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ARMY ENVIRONMENTAL HYGIENE AGENCY ABERDEEN PROVING GR--ETC F/8 6/80  
TOPICAL HAZARD EVALUATION PROGRAM OF CANDIDATE INSECT REPELLENT--ETC(U)  
FEB 81 M J TOPPER, M H WEEKS  
USAEHA-75-51-0144-81

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**UNITED STATES ARMY  
ENVIRONMENTAL HYGIENE  
AGENCY**

**ABERDEEN PROVING GROUND, MD 21010**

TOPICAL HAZARD EVALUATION PROGRAM  
OF CANDIDATE INSECT REPELLENT  
AI3-37443a  
US DEPARTMENT OF AGRICULTURE PROPRIETARY CHEMICAL  
STUDY NO. 75-51-0144-81  
SEPTEMBER 1978 - NOVEMBER 1980

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20. ABSTRACT (Continue on reverse side if necessary and identify by block number) Preliminary hazard evaluation of AI3-37443a was performed by means of laboratory animal studies using rats, rabbits, and guinea pigs. The technical grade chemical did not cause skin, eye, or photo irritation. It did not prove to be a skin sensitizer or to be acutely toxic by ingestion. It was recommended that the chemical be approved for further testing as a candidate insect repellent.			

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 ABERDEEN PROVING GROUND, MARYLAND 21010

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5 FEB 1981

SUBJECT: Topical Hazard Evaluation Program of Candidate Insect Repellent  
 AI3-37443a, US Department of Agriculture Proprietary Chemical,  
 Study No. 75-51-0144-81, September 1978 - November 1980

Executive Secretary  
 Armed Forces Pest Management Board  
 Forest Glen Section, WRAMC  
 Washington, DC 20012

A summary of the pertinent findings and recommendations of the inclosed report follows:

Preliminary hazard evaluation of AI3-37443a was performed by means of laboratory animal studies using rats, rabbits, and guinea pigs. The technical grade chemical did not cause skin, eye, or photo irritation. It did not prove to be a skin sensitizer or to be acutely toxic by ingestion. It was recommended that the chemical be approved for further testing as a candidate insect repellent.

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

TOPICAL HAZARD EVALUATION PROGRAM  
OF CANDIDATE INSECT REPELLENT  
AI3-37443a  
US DEPARTMENT OF AGRICULTURE PROPRIETARY CHEMICAL  
STUDY NO. 75-51-0144-81  
SEPTEMBER 1978 - NOVEMBER 1980

1. AUTHORITY.

a. Letter, US Department of Agriculture - Agricultural Research Service, Southern Region, Insects Affecting Man Research Laboratory, Gainesville, FL, 13 September 1978.

b. 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. REFERENCE. Toxicology Division Procedural Guide, US Army Environmental Hygiene Agency (USAEHA), 1972, revised 1976.

3. PURPOSE. The purpose of this program is to provide guidance for further entomological testing of candidate insect repellent AI3-37443a.

4. SUMMARY OF FINDINGS. Hazard evaluation of the candidate repellent AI3-37443a, US Department of Agriculture (USDA) Proprietary Chemical, was conducted by this Agency using New Zealand White rabbits for skin and eye studies, Hartley guinea pigs for a skin sensitization study, and Sprague-Dawley rats for determination of oral toxicity. A tabular presentation of animal toxicity data developed in this Agency follows:\*†

\* In conducting the studies described in this report, the investigators adhered to the "Guide for the Care and Use of Laboratory Animals," US Department of Health, Education and Welfare Publication No. (NIH) 74-23, revised 1978.

