SIGNIFICANT LABORATORY DATA WITH POSSIBLE RELEVANCE TO HUMAN HEALTH HAZARD EVALUATION:

Studies involving the sustained occluded contact of undiluted material, similar to a component, with rabbit skin indicate that such conditions may result in the development of inflammatory changes in the lung.

Xylene has been shown to cause embryofetal toxicity and birth defects in laboratory animals, but only at doses which also cause maternal toxicity. There is no information available with respect to its possible developmental effects in humans.

Animals exposed repeatedly to high vapor concentrations (800 ppm and greater) of mixed xylenes suffered hearing loss.

OTHER EFFECTS OF OVEREXPOSURE:

Because of its irritant and surfactant properties, breathing vapor or mist of this material, as might be generated in spraying or heating applications, may result in lung injury similar to that observed following exposure by direct deposition of surfactant into the lung.

EMERGENCY AND FIRST AID PROCEDURES

SWALLOWING: If patient is fully conscious, give two glasses of water. Obtain medical attention without delay. If medical device is delayed, give three to four ounces of hard liquor, such as whiskey.

SKIN: Remove contaminated clothing and flush skin with water. If irritation

ATTACHMENT 1 (Continued)

PRODUCT NAME: TRITON X-193 Ag Emulsifier

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persists, seek medical attention.

INHALATION: Remove to fresh air. Give artificial respiration if not breathing. Oxygen may be given by qualified personnel if breathing is difficult. Obtain medical attention.

EYES: Immediately flush eyes thoroughly with water and continue washing for several minutes. Obtain medical attention.

NOTES TO PHYSICIAN: The combination of visual disturbances, metabolic acidosis, and formic acid in the urine is evidence of methanol poisoning. The therapeutic intravenous administration of ethanol (10 ml per hour) allows it to be preferentially oxidized and reduces production of methanol metabolites. Acidosis must be treated by means of intravenous sodium bicarbonate, and methanol elimination may be increased by hemodialysis, as indicated. Treatment should be based on blood methanol levels and acid-base balance. Folate may be administered to enhance the metabolism of formaldehyde. 4-Methyl pyrazole has been suggested as an antidote. Because of its alcohol dehydrogenase inhibiting effects, it reduces the production of formate and the development of metabolic acidosis. However, the value of this antidote remains to be proven in humans.

VI. REACTIVITY DATA

STABILITY: Stable

CONDITIONS TO AVOID: Prolonged excessive heat may cause product decomposition.

INCOMPATIBILITY (materials to avoid): Avoid contact with strong oxidizing and reducing agents. Avoid strong bases at high temperatures, strong acids, and materials reaction with hydroxyl compounds.

HAZARDOUS COMBUSTION OR DECOMPOSITION PRODUCTS: Burning can produce carbon monoxide and/or carbon dioxide, and sulfur oxides.

HAZARDOUS POLYMERIZATION: We Not Occur

CONDITIONS TO AVOID: None

VII. SPILL OR LEAK PROCEDURES

STEPS TO BE TAKEN IF MATERIAL IS RELEASED OR SPILLED: Extinguish and do not turn on any ignition source until area is determined to be free from explosion or fire hazards. Wear suitable protective equipment. Small spills should be flushed with large quantities of water. Larger spills should be collected for disposal.

WASTE DISPOSAL METHOD: Incinerate in a furnace where permitted under appropriate Federal, State, and local regulations.

VIII. SPECIAL PROTECTION INFORMATION

RESPIRATORY PROTECTION (specify type): Self-contained breathing apparatus in high vapor concentrations. However, where misting may occur, wear a NIOSH approved (or equivalent) full-face or purifying respirator.

ATTACHMENT 1 (Continued)

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PRODUCT NAME: TRITON X-193 Ag Emulsifier

VENTILATION:

This product should be confined within vapor-tight equipment, in which case general (mechanical) room ventilation should be satisfactory. Special local ventilation may be needed at points where vapors are expected to escape to the workplace or.

