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UNITED STATES ARMY ENVIRONMENTAL HYGIENE AGENCY

ABERDEEN PROVING GROUND, MD 21010-5422

TOPICAL HAZARD EVALUATION PROGRAM
OF
CANDIDATE INSECT REPELLENT A13-39053a
U.S. DEPARTMENT OF AGRICULTURE PROPRIETARY CHEMICAL
STUDY NO. 75-51-0473-87
MAY 1987

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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

8 July 1987

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

SUBJECT: Topical Hazard Evaluation Program of Candidate Insect Repellent AI3-39053a, U.S. Department of Agriculture Proprietary Chemical, Study No. 75-51-0473-87, May 1987

EXECUTIVE SUMMARY

The purpose and recommendations of the enclosed report follow:

a. Purpose. To provide guidance for further entomological testing of the Candidate Insect Repellent AI3-39053a by means of laboratory animal studies using Sprague-Dawley rats, New Zealand White rabbits, and Albino-Hartley guinea pigs. In addition, these data may be useful in developing preliminary safety guidelines for handling this compound.

b. Recommendations. Based on professional scientific judgement, the following recommendations are offered.

(1) AI3-39053a should be approved for more extensive entomological and toxicological testing.

(2) Ethanol solutions of chemicals AI3-39053a may cause skin irritation in some sensitive individuals. Personnel experiencing this reaction should wash off the solution as soon as possible.

FOR THE COMMANDER:

Encl

W. JOE THOMPSON
Colonel, MC
Director, Occupational and Environmental Health

CF:
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Dir, Advisory Cen on TOX, NRC (2 cy) (w/encl)
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USDA, ARS (Dr. Terrence McGovern) (w/encl)
USDA, ARS-Southern Region (3 cy) (w/encl)
USDA, ARS-Southern Region (COL Moussa) (w/encl)
Cdr, USAMRDC, ATTN: SGRD-DPM (COL Reinert) (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
OF
CANDIDATE INSECT REPELLENT AI3-39053a
U.S. DEPARTMENT OF AGRICULTURE PROPRIETARY CHEMICAL
STUDY NO. 75-51-0473-87
MAY 1987

1. AUTHORITY.

a. Letter, U.S. Department of Agriculture-Agricultural Research Service, Northeastern Region, Beltsville Agricultural Research Service, Beltsville, Maryland, 03 September 1986.

b. Letter, U.S. Department of Agriculture-Agricultural Research Service, Southern Region, Insects Affecting Man and Animals Research Laboratory, Gainesville, Florida, 06 December 1983.

c. Memorandum of Understanding between the US Army Environmental Hygiene Agency; the US Army Health Services Command; the Department of The Army, Office of The Surgeon General; the Armed Forces Pest Control Board; and the US Department of Agriculture, Agricultural Research, Science and Education Administration; titled, Coordination of Biological and Toxicological Testing of Pesticides, effective 23 January 1979.

2. PURPOSE. The purpose of this program was to provide guidance for further entomological testing of the Candidate Insect Repellent AI3-39053a, U.S. Department of Agriculture (USDA) Proprietary Chemical.

3. MATERIALS AND METHODS. *+

a. Testing for primary skin irritation, photochemical skin irritation, and primary eye irritation was conducted using New Zealand White rabbits from either Hazleton-Dutchland Laboratories, Denver, Pennsylvania, or

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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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Buckshire Farms, Perkasie, Pennsylvania. Albino-Hartley guinea pigs from Hazleton-Dutchland Laboratories, Denver, Pennsylvania, were used for sensitization studies, and Sprague-Dawley rats from Charles River Laboratories, Wilmington, Massachusetts, were used for determination of a Approximate Lethal Dose (ALD) (reference 7b).

b. The subject chemical tested in these studies was synthesized by Dr. Terrence P. McGovern, Organic Chemical Synthesis Laboratory, USDA, Beltsville, Maryland.

4. SUMMARY OF FINDINGS. A tabular presentation of animal toxicity data developed by this Agency on the Candidate Insect Repellent AI3-39053a follows:

TABLE. PRESENTATION OF DATA

Test	Results	Interpretation
SKIN IRRITATION STUDIES		
Rabbits		
Single 24-hour application to intact and abraded skin of New Zealand White rabbits. 0.5 mL technical grade chemical applied to each of six rabbits.	Chemical AI3-39053a did not cause skin irritation	USAEHA Category I (ref App A)
EYE IRRITATION STUDIES		
Rabbits		
Single 24-hour application of 0.1 mL technical grade chemical to one eye of each of six New Zealand White rabbits.	Chemical AI3-39053a was noninjurious to the eye of rabbits	USAEHA Category A (ref App A)
APPROXIMATE LETHAL DOSE (ALD)		
Oral		
Rats (male)-no diluent	ALD-1480 mg/kg Signs of toxicity were lethargy, salivation and death.	This chemical is mildly toxic by ingestion.

