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UNITED STATES ARMY ENVIRONMENTAL HYGIENE AGENCY

ABERDEEN PROVING GROUND, MD 21010-5422

TOPICAL HAZARD EVALUATION PROGRAM (THEP)
ASSESSMENT OF THE RELATIVE TOXICITY OF
CANDIDATE INSECT REPELLENTS

AI3-38306	AI3-39076
AI3-38315	AI3-39077
AI3-38530	AI3-39078
AI3-39041	AI3-39085

U.S. DEPARTMENT OF AGRICULTURAL
PROPRIETARY CHEMICALS
STUDY NOS.
75-51-0623-89
75-51-0624-89
75-51-0625-89
75-51-0626-89
75-51-0627-89
75-51-0628-89
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JUNE 1989

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Maurice H. Weeks

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19. ABSTRACT (Continue on reverse if necessary and identify by block number)

The purpose of the Topical Hazard Evaluation Program (THEP) is to investigate relevant health endpoints of proposed insect repellent chemicals. Data from these studies are used to recommend the course of further entomological and toxicological evaluations with subject chemicals.

The results from the current animal sensitization studies showed that two of the eight test compounds AI3-39076 and AI3-39077 have some potential for causing an allergic response in man. A positive result from a sensitization test is a prime basis for rejecting a material as a topical insect repellent.

The results from the overall battery of biological tests showed that the candidate insect repellents AI3-38530, AI3-39041, and AI3-39078 produced relatively unremarkable toxicological responses.

Approve compounds AI3-38530, AI3-39041 and AI3-39078 for further entomological testing.

Based on the demonstrated skin/eye or photo irritation responses and/or sensitization potential it is recommended that the following compounds be disapproved for further entomological testing. These compounds are AI3-38306, AI3-38315, AI3-39076, AI3-39077 and AI3-39085. Consideration should be given to the toxicological reevaluation of these chemicals if the Armed Forces Pest Management Board considers them to be superior and/or especially efficacious insect repellents.

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DEPARTMENT OF THE ARMY
U. S. ARMY ENVIRONMENTAL HYGIENE AGENCY
ABERDEEN PROVING GROUND, MARYLAND 21010-5422

REPLY TO ATTENTION OF

HSHB-MO-T (40)

25 JUL 1989

MEMORANDUM FOR Executive Director, Armed Forces Pest Management Board, Forest Glen Section, WRAMC, Washington, DC 20307-5001

SUBJECT: Topical Hazard Evaluation Program (THEP), Assessment of the Relative Toxicity of Candidate Insect Repellents, AI3-38306, AI3-38315, AI3-38530, AI3-39041, AI3-39076, AI3-39077, AI3-39078, and AI3-39085, U.S. Department of Agriculture Proprietary Chemicals, Study Nos. 75-51-0623-89, 75-51-0624-89, 75-51-0625-89, 75-51-0626-89, 75-51-0627-89, 75-51-0628-89, 75-51-0629-89, 75-51-0630-89, June 1989

EXECUTIVE SUMMARY

1. PURPOSE. The purpose of this program is to provide guidance for further entomological testing of candidate insect repellents, U.S. Department of Agriculture (USDA) Proprietary Chemicals.

2. RECOMMENDATIONS.

1. Approve candidate insect repellents AI3-38530, AI3-39041 and AI3-39078 for further entomological testing.

2. Conduct no further entomological studies on candidate repellents AI3-38306, AI3-38315, AI3-39076, AI3-39077 and AI3-39085 as they exhibited potential for causing deleterious biological effects in man.

Encl

CHARLES B. KENISON
Colonel, MS
Commanding

CF:
HQDA(SGPS-PSP-E) (wo/encl)
Dir, Advisory Ctr Tox, NRC (2 cy) (w/encl)
Cdr, HSC, ATTN: HSCL-P (w/encl)
Comdt, AHS, ATTN: HSHA-IPM (w/encl)
USDA, ARS (Dr. Terrance McGovern) (w/encl)
USDA, ARS-Southern Region (3 cy) (w/encl)
USDA, ARS-Southern Region (CAPT Santana) (w/encl)
Cdr, USAMMDA, ATTN: SGRD-UMA (COL Schiefer) (w/encl)
Cdr, WRAMC, ATTN: SGRD-UWF-B (LTC Roberts) (w/encl)