PROTECTIVE GLOVES:

Butyl or nitrile rubber gloves.

EYE PROTECTION:

Monogoggles

OTHER PROTECTIVE EQUIPMENT:

Eye bath, safety shower, and chemical apron

IX. SPECIAL PRECAUTIONS

PRECAUTIONS TO BE TAKEN IN HANDLING AND STORAGE.

DANGER: Harmful or fatal if swallowed. Flammable.
May cause eye damage and blindness if swallowed.
Harmful if inhaled.
Causes eye and skin irritation.
Aspiration may cause lung damage.
May cause dizziness and drowsiness.
May cause heart muscle damage.
May cause liver and kidney injury.

Do not swallow.
Keep away from heat, sparks and flame.
Avoid breathing vapor.
Avoid contact with eyes, skin and clothing.
Keep container closed.
Use with adequate ventilation.

Vapors form from this product and may travel or be moved by air currents and ignited by pilot lights, other flames, smoking, sparks, heaters, electrical equipment, static discharges or other ignition sources at locations distant from product handling point.
Wash thoroughly after handling.

FOR INDUSTRY USE ONLY

OTHER PRECAUTIONS:

This product may contain trace amounts of Ethylene Oxide (CAS No. 75-21-8), a condition which creates the potential for accumulation of Ethylene Oxide in the head space of shipping and storage containers and in enclosed areas where the product is being handled or used. Ethylene Oxide is considered by OSHA, IARC, and NTP as a potential carcinogen for humans. OSHA considers that, at excess levels, Ethylene Oxide may present reproductive, mutagenic, genotoxic, neurologic and sensitization hazards in humans. If this product is handled with adequate ventilation, the presence of these trace amounts is not expected to result in any short or long term hazard.

This product may not be exempt from OSHA's Ethylene Oxide standard, 29CFR 1910.1047. Users should comply with all applicable provisions. Personnel should be monitored to determine levels of exposure to Ethylene Oxide. If necessary, protective measures should be taken. The OSHA permissible exposure limit for Ethylene Oxide is 1 ppm TWAB, the action level is 0.5 ppm TWAB, the ACGIH TLV is 1 ppm TWAB and OSHA has established an excursion limit of 5 ppm (15 minute average).

WARNING: Sudden release of hot organic chemical vapors or mists from process equipment operating at elevated temperature and pressure, or sudden ingress of air into vacuum equipment, may result in ignitions without the presence of obvious ignition sources. Published "auto-ignition" or "ignition" temperature values cannot be treated as safe operating temperatures in chemical processes without analysis of the actual process conditions.

Any use of this product in elevated-temperature processes should be thoroughly evaluated to establish and maintain safe operating conditions. Further information is available in a technical bulletin entitled "Ignition Hazards of Organic Chemical Vapors".

X. REGULATORY INFORMATION

STATUS ON SUBSTANCE LISTS:

ATTACHMENT 1 (Continued)

PRODUCT NAME: TRITON X-193 Ag Emulsifier

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The concentrations shown are maximum or ceiling levels (weight %) to be used for calculations for regulations. Trade Secrets are indicated by "TS".

FEDERAL EPA

Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA) requires notification of the National Response Center of release of quantities of Hazardous Substances equal to or greater than the reportable quantities (RQs) in 40 CFR 302.4.

Components present in this product at a level which could require reporting under the statute are:

CHEMICAL	CAS NUMBER	UPPER BOUND CONCENTRATION %
Calcium Dodecylbenzene Sulfonate	26264-06-2	21.0
Xylene	1330-20-7	1.5
Methanol	67-56-1	60
Ethylene Oxide	75-21-8	.0011
Dioxane	123-91-1	.0016

Superfund Amendments and Reauthorization Act of 1986 (SARA) Title III

requires emergency planning based on Threshold Planning Quantities (TPQs) and release reporting based on Reportable Quantities (RQs) in 40 CFR 355 (used for SARA 302, 304, 311 and 312)

Components present in this product at a level which could require reporting under the statute are
*** NONE ***

