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ARMY ENVIRONMENTAL HYGIENE AGENCY ABERDEEN PROVING GR--ETC F/S 6/20
TROPICAL HAZARD EVALUATION PROGRAM OF CANDIDATE INSECT REPELLEN--ETC(U)
FEB 81 M J TOPPER, M H WEEKS
USAEHA-75-51-0134-81

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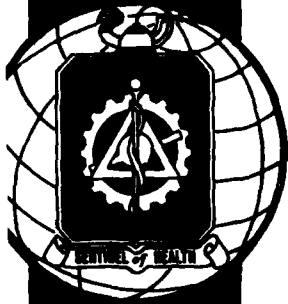
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**UNITED STATES ARMY
ENVIRONMENTAL HYGIENE
AGENCY**

ABERDEEN PROVING GROUND, MD 21010

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TOPICAL HAZARD EVALUATION PROGRAM
OF CANDIDATE INSECT REPELLENT AI3-37429-B,
US DEPARTMENT OF AGRICULTURE PROPRIETARY CHEMICAL,
~~STUDY NO. 75-51-0134-81~~
SEPTEMBER 1978 - NOVEMBER 1980

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20. ABSTRACT (Continue on reverse side if necessary and identify by block number) Preliminary hazard evaluations of the candidate insect repellent AI3-37429-a was performed by means of laboratory animal studies using rats, rabbits, and guinea pigs. The technical grade chemical showed a potential for producing mild primary irritation of the intact skin and the skin surrounding an abrasion, causing mild injury to the cornea and, in addition, some injury to the conjunctiva, and some skin irritation from ethanol solutions. It caused no other irritation reactions from photochemical or sensitization testing and does not present an acute ingestion hazard. It is recommended that AI3-37429-a,			

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20. ABSTRACT (continued)

→ US Department of Agriculture Proprietary 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 CPT Topper/pm/AUTOVON
ABERDEEN PROVING GROUND, MARYLAND 21010 584-3980

11 FEB 1981

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SUBJECT: Topical Hazard Evaluation Program of Candidate Insect Repellent
AI3-37429-a, US Department of Agriculture Proprietary Chemical,
Study No. 75-51-0134-81, September 1978 - November 1980

Executive Secretary
Armed Forces Pest Management Board
Forest Glen Section, WRAMC
Washington, DC 20021

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

Preliminary hazard evaluations of the candidate insect repellent AI3-37429-a
was performed by means of laboratory animal studies using rats, rabbits, and
guinea pigs. The technical grade chemical showed a potential for producing
mild primary irritation of the intact skin and the skin surrounding an abrasion,
causing mild injury to the cornea and, in addition, some injury to the
conjunctiva, and some skin irritation from ethanol solutions. It caused no
other irritation reactions from photochemical or sensitization testing and
does not present an acute ingestion hazard. It is recommended that AI3-37429-a,
US Department of Agriculture Proprietary Chemical, be approved for further
testing as a candidate insect repellent.

FOR THE COMMANDER:

John F. Mazur

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

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TOPICAL HAZARD EVALUATION PROGRAM
OF CANDIDATE INSECT REPELLENT AI3-37429-a
US DEPARTMENT OF AGRICULTURE PROPRIETARY CHEMICAL
STUDY NO. 75-51-0134-81
SEPTEMBER 1978 - NOVEMBER 1980

1. AUTHORITY.

a. Letter, US Department of Agriculture - Agricultural Research Service, Southern Region, Insects Affecting Man Research Laboratory, Gainesville, Florida, 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 AI3-37429-a.

4. SUMMARY OF FINDINGS. Hazard evaluation of the candidate repellent AI3-37429-a 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) 78-23, 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. 75-51-0134-81, 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. 0.5 mL technical grade chemical applied to each of six rabbits.	Chemical AI3-37429-a produced mild erythematous irritation of the intact skin and of the skin surrounding an abrasion without edema. (See Appendix B for details.)	USAEHA Category II (ref Appendix A)
<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 AI3-37429-a produced mild injury to the cornea and in addition mild injury to the conjunctiva of rabbits in four out of six rabbits at 24 hrs but showed no irritation at 48 hrs. (See Appendix C for details)	USAEHA Category C (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.

Study No. 75-51-0134-81, Sep 78 - Nov 80

Test	Results	Interpretation
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PHOTOCHEMICAL SKIN IRRITATION STUDIES

Rabbits

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 AI3-37429-a in ethanol did not cause a photochemical irritation reaction under test conditions. Ethanol solutions of AI3-37429-a caused moderate irritation at both UV- and non-UV skin sites. (See Appendix D for details)

Chemical AI3-37429-a did not cause a photochemical irritation reaction under test conditions and is not expected to cause a photochemical irritation in humans. Ethanol solutions of AI3-37429-a may cause skin irritation in some sensitive individuals. Personnel experiencing this reaction should wash off the solution as soon as possible.

Control

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.

Study No. 75-51-0134-81, Sep 78 - Nov 80

Test	Results	Interpretation
<u>SENSITIZATION STUDIES</u>		
<u>Guinea Pigs (Male)</u>		
Intradermal injections of 0.1 mL of a 0.1-percent solution (w/v) of AI3-37429-a or of dinitrochlorobenzene (DNCB)* in a mixture containing 1 volume of propylene glycol and 29 volumes of saline.	Challenge doses of AI3-37429-a did not produce a sensitization reaction. (See Appendix E for details.)	Chemical AI3-37429-a did not produce sensitization reactions under test conditions and is not expected to produce sensitization reactions in man.
Ten positive control guinea pigs were sensitized over 3 weeks with DNCB. After 2 weeks' rest, they were challenged with ID injections of DNCB.	Challenge dose of DNCB in positive control guinea pigs produced a marked sensitization reaction in 10 out of 10 guinea pigs.	DNCB produced a marked reaction, indicating the guinea pigs respond to sensitizing agents.