DEPARTMENT OF THE ARMY
U. S. ARMY ENVIRONMENTAL HYGIENE AGENCY
ABERDEEN PROVING GROUND, MARYLAND 21010-5422

REPLY TO ATTENTION OF

HSHB-MO-T

TOPICAL HAZARD EVALUATION PROGRAM (THEP) ASSESSMENT OF THE RELATIVE TOXICITY OF CANDIDATE INSECT REPELLENTS

AI3-38306 AI3-39076
AI3-38315 AI3-39077
AI3-38530 AI3-39078
AI3-39041 AI3-39085

U.S. DEPARTMENT OF AGRICULTURAL PROPRIETARY CHEMICALS STUDY NOS.
75-51-0623-89
75-51-0624-89
75-51-0625-89
75-51-0626-89
75-51-0627-89
75-51-0628-89
75-51-0629-89
75-51-0630-89

JUNE 1989

1. REFERENCES. A list of references can be found in Appendix A.

2. AUTHORITY.

a. Letter, U.S. Department of Agriculture, Agricultural Research Service, Northeastern Region, Beltsville, Agricultural Research Service, Beltsville, Maryland, dated 3 Sept 1986, subject: Chemical Transmittal for THEP.

b. Memorandum of Understanding between the U.S. Army Health Services Command; the Department of The Army, Office of The Surgeon General; the Armed Forces Pest Management Board; and the U.S. Department of Agriculture, Agricultural Research, titled Biological and Toxicological Testing of Pesticides, effective 7 October 1987.

Use of trademarked names does not imply endorsement by the U.S. Army, but is intended only to assist in identification of a specific product.

3. PURPOSE. The purpose of this program is to provide guidance for further entomological testing of the Candidate Insect Repellents, U.S. Department of Agriculture (USDA) Proprietary Chemicals, AI3-38306, AI3-38315, AI3-38530, AI3-39041, AI3-39076, AI3-39077, AI3-39078 and AI3-39085.

4. MATERIALS.*+

a. Test Compounds. All samples of the eight candidate insect repellents used in these studies were synthesized by Dr. Terrance P. McGovern, Organic Chemical Synthesis Laboratory, USDA, Beltsville, Maryland.

b. Animals.

(1) Testing for primary skin irritation, photochemical skin irritation and primary eye irritation was conducted using New Zealand White rabbits from Hazleton-Dutchland Laboratories, Denver, Pennsylvania. Albino-Hartley guinea pigs, also from Hazleton-Dutchland Laboratories, were used for sensitization studies. Sprague-Dawley rats from Charles River Laboratories, Wilmington, Massachusetts, were used for determination of the oral toxicity of the test compounds.

(2) Quality control determinations made during a 2-week quarantine period showed the animals to be of acceptable health. The rabbits and guinea pigs were housed individually in wire-bottom stainless steel cages. Rats were group-housed with a maximum of three animals per cage in wire bottom stainless steel cages. Water and feed (Purina Rabbit Chow 5322; Ziegler Rodent Ration 35-553 and Ziegler Certified Guinea Pig Ration 35-564) were available ad libitum. The light/dark cycle was set at 12-hour intervals. Ambient temperatures were maintained at 21 to 25 °C with relative humidity between 40 and 60 percent. (Appendix A reference 1).

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* In conducting the studies described in this report, the investigators adhered to the "Guide for the Care and Use of Laboratory Animals," U.S. Department of Health, Education and Welfare Publication No. (NIH) 85-23, 1985.

+ The studies reported herein were performed in animal facilities fully accredited by the American Association for the Accreditation of Laboratory Animal Care.

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c. Contract Studies. Mutagenicity evaluation of subject compounds was performed using a Ames Salmonella/Microsome Reverse Mutation Assay (Appendix A, References 3, 4, 5, 6).

5. METHODS. Methods used for these studies are described in detail in Appendix A, Reference 2.

a. Skin Irritation. An acute dermal toxicity test conducted according to the method of Draize was utilized to determine the degree of primary skin irritation. All hair was clipped from the backs and sides of test rabbits 24 hours prior to exposure. One-half milliliter undiluted technical grade material was applied for a single 24-hour period under a porous gauze patch to the intact and abraded skin of six rabbits. The patches were held in place with surgical adhesive tape and the entire shaved area was covered with a self-adherent wrap of Coban.® After 24 hours, the wrap and patches were carefully removed; excess material was wiped from the skin; and the test areas were evaluated for irritation. Evaluations were also performed at 24, 72 hours and 7 days. Scoring of irritation effects was based on the Draize method in which erythema and edema were evaluated on a grade of 0 to 4 for severity. Categorization of effects under AEHA SOP was based upon the 24- and 72- hour readings.

b. Eye Irritation. Eye irritation studies were performed by administering single 0.1 mL doses of technical grade compound to one eye of each of six rabbits. The opposite eye was left untreated and served as a control. Eyes were examined for gross signs of irritation at 24, 48, 72 hours and 7 days following application. Scoring of irritation effects was based on the Draize method in which the total score for the eye is the sum of all scores obtained for the cornea, iris, and conjunctiva. No gross pathology or histopathology was performed. Categorization of effects under AEHA SOP was based upon the 24-hour reading.

c. Sensitization.

