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ARMY ENVIRONMENTAL HYGIENE AGENCY ABERDEEN PROVING GR--ETC F/G 6/20
TOPICAL HAZARD EVALUATION PROGRAM OF CANDIDATE INSECT REPELLENT--ETC(U)
APR 81 M J TOPPER; M H WEEKS
USAEHA-75-51-0193-81

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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 REPELLENTS
AI3-37579 and AI3-37580
US DEPARTMENT OF AGRICULTURE PROPRIETARY CHEMICALS
STUDY NUMBERS 75-51-0193-81 AND 75-51-0194-81



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20. ABSTRACT (Continue on reverse side if necessary and identify by block number) Preliminary hazard evaluations of AI3-37579 and AI3-37580 were performed by means of laboratory animal studies using rats, rabbits and guinea pigs. Chemical AI3-37579 produced a mild primary skin irritation while AI3-37580 produced no primary skin irritation. However, neither chemical demonstrated potential to cause eye or photochemical irritation to sensitize guinea pigs or demonstrate an acute ingestion hazard. It was recommended that AI3-37579 and AI3-37580 be approved for further testings as candidate insect repellents.		



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

CPT Topper/jg/AUTOVON
 584-3980

REPLY TO
 ATTENTION OF
 HSE-LT-T/WP

14 APR 1981

SUBJECT: Topical Hazard Evaluation Program of Candidate Insect Repellents
 AI3-37579 and AI3-37580, US Department of Agriculture Proprietary
 Chemicals, Study Numbers 75-51-0193-81 and 75-51-0194-81, October
 1978 - January 1981

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 evaluations of AI3-37579 and AI3-37580 were performed by
 means of laboratory animal studies using rats, rabbits, and guinea pigs.
 Chemical AI3-37579 produced a mild primary skin irritation, while AI3-37580
 produced no primary skin irritation. The technical grade chemicals did not
 cause eye or photo irritation. They did not prove to be skin sensitizers or
 to be acutely toxic by ingestion. It was recommended that both chemicals be
 approved for further testing as candidate insect repellents.

FOR THE COMMANDER:

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

REPLY TO
ATTENTION OF

HSE-LT-T/WP

TOPICAL HAZARD EVALUATION PROGRAM
OF CANDIDATE INSECT REPELLENTS
AI3-37579 and AI3-37580
US DEPARTMENT OF AGRICULTURE PROPRIETARY CHEMICALS
STUDY NUMBERS 75-51-0193-81 AND 75-51-0194-81

1. AUTHORITY.

a. Letter, US Department of Agriculture - Agricultural Research Service, Southern Region, Insects Affecting Man and Animal Research Laboratory, Gainesville, Florida, 13 October 1978.

b. Memorandum of Understanding between the Department of the Army; Office of The Surgeon General; the US Army Health Services Command; the US Army Environmental Hygiene Agency; 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, USAEHA, 1972, revised 1976.

3. PURPOSE. The purpose of this program is to provide guidance for further entomological testing of the candidate insect repellents AI3-37579 and AI3-37580.

4. SUMMARY OF FINDINGS. Hazard evaluations of the candidate insect repellents AI3-37579 and AI3-37580, US Department of Agriculture (USDA) Proprietary Chemicals, were 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 Accreditation of Laboratory Animal Care.

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Study Nos. 75-51-0193-81 and 75-51-0194-81, Oct 78 - Jan 81

TABLE. PRESENTATION OF DATA

<u>Test</u>	<u>Results</u>	<u>Interpretation</u>
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SKIN IRRITATION STUDIES

Rabbits

Single 24-hour application to intact and abraded skin of New Zealand White rabbits.

Chemical AI3-37579 did cause a mild primary irritation of the intact skin and the skin surrounding an abrasion.

AI3-37579 USAEHA Category II (ref Appendix A)

0.5 mL technical grade chemical applied to each of six rabbits.

Chemical AI3-37580 did not cause any irritation of the skin surrounding an abrasion (ref Appendices B and C for details).

AI3-37580 USAEHA Category I (ref Appendix 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.

Chemicals AI3-3759 and AI3-37580 did not cause any irritation to the eyes of rabbits (ref Appendices D and E for details).

Both chemicals USAEHA Category A (ref Appendix A)

APPROXIMATE LETHAL DOSE (ALD)

Oral

Rats (male)-no diluent

AI3-37579 ALD = 6500
AI3-37580 ALD = 9700

Neither chemical presents a lethal hazard from accidental ingestion.

Study Nos. 75-51-0193-81 and 75-51-0194-81, Oct 78 - Jan 81

<u>Test</u>	<u>Results</u>	<u>Interpretation</u>
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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.

Neither chemical caused a photochemical irritation reaction under test conditions (ref Appendices F and G for details).

Neither chemical caused a photochemical irritation reaction under test conditions and they are not expected to cause a photochemical irritation in humans.

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.

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Test	Results	Interpretation
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SENSITIZATION STUDIES

Guinea Pigs (Male)

Intradermal injections of 0.1 mL of a 0.1 percent solution (w/v) of test chemicals or of dinitrochlorobenzene (DNCB)* in a mixture containing 1 volume of propylene glycol and 29 volumes of saline.

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.

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 doses of test chemicals did not produce a sensitization reaction (ref Appendices H and I for details).

Challenge dose of DNCB in positive control guinea pigs produced a marked sensitization reaction in 10 out of 10 guinea pigs.

Chemicals AI3-37579 and AI3-37580 did not produce sensitization reactions under test conditions and are not expected to produce sensitization reactions in man.

DBCBC produced a marked reaction, indicating the guinea pigs respond to sensitizing agents.

* A known skin sensitizer.

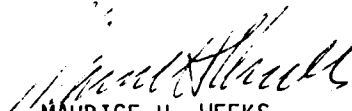
Study Nos. 75-51-0193-81 and 75-51-0194-81, Oct 78 - Jan 81

5. CONCLUSION. Technical grade chemicals AI3-37579 and AI3-27580 did not cause any eye, or photo irritation, no sensitization reaction, and did not prove to be an acute ingestion hazard. Chemical AI3-37579 did produce a mild primary skin irritation, while AI3-37580 did not.

6. RECOMMENDATION. Under the provisions of the Memorandum of Understanding (paragraph 1b), it is recommended that AI3-37679 and AI3-37580 be approved for further testing as candidate insect repellents.