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

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Study No. 75-51-0144-81, Sep 78 - Nov 80

TABLE. PRESENTATION OF DATA

<u>Test</u>	<u>Results</u>	<u>Interpretation</u>
<u>SKIN IRRITATION STUDIES</u>		
<u>Rabbits</u>		
Single 24-hour application to intact and abraded skin of New Zealand White rabbits.	Chemical A13-37443a did not cause any irritation of the intact skin or of the skin surrounding an abrasion.	USAEHA Category I (ref Appendix A).
0.5 mL technical grade chemical applied to each of six rabbits.	Details are shown in Appendix B.	
<u>EYE IRRITATION STUDIES</u>		
<u>Rabbits</u>		
Single 24-hour application of 0.1 mL technical grade chemical to one eye of each of six New Zealand White rabbits.	Chemical A13-37443a did not cause any irritation to the eyes of rabbits. Details are shown in Appendix C.	USAEHA Category A (ref Appendix A).
<u>APPROXIMATE LETHAL DOSE (ALD)</u>		
<u>Oral</u>		
Rats (male) - no diluent	ALD = 2900 mg/Kg	Presents little lethal hazard from accidental ingestion.

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Test	Results	Interpretation
<u>PHOTOCHEMICAL SKIN IRRITATION STUDIES</u>		
<u>Rabbits</u>		
A single 0.05 mL application of a 25 percent (w/v) solution of each chemical and a 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 UV light (365 nm) for 30 minutes at a distance of 10-15 cm.	A 25 percent solution of AI3-3743a in ethanol did not cause a photochemical irritation reaction under test conditions.  Ethanol solution of AI3-37443a caused moderate erythematous and edematous reactions on both non-UV and UV skin sites.	Chemical AI3-37443a did not cause a photochemical irritation reaction under test conditions and is not expected to cause a photochemical irritation in humans.
<u>Control</u>		
Following UV exposures 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.	Positive control application and irradiation caused greater irritant effects than in unirradiated skin areas. Details are shown in Appendix D.	Ethanol solutions of this chemical may cause moderate skin irritation in sensitive individuals. Persons experiencing this reaction should wash off the solution as soon as possible.

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Test	Results	Interpretation
<u>SENSITIZATION STUDIES</u>		
<u>Guinea Pigs (Male)</u>		
Intradermal injection of 0.1 mL of a 0.1 percent solution (w/v) of AI3-37443a or of dinitrochlorobenzene (DNCB)* in a mixture containing 1 volume of propylene glycol and 29 volumes of saline.	Challenge doses of AI3-37443a did not produce a sensitization reaction.	Chemicals AI3-37443a did not produce sensitization reactions under test conditions and is not expected to produce sensitization reactions in man.
Ten test guinea pigs for each chemical were given 10 sensitizing doses over a 3-week period. After 2 weeks rest, they were challenged with ID injections of each test chemical.	Challenge dose of DNCB produced a marked sensitization reaction in 10 out of 10 guinea pigs. Details are shown in Appendix E.	DNCB produced a marked reaction, indicating the guinea pigs respond to sensitizing agents.

\* A known skin sensitizer.

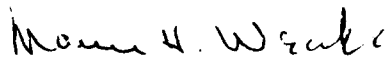
Study No. 75-51-0144-81, Sep 78 - Nov 80

5. CONCLUSION. Technical grade chemical AI3-37443a did not cause any skin, eye, or photo irritation, no sensitization reaction, and did not prove to be an acute ingestion hazard.

6. RECOMMENDATION. Under the provisions of the Memorandum of Understanding (paragraph 1b), it is recommended that AI3-37443a be approved for further testing as a candidate insect repellent. Persons experiencing irritation when working with ethanol solutions of AI3-37443a should wash the site with copious amounts of water.



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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 and, in addition, producing necrosis, vesiculation, and/or eschars. (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. (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.

D. Compounds producing moderate injury to the cornea. INTERPRETATION: Should be used with extreme caution around the eyes.

E. Compounds producing moderate injury to the cornea, and in addition producing some injury to the conjunctiva. INTERPRETATION: Should be used with extreme caution around the eyes and mucosa.

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.