(1) Sensitization studies were performed to determine the potential of the candidate insect repellents for causing sensitization reactions in humans. Female albino Hartley guinea pigs weighing between 375 and 425 gms were used for the tests.

(2) The test procedure was based on the Buehler method. Technical grade test compound in 0.3 mL aliquots was applied on Webril® patches to the shaved flanks of 10 guinea pigs, under

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® Webril is a registered tradename of Kendall Company, Fiber Products Division, Boston, Massachusetts.

occlusion, for 6 hours once per week for 3 weeks. Challenge doses followed a 2-week rest period, following the same procedure, and included five previously untreated control animals. The skin responses were scored at 24 and 48 hours postchallenge application by the Draize method of scoring. Three hours prior to scoring all animals were depilated with NEET® cream and thoroughly washed with warm water and toweled dry.

(3) A positive control group was run concurrently with the test compound and received dinitrochlorobenzene (DNCB) that was applied following the same procedure. Induction was done at 0.1 percent (w/v) in 80 percent ethanol and the challenge at 0.01 percent (w/v) in 80 percent ethanol.

(4) Erythema and/or edema at the challenge site which was greater than that observed on the cage control (naive) animals was considered an allergic response. The percentage of animals exhibiting an allergic response determined the potential and degree of sensitization. If grades of 2 or more are displayed on two or more of the test animals, provided skin grades of less than one are seen in control animals, the test substance was considered to be a sensitizer as defined by this test. If more than one control animal displayed skin grades of one or more, a rechallenge was done using a lower concentration of test substance. A rechallenge was also performed if the test animals produced equivocal responses, and controls produced no response, at a slightly higher concentration.

d. Oral Toxicity. An approximate lethal dose (ALD) study using a small number of animals was performed to determine the minimum lethal oral dose of the test chemical. Single oral graded dosages of technical grade material were given by gavage to young male rats weighing between 175 and 225 g. Just prior to dosing, each rat was weighed to determine dose volume. Following administration of the test compound, rats were examined daily, and any signs of toxicity were recorded. All animals which were alive at the end of the 14-day observation period were sacrificed for gross pathological examination. The ALD of the test substance is the lowest dose that causes death during a 14-day observation period.

e. Photochemical Skin Irritation. A photochemical skin irritation study was performed to determine the potential of the test compound to become chemically reactive as a result of

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exposure to UV irradiation. Studies were performed by administering a single 0.05 mL dose of a 25 percent (w/v) solution of each candidate insect repellent and a 10 percent (w/v) Oil of Bergamot solution (positive control) in 95 percent ethyl alcohol to the intact shaved skin of six rabbits. Five minutes after application, the rabbits were exposed to ultraviolet (UV) light (365 um) for 30 minutes at a distance of 10-15 cm. Following UV exposure of the rabbits, 0.05 mL of test chemical, positive control and diluent were applied to additional skin areas to serve as unirradiated control sites. Application areas were checked for skin irritation at 24, 48, and 72 hours. Scoring of irritation effects was based on the Draize Method for erythema and edema. A positive photochemical skin reaction is characterized by the development of moderate erythema and edema reactions during the 72- hour period following irradiation.

f. In Vitro Mutagenicity Assays. Selected candidate chemical insect repellents were evaluated for mutagenic activity in the Ames Salmonella/Microsome Plate assay. The Ames test was used with Salmonella typhimurium indicator strains TA-1535, TA-1537, TA-1538, TA-98 and TA-100. The assays were conducted in duplicate in the presence and absence of metabolic activation. The assays were conducted at doses that had been selected on a preliminary toxicity test with the strain TA-100. For the actual assay, doses were selected with the highest dose exhibiting $\leq$ 90 percent toxicity and ranged over a series of 5 doses ranging from 5 ul/plate to 50 ul/plate.