Superfund Amendments and Reauthorization Act of 1986 (SARA) Title III

requires submission of annual reports of release of toxic chemicals that appear in 40 CFR 372 (for SARA 313) This information must be included in all MSDSs that are copied and distributed for this material

Components present in this product at a level which could require reporting under the statute are:

CHEMICAL	CAS NUMBER	UPPER BOUND CONCENTRATION %
Xylene	1330-20-7	1.5
Methanol	67-56-1	60
Glycol Ether	Not Applic	<1.0

STATE RIGHT-TO-KNOW

CALIFORNIA Proposition 65

This product contains trace levels of Dioxane, Propylene Oxide and Ethylene Oxide which the State of California has found to cause cancer, birth defects or other reproductive harm.

MASSACHUSETTS Right-To-Know, Substance List (MSL) Hazardous Substances and Extraordinarily Hazardous Substances on the MSL must be identified when present in products.

Components present in this product at a level which could require reporting under the statute are:

EXTRAORDINARILY HAZARDOUS SUBSTANCES (\geq 0.0001%)

CHEMICAL	CAS NUMBER	UPPER BOUND CONCENTRATION %
Ethylene Oxide	75-21-8	.0011

ATTACHMENT 1 (Continued)

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PRODUCT NAME: TRITON X-193 Ag Emulsifier

CHEMICAL	CAS NUMBER	UPPER SOUND CONCENTRATION %
Dioxane	123-91-1	.0014
Propylene Oxide	75-56-8	.0012
HAZARDOUS SUBSTANCES (\geq 1%)		
Calcium Dodecylbenzene Sulfonate	26264-06-2	21.0
Methanol	67-66-1	6.0
Xylene	1330-20-7	1.5

PENNSYLVANIA Right-To-Know, Hazardous Substance List Hazardous Substances and Special Hazardous Substances on the List must be identified when present in products.

Components present in this product at a level which could require reporting under the statute are:

SPECIAL HAZARDOUS SUBSTANCES (\geq 0.01%)

CHEMICAL	CAS NUMBER	UPPER SOUND CONCENTRATION %
*** None ***		
HAZARDOUS SUBSTANCES (\geq 1%)		
Calcium Dodecylbenzene Sulfonate	26264-06-2	21.0
Methanol	67-66-1	6.0
Xylene	1330-20-7	1.6

Toxic Substances Control Act (TSCA) STATUS:

The ingredients of this product are on the TSCA inventory.

CALIFORNIA SCAQMD RULE 443.1 VOC'S

Not presently available

OTHER REGULATORY INFORMATION

*** None known ***

NOTE ----

The opinions expressed are those of qualified experts within Union Carbide. We believe that the information contained is current as of the date of the Material Safety Data Sheet. Since the use of this information and of these opinions and the conditions of the use of the product are not within the control of Union Carbide, it is the user's obligation to determine the conditions of safe use of the product.

PC 85589

F NUMBER: ND356

ATTACHMENT 2

Scoring System for Skin Irritation

<u>Erythema and Eschar Formation</u>	<u>Value</u>
No erythema.....	0
Very slight erythema (barely perceptible).....	1
Well-defined erythema.....	2
Moderate to severe erythema.....	3
Severe erythema (best redness to slight eschar formation (injuries in depth).....	4
Maximum possible.....	4

Edema Formation

No edema.....	0
Very slight edema.....	1
Slight edema (edges of area well defined by definite raising.....	2
Moderate edema (raised approximately 1 millimeter).....	3
Severe edema (raised more than 1 millimeter and extending beyond area of exposure.....	4
Maximum possible.....	4

ATTACHMENT 3

Scoring System for Eye Irritation

CORNEA

Opacity: degree of density (area most dense taken for reading).