APPENDIX B

COMPOUND: AI3-37443a - USDA Proprietary Chemical		TOXICITY CATEGORY		Response		Total Score	Comments
PRIMARY SKIN EFFECTS NEW ZEALAND WHITE RABBITS		AEHA I		Rabbit No.			
CONDITIONS - 0.5 mL of technical grade chemical applied under 2" by 2" gauze patch for 24 hours.		477	478	479	480	481	482
Time of Observation (Hours)		Response					
		477	478	479	480	481	482
<u>Erythema &amp; Eschar</u>							
24	Intact Skin		1		2		0
72	Intact Skin		0		0		0
24	Abraded Skin	1		2		1	
72	Abraded Skin	0		1		0	
							Subtotal
							3
							0
							5
							1
							<u>9</u>
<u>Edema Formulation</u>							
24	Intact Skin		0		0		0
72	Intact Skin		0		0		0
24	Abraded Skin	1		0		0	1
72	Abraded Skin	0		0		0	0
							Subtotal
							1
							<u>10</u>

APPENDIX C

COMPOUND: AI3-37443a - USDA Proprietary Chemical		USAEHA STUDY No. 75-51-0144-81					
ACUTE EYE EFFECTS NEW ZEALAND WHITE RABBITS		TOXICITY CATEGORY	CONDITIONS - 0.1 mL of chemical instilled in conjunctival sac of left eye of each rabbit. No rinse.				
Time of Reading	Structure	AEHA A	Mean Score	Comments			
					Scores		
Hrs-Days		324	325	326	327	328	329
24	cornea	0	0	0	0	0	0
	iris	0	0	0	0	0	0
	conjunctivae	0	0	0	0	1	0
48	cornea	0	0	0	0	0	0
	iris	0	0	0	0	0	0
	conjunctivae	0	0	0	0	0	0
72	cornea	0	0	0	0	0	0
	iris	0	0	0	0	0	0
	conjunctivae	0	0	0	0	0	0
7-days	cornea						
	iris						
	conjunctivae						

APPENDIX D

COMPOUND: AI3-37443a - USDA Proprietary Chemical USAEHA Study No. 75-51-0144-81

**PHOTO CHEMICAL IRRITATION NEW ZEALAND WHITE RABBITS**

Comments: Moderately irritating in 95% ethyl alcohol with or without UV exposure.

Procedure: 0.05 mL of a 25% solution of compound in 95% ethanol are applied to two sites on back of rabbit. One compound is exposed to UV light for 30 minutes. 0.05 mL of a 10% solution of bergamot oil is a positive control.

Observation Time	Mean Skin Irritation Score							
	Test Compound		Positive Control		Positive Control			
	UV Exposure	No UV Exposure	UV Exposure	No UV Exposure	No UV exposure	Edema		
24 Hours	Erythema 2.0	Edema 2.5	Erythema 2.0	Edema 1.8	Erythema 1.8	Edema 1.3	Erythema 1.0	Edema 0.3
48 Hours	2.0	1.7	1.8	1.0	1.7	0.7	0.2	0.0
72 Hours	2.0	1.3	2.0	1.2	1.8	0.5	0.2	0.0
Total Mean Irritant Responses	2.0	1.8	1.9	1.7	1.8	0.8	0.5	0.1

APPENDIX E

COMPOUND: AI3-37443a, USDA Proprietary Chemical		USAEHA STUDY NO. 75-51-0144-81			
GUINEA PIG SENSITIZATION MALE HARTLEY STRAIN		Substance: Injected 0.1 mL intradermally of a 3% suspension of AI3-37443a			
		Identify: AI3-37443a			
		Positive Control: Dinitrochlorobenzene			
Scoring Time 24 hours	Mean Body Wt (G)		Mean Irritation Scores		Comments
	Initial	Final	Diluent Initial	Test Compound Initial	
Test Compound	487 + 48	713 + 72	0.0	1.8	1.8
Positive Control	491 + 29	736 + 56	0.0	1.8	356
Test Compd 48 hours	Mean Body Wt (G)		Mean Irritation Scores		Final Scores >100 - Strong Sensitizing 25-100 - Mild Sensitizing <25 - No Sensitizing
	Initial	Final	Diluent Initial	Test Compound Initial	
Test Compound	---	---	0	0.4	0.6
Positive Control	---	---	0	5	272

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