6. RESULTS.

a. Skin Irritation. A tabular presentation of the skin irritation data developed on the subject candidate insect repellents follows:

Tox Eval No's. 75-51-0623 through 0630-89, June 1989

TABLE 1. SKIN IRRITATION DATA

Project No.	Compound	Results	USAEHA Category Appendix C
75-51-0623-89	AI3-38306	Irritation scores ranged from 1 to 0 with a mode of 0	I
75-51-0624-89	AI3-38315	Very mild irritation with scores ranging from 1 to 0 with a mode of 0.	I
75-51-0625-89	AI3-38530	Very mild irritation with irritation scores ranging from 1 to 0 with a mode of 0.	II
75-51-0626-89	AI3-39041	No skin irritation	I
75-51-0627-89	AI3-39076	Very mild irritation with scores ranging from 2 to 0 with a mode of 1	II
75-51-0628-89	AI3-39077	Very mild irritation with scores ranging from 2 to 0 with a mode of 1	II
75-51-0629-89	AI3-39078	Very mild irritation with scores ranging from 1 to 0 with a mode of 0	II
75-51-0630-89	AI3-39085	Moderate to severe irritation with scores ranging from 2 to 4 with a mode of 2.	III

b. Eye Irritation. A tabular presentation of the eye irritation data developed on the subject candidate insect repellents follows:

TABLE 2. EYE IRRITATION DATA

Project No.	Compound	Results	USAEHA Category Appendix D
75-51-0623-89	AI3-38306	Moderate opacity with moderate to severe conjunctiva irritation; not resolved within 7 days.	E
75-51-0624-89	AI3-38315	Mild to moderate opacity with iritis and moderate conjunctiva irritation not resolved within 7 days.	E
75-51-0625-89	AI3-38530	No effects	A
75-51-0626-89	AI3-39041	Very slight opacity and mild conjunctiva irritation; resolved within 7 days.	C
75-51-0627-89	AI3-39076	Slight opacity and mild conjunctiva irritation; resolved within 7 days.	C
75-51-0628-89	AI3-39077	Slight opacity and conjunctiva irritation; resolved within 7 days.	B
75-51-0629-89	AI3-39078	No effects	A
75-51-0630-89	AI3-39085	Slight to mild conjunctiva irritation; resolved within 7 days.	B

c. Photochemical Skin Irritation. A tabular presentation of the photochemical skin irritation data developed on the subject repellents follows:

Project No.	Compound	Results
75-51-0623-89	AI3-38306	Positive photo irritant response
75-51-0624-89	AI3-38315	No photo irritation response
75-51-0625-89	AI3-38530	No photo irritation response
75-51-0626-89	AI3-39041	No photo irritation response
75-51-0627-89	AI3-39076	No photo irritation response
75-51-0628-89	AI3-39077	No photo irritation response
75-51-0629-89	AI3-39078	No photo irritation response
75-51-0630-89	AI3-39085	No photo irritation response

d. Oral Toxicity Studies. A tabular presentation of the oral ALDs developed on the subject repellents follows:

TABLE 3. APPROXIMATE LETHAL DOSE (ALD)

Project No.	Compound	ALD	Signs
75-51-0623-89	AI3-38306	Not done	---------
75-51-0624-89	AI3-38315	3333 mg/kg	Labored breathing, lethargy
75-51-0625-89	AI3-38530	>3333 mg/kg	Ataxia
75-51-0626-89	AI3-39041	987 mg/kg	Ataxia, prostration, gasping
75-51-0627-89	AI3-39076	>3333 mg/kg	No signs
75-51-0628-89	AI3-39077	>3333 mg/kg	No signs
75-51-0629-89	AI3-39078	>3333 mg/kg	No signs
75-51-0630-89	AI3-39085	195 mg/kg	Rough pelt, very rapid response to lethal dosages.

e. Sensitization. The challenge doses of the candidate insect repellents did not produce a sensitization reaction. A tabular presentation of the results from the sensitization studies on the subject repellents follows:

Project No.	Compound	Results
75-51-0623-89	AI3-38306	- Not done -
75-51-0624-89	AI3-38315	No sensitization reaction
75-51-0625-89	AI3-38530	No sensitization reaction
75-51-0626-89	AI3-39041	No sensitization reaction
75-51-0627-89	AI3-39076	Positive sensitization reaction
75-51-0628-89	AI3-39077	Positive sensitization reaction
75-51-0629-89	AI3-39078	No sensitization reaction
75-51-0630-89	AI3-39085	- Not done -

f. In Vitro Mutagenicity Assays.