- No ulceration or opacity..... 0
- Scattered or diffuse areas of opacity (other than slight dulling of normal luster), details of iris clearly visible..... 1*
- Easily discernible translucent areas, details of iris slightly obscured..... 2*
- Nacreous (opalescent) area, no details of iris visible, size of pupil barely discernible..... 3*
- Opaque cornea, iris not discernible through the opacity..... 4*

Area of Cornea Involved

- One-quarter (or less) but not 0..... 1
- Greater than one-quarter, less than one-half..... 2
- Greater than one-half, less than three-quarters..... 3
- Greater than three-quarters up to whole area..... 4

IRIS

- Normal..... 0
- Markedly deepened rugae (folds), congestion, swelling, moderate circumcorneal hyperemia, or injection, any of these or combination of any thereof, iris still reacting to light (sluggish reaction is positive)..... 1*
- No reaction to light, hemorrhage, gross destruction (any or all of these)..... 2*

CONJUNCTIVAE

Redness: (refers to palpebral and bulbar conjunctivae, cornea, and iris)

- Blood vessels normal..... 0
- Some blood vessels definitely hyperemic (injected)..... 1
- Diffuse, crimson color, individual vessels not easily discernible... 2*
- Diffuse, beefy red..... 3*

Chemosis: Lids and/or nictitating membranes

- No swelling..... 0
- Any swelling above normal (includes nictitating membranes)..... 1
- Obvious swelling with partial eversion of lids..... 2*
- Swelling with lids about half closed..... 3*
- Swelling with lids more than half closed..... 4*

Discharge:

- No discharge..... 0
- Any amount of discharge different from normal..... 1
- Discharge with moistening of the lids and hairs adjacent to lids.... 2
- Discharge with considerable moistening around the eyes..... 3

*Starred figures indicate positive effect.



BUSHY RUN RESEARCH CENTER

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PROTOCOL AMENDMENT #1

TITLE: TRITON® X-193 AC Emulsifier: Acute Toxicity and Irritancy Testing Using the Rat (Peroral Toxicity) and the Rabbit (Cutaneous and Eye Tests)

BRC PROJECT NUMBER: 91-22-11366

SPONSOR: Industrial Chemicals Division
Union Carbide Chemicals
and Plastics Company Inc.
39 Old Ridgebury Road
Danbury, CT 06817-0001

TESTING FACILITY: Bushy Run Research Center (BRC)
Union Carbide Chemicals and
Plastics Company Inc.
6702 Mellon Road
Export, PA 15632-8902

Reviewed and Approved by:

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Manager of Occupational Health
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Union Carbide Chemicals and Plastics Company Inc.
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Location of Protocol Change: Test Procedures (pages 7 and 9)

Description of Protocol Change: The extent of tissue collection as described for the peroral and cutaneous tests has been changed as follows:

1. Central nervous system (CNS) tissues (brain and spinal cord) will not be saved unless there are clinical signs indicative of serious CNS effect.
2. For the peroral test, the stomach and upper intestine will be saved.
3. Tissues will not be saved from animals that die overnight unless it is apparent that death had just occurred and tissue degradation is minimal.
4. Tissues will be saved from all animals that are found dead during work hours as long as it is apparent that death had just occurred and tissue degradation is minimal. Tissues will be saved from any animal that is sacrificed because of a moribund or distressed appearance.
5. Tissues will be saved from 2 or 3 animals that survive a dose that has killed others of that same dose group (lethal dose level). Tissues will also be saved (at sacrifice) from 2 or 3 animals that received the highest non-lethal dose level but not from lower non-lethal dose levels, if such levels are obtained. Whenever possible, tissues from 1 or 2 male animals will be included in the above.

Reason for the Change: Evaluation of the progress of this and related studies revealed that tissue collection as originally specified in the protocol required much more time and resources than anticipated. This was discussed with the Sponsor and it was agreed that the above changes could be made to reduce the extent of tissue collection without compromising the objectives of the study.

CERTIFICATE OF AUTHENTICITY

THIS IS TO CERTIFY that the microimages appearing on this microfiche are accurate and complete reproductions of the records of U.S. Environmental Protection Agency documents as delivered in the regular course of business for microfilming.

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(Month) (Day) (Year) Camera Operator

Place Syracuse New York
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END