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Test	Results	Interpretation
PHOTOCHEMICAL SKIN IRRITATION STUDIES		
Rabbits		
A single 0.05 mL application of a 25 percent (w/v) solution of the chemical and 10 percent (w/v) Oil of Bergamot solution (positive control) in 95 percent ethyl alcohol were applied to the intact skin of six rabbits. Five minutes after application, the rabbits were exposed to ultraviolet (UV) light (365 nm) for 30 minutes at a distance of 15 cm.	A 25-percent solution of the tested chemical in ethanol did not cause a photochemical irritation reaction under test conditions. However, ethanol solutions of the test chemical produced mild primary irritation of the skin at the sites of application, both irradiated and unirradiated	The tested chemical did not cause a photochemical irritation reaction under test conditions and is not expected to cause photochemical irritation in humans.
Control		
Following UV exposures of the rabbits, 0.05 mL of test chemical, positive control (oil of Bergamot), and diluent were applied to additional skin areas to serve as unirradiated control sites. Application areas were checked for skin irritations at 24, 48 and 72 hours.	Positive control application and irradiation caused greater irritant effects than in unirradiated skin areas.	
SENSITIZATION STUDIES		
Test conducted according to the method of Buehler, (ref 7b). Technical grade test compounds in the amount of 0.2 ml applied on Webril™ patches once per week for 3 weeks. Challenged following a 2-week rest with same application.	Guinea Pigs receiving and challenged with AI3-39053a did not show any sensitization reactions. Positive control (DNCB) produced a strong sensitization reaction in 10/10 guinea pigs.	Test compound to AI3-39053a did not exhibit any sensitization potential in guinea pigs and is not expected to cause a sensitization reaction in humans

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Test	Results	Interpretation
MUTAGENICITY PLATE ASSAY**		
AI3-39053a was examined for genetic activity in a series of in vitro microbial assays employing Salmonella indicator organisms. The compound was tested directly and in the presence of liver microsomal enzyme preparations from Aroclor-1254™ induced rats.	The test material was toxic to strains TA-98 and TA-100 at 25 µL and 50 µL doses. It was also slightly toxic at 5 and 10 µL doses for the strains TA-1535 and TA-1537 and at 10 µL doses for TA-1538 and TA-100.	AI3-39053a is not considered mutagenic under these test conditions.
The dose range employed for the evaluation of this compound was from .010 µL to 1 µL per plate.	The results of the test in the presence and absence of a rat liver activation system were negative.	
Five strains of Salmonella typhimurium, TA-1535, TA-1537, TA-1538, TA-98, and TA-100 were used in evaluating mutagenic potential.		

™Aroclor is a registered trademark of the Monsanto Chemical Co., St. Louis, MO.

** Work performed under contract by Hazelton Laboratories America, Inc., Kensington, Maryland. HLA Project No. 20988, Genetics Assay No. 9383.

5. CONCLUSION. Chemica AI3-39053a produced no irritation to the intact and abraded skin of rabbits (Appendix A, Category I). It was not a photoirritant within the limits of our test and did not cause injury to the eyes of rabbits (Appendix A, Category A). The ALD in male rates was 1480 mg/kg and is considered mildly toxic upon ingestion. Ethanol solutions may cause mild skin irritation in sensitive individuals. These studies were monitored by the Analytical Quality Assurance Office (see Appendix B).

6. RECOMMENDATIONS. Based on professional scientific judgment, the following recommendations are offered.

a. Recommend that chemical AI3-39053a be approved for further entomological testing.

b. Ethanol solutions of chemical AI3-39053a may cause skin irritation in some sensitive individuals. Personnel experiencing this reaction should wash off the solution as soon as possible.

7. REFERENCES.

a. Toxicology Division Standing Operating Procedures, US Army Environmental Hygiene Agency (USAEHA), 1982.

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

c. "Mutagenicity Evaluation of AI3-39053a, in the Ames Salmonella/Microsome Reverse Mutation Assay", Contract No. DAAD05-86-M-L723, Hazelton Laboratories America, Inc., January 1987.

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SGT, USA
Animal Care Specialist

Maurice H. Weeks

MAURICE H. WEEKS
Chief, Toxicology Division

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APPENDIX A

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 on humans.)

EYE CATEGORIES:

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.

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

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

D. Compounds producing moderate injury to the cornea. INTERPRETATION: To be used with extreme caution around eyes. Keep away from ocular area.

E. Compounds producing moderate injury to the cornea and, in addition, producing some injury to the cornea. INTERPRETATION: To be used with extreme caution around eyes and mucosa (e.g., nose and mouth). Keep away from ocular areas.

F. Compounds producing severe injury to the cornea and conjuctiva. INTERPRETATION: To be used with extreme caution, recommended that use be restricted to areas other that the face.

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APPENDIX B

ANALYTICAL QUALITY ASSURANCE

The Analytical Quality Assurance Office certifies the following with regard to this study:

a. This study was 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 the study.

TIMOTHY L. FISHER
Chief, Analytical Quality
Assurance Office