(1) No tests for mutagenicity activity were conducted on AI3-38306, AI3-38315, AI3-39077, and AI3-39085 because of deleterious reactions in one or more of the previous tests.

(2) The candidate repellents AI3-38530, AI3-39041, AI3-39076 and AI3-39078 did not exhibit mutagenic activity with tester stains TA-1535, TA-1537, TA-1538, TA-98 and TA-100. These data suggest that the four compounds are devoid of mutagenic activity at doses up to 50 uL per plate both in the presence and absence of a metabolic activation system.

7. DISCUSSION.

a. The purpose of the Topical Hazard Evaluation Program (THEP) is to investigate relevant health endpoints of proposed insect repellent chemicals. Data from these studies are used to recommend the course of further entomological and toxicological evaluations with subject chemicals.

b. The Armed Forces Pest Management Board (AFPMB) has recently recommended the review and evaluation of compounds that showed outstanding entomologic efficacy in the initial sleeve test (Category I Priority Chemicals) but had previously been

disapproved for testing based on the potential for causing eye irritation. The results from a previously reported study with two of these compounds are shown in Table 4.

TABLE 4. RESULTS OF PREVIOUS STUDIES (Appendix C reference 7)

Compound	Skin Irritation Category	Eye Irritation Category
AI3-38306	II	E
AI3-38315	II	E

e. The results from the current animal toxicity studies are summarized in Table 5.

TABLE 5. RESULTS OF PRESENT STUDIES

Compound	Skin Irritation AEHA Category	Eye Irritation AEHA Category	Sensitization	Photo Irritation	Oral ALD mg/kg	AMES
AI3-38306	I	E	Not done	Positive	Not done	Not done
AI3-38315	I	E	Negative	Negative	3333	Not done
AI3-38530	II	A	Negative	Negative	>3333	Negative
AI3-39041	I	C	Negative	Negative	987	Negative
AI3-39076	II	C	Positive	Negative	>3333	Negative
AI3-39077	II	B	Positive	Negative	>3333	Not done
AI3-39078	II	A	Negative	Negative	>3333	Negative
AI3-39085	III	B	Not done	Negative	195	Not done

e. The results from the current animal sensitization studies showed that two of the eight test compounds AI3-39076 and AI3-39077 have some potential for causing an allergic response in man. A positive result from a sensitization test is a prime basis for rejecting a material as a topical insect repellent (Appendix A reference 2).

f. The use of eye irritation responses as a criterion of acceptance for candidate insect repellents has been under discussion recently by various committees and organizations. The THEP program of USAEHA has now modified it's position of using moderate irritation injury as a basis for rejection to that of acceptance of compounds where eye injury is resolved within 7 days. This definition is found in Category C. However, even using the modified criterion, the present studies reaffirm the original evaluation of non-acceptance for AI3-38306 and AI3-38315.

g. The primary objective of short term mutagenicity testing, i.e. Ames, is to indicate with a simple test the potential for a chemical to cause genetic alterations. The test is normally conducted on those compounds that show promise in entomological testing and demonstrate a low order of toxicity. The present results indicated no mutagenic activity with four test chemicals.

h. The results from the overall battery of biological tests showed that the candidate insect repellents AI3-38530, AI3-39041, and AI3-39078 produced relatively unremarkable toxicological responses.

8. RECOMMENDATIONS.

a. Approve compounds AI3-38530, AI3-39041 and AI3-39078 for further entomological testing.

b. Based on the demonstrated skin/eye or photo irritation responses and/or sensitization potential, it is recommended that the following compounds be <u>disapproved</u> for further entomological testing. These compounds are AI3-38306, AI3-38315, AI3-39076, AI3-39077 and AI3-39085. Consideration should be given to the toxicological reevaluation of these chemicals if the AFPMB considers them to be superior and/or especially efficacious insect repellents.

MAURICE H. WEEKS
Chief, Toxicology Division

APPENDIX A

REFERENCES

1. Toxicology Division Standing Operating Procedure, USAEHA, 1982.

2. Toxicology Division, Topical Hazard Evaluation Program Procedural Guide, October 1985.

3. "Ames Bacterial/Microsomal Plate Incorporation Assay" of insect repellent AI3-39078A, Project 75-51-0629-89. Toxikon Project #87G-103, Toxikon Corporation, 225 Wildwood Avenue, Woburn, MA 01801, Nov 11, 1987.

4. "Ames Bacterial/Microsomal Plate Incorporation Assay" of insect repellent AI3-39076, Project 75-51-0627-89. Toxikon Project #87G-0110, Toxikon Corporation, 225 Wildwood Avenue, Woburn, MA 01801.