* A known skin sensitizer

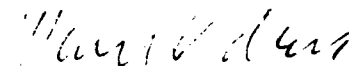
Study No. 75-51-0134-81, Sep 78 - Nov 80

5. CONCLUSION. Technical grade chemical AI3-37429-a showed a potential for producing mild primary irritation of the intact skin and the skin surrounding an abrasion, causing mild injury to the cornea and, in addition, some injury to the conjunctiva, and some skin irritation from ethanol solutions. It caused no other irritation reactions from photochemical or sensitization testing and does not present an acute ingestion hazard.

6. RECOMMENDATIONS. Under the provisions of the Memorandum of Understanding (paragraph 1b), it is recommended that AI3-37429-a, USDA Proprietary Chemical, be approved for further testing as a candidate insect repellent. Ethanol solutions of this chemical may cause skin irritation in sensitive individuals and, if experienced, the site should be washed 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: A13-37429-a USDA Proprietary Chemical		USAEHA STUDY NO. 75-51-0134-81						
PRIMARY SKIN EFFECTS NEW ZEALAND WHITE RABBITS		AEHA TOXICITY CATEGORY		CONDITIONS - 0.5 mL applied to intact and abraded skin sites. Sites covered with 2" by 2" gauze for 24 hours.				
		II						
	Time of Observation (Hours)	Response Rabbit No.					Mean Score	Comments
		465	466	467	468	469		
<u>Erythema & Eschar</u>								
Intact Skin	24	0	0	2	0	0	0.67	
Intact Skin	72	0	0	2	0	0	0.67	
Abraded Skin	24	0	0	2	2	2	1.33	
Abraded Skin	72	0	0	0	0	1	0.33	
<u>Edema Formulation</u>								
Intact Skin	24	0	0	0	0	0	0	
Intact Skin	72	0	0	0	0	0	0	
Abraded Skin	24	0	0	0	0	0	0	
Abraded Skin	72	0	0	0	0	0	0	
							Intact Score	0.55
							Abraded Score	0.83
							Total Score	0.75

USAEHA FORM 1-3, 21 FEB 79 (EHEE-LIT)

APPENDIX C

COMPOUND: AI3-37429-a, USDA Proprietary Chemical		USAEHA STUDY NO. 75-51-0134-81								
ACUTE EYE EFFECTS NEW ZEALAND WHITE RABBITS		AEHA TOXICITY CATEGORY								
		C								
		CONDITIONS - 0.1 ml of technical compound put in left eye of rabbits. Right eye served as the control.								
Time of Reading	Structure	Scores							Score	Comments
		Rabbit No.								
Hrs-Days		288	289	290	291	292	293			
24	cornea	0	10	10	5	0	15	40		
	iris	0	5	5	5	0	0	15		
	conjunctivae	0	2	12	16	0	4	34		
48	cornea	0	0	0	0	0	0	0		
	iris	0	0	0	0	0	0	0		
	conjunctivae	0	0	0	0	0	0	0		
72	cornea	0	0	0	0	0	0	0		
	iris	0	0	0	0	0	0	0		
	conjunctivae	0	0	0	0	0	0	0		
7-days	cornea	0	0	0	0	0	0	0		
	iris	0	0	0	0	0	0	0		
	conjunctivae	0	0	0	0	0	0	0		

Total 89
Average 14.9

USAEHA FORM 1-78, 21 JUN 79 (E02-17)

APPENDIX D

Study No. 75-51-0134-81, Sep 78 - Nov 80

Compound: AI3-37429-a, USDA Proprietary Chemical

USAHA Study No. 75-51-0134-81

Photo-chemical Irritation: Non-photochemical irritation but ethanol solutions caused moderate irritation at both UV and non-UV skin sites.

New Zealand White Rabbits Procedure: 0.05 ml of a 25% solution of compound and a 10% solution of Oil of Bergamot (positive control) in 95% ethyl alcohol were applied to intact skin of six rabbits. Half the sites were then exposed to UV light for 30 minutes.

MEAN SKIN IRRITATION SCORE

Observation Time	Test compound UV Exposure		Test Compound Non-UV Exposure		Positive Control UV Exposure		Positive Control Non-UV Exposure	
	Erythema	Edema	Erythema	Edema	Erythema	Edema	Erythema	Edema
24 Hours	11	14	9	12	11	8	6	2
48 Hours	12	6	12	4	10	4	1	0
72 Hours	12	7	11	4	11	3	1	0
Total Mean Irritant Responses	1.94	1.50	1.78	1.11	1.78	0.83	0.44	0.11

APPENDIX E

COMPOUND: AI3-37429-a, USDA Proprietary Chemical		USAEHA STUDY NO. 75-51-0134-81		
<p>GUINEA PIG SENSITIZATION MALE HARTLEY STRAIN</p> <p><u>Substance:</u> AI3-37429-a <u>Identify:</u> 0.1 mL of a 0.1% solution intradermally <u>Positive Control:</u> Dinitrochlorobenzene</p>				
Scoring Time 24 hours	Mean Body Wt (G) Initial	Mean Irritation Scores		Comments
		Diluent	Test Compound	
		Initial	Final	
Test Compound	464	0	0	2.4 5.3
Positive Control	491	0	0	19 356
Test Compd 48 hours	Mean Body Wt (G) Initial	Mean Irritation Scores		
		Diluent	Test Compound	
		Initial	Final	
Test Compound	—	0	0	0.8 1.7
Positive Control	—	0	0	9 271
				Final Scores >100 - Strong Sensitizing 25-100 - Mild Sensitizing <25 - No Sensitizing

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