5. "Ames Bacterial/Microsomal Plate Incorporation Assay" of insect repellent AI3-39041, Project 75-51-0626-89. Toxikon Project #87G-0102, Toxikon Corporation, 225 Wildwood Avenue, Woburn, MA 01801.

6. "Ames Bacterial/Microsomal Plate Incorporation Assay" of insect repellent AI3-38530, Project 75-51-0625-89. Toxikon Project 87G-0101, Toxikon Corporation, 225 Wildwood Avenue, Woburn, MA 01801.

7. USAEHA report "Topical Hazard Evaluation Program of Candidate Insect Repellents" AI3-38305, AI3-38306, AI3-3813, AI3-38314 and AI3-38315, April 1983.

Tox Eval No's. 75-51-0623 through 0630-89, June 1989

APPENDIX B

ANALYTICAL QUALITY ASSURANCE

The Analytical Quality Assurance office certifies the following:

a. These studies were conducted in accordance with:

(1) Standing Operating Procedures Developed by the Toxicology Division, USAEHA.

(2) Title 21, Code of Federal Regulations (CFR), 1986 rev, Part 58, Good Laboratory Practice for Nonclinical Laboratory Studies.

b. Facilities were inspected during its operational phase to ensure compliance with paragraph a above.

c. The information presented in this report accurately reflects the raw data generated during the course of conducting these studies.

Timothy L. Fisher

TIMOTHY L. FISHER
Chief, Analytical Quality
Assurance Division

APPENDIX C

TOPICAL HAZARD EVALUATION PROGRAM
DEFINITIONS OF CATEGORIES OF COMPOUNDS BEING CONSIDERED FOR ACUTE SKIN APPLICATION

CATEGORY I - Compounds producing no primary irritation of the intact skin or no greater than mild primary irritation of the skin surrounding an abrasion. (INTERPRETATION: No restriction for acute application to the human skin.)

CATEGORY II - Compounds producing mild primary irritation of the intact skin and the skin surrounding an abrasion. (INTERPRETATION: Should be used only on human skin found by examination to have no abrasions or may be used as a clothing impregnant.)

CATEGORY III - Compounds producing moderate primary irritation of the intact skin and the skin surrounding an abrasion. (INTERPRETATION: Should not be used directly on the skin without a prophetic patch test having been conducted on humans to determine irritation potential to human skin. May be used without patch testing, with extreme caution, as clothing impregnants. Compound should be resubmitted in the form and at the intended use concentration so that its irritation potential can be reexamined using other test techniques on animals.)

CATEGORY IV - Compounds producing moderate to severe primary irritation of the intact skin and of the skin surrounding an abrasion. (INTERPRETATION: Should be resubmitted for testing in the form and at the intended use concentration. Upon resubmission, its irritation potential will be reexamined using other test techniques on animals, prior to possible prophetic patch testing in humans, at concentrations which have been shown not to produce primary irritation in animals.)

CATEGORY V - Compounds impossible to classify because of staining of the skin or other masking effects owing to physical properties of the compound or compounds producing necrosis, vesiculation, or eschars. (INTERPRETATION: Not suitable for use in humans.)

APPENDIX D

TOPICAL HAZARD EVALUATION PROGRAM
DEFINITIONS OF CATEGORIES OF EYE EFFECTS

EYE CATEGORIES:

CATEGORY A - Compounds noninjurious to the eye. (INTERPRETATION: Irritation of human eyes is not expected if the compound should accidentally get into the eyes, provided it is washed out as soon as possible.)

CATEGORY B - Compounds producing mild injury to the cornea. (INTERPRETATION: Should be used with caution around eyes.)

CATEGORY C - Compounds producing mild injury to the cornea, and in addition some injury to the conjunctiva. Injury resolved within 7 days. INTERPRETATION: Should be used with caution around the eyes and mucosa (e.g., nose and mouth).

CATEGORY D - Compounds producing moderate injury to the cornea. (INTERPRETATION: Should be used with extreme caution around the eyes and mucosa.)

CATEGORY E - Compounds producing moderate injury to the cornea, and in addition producing some injury to the conjunctiva that is not resolved within 7 days. (INTERPRETATION: Should be used with extreme caution around the eyes and mucosa.)

CATEGORY F - Compounds producing severe injury to the cornea and to the conjunctiva. INTERPRETATION: Should be used with extreme caution, it is recommended that use be restricted to areas other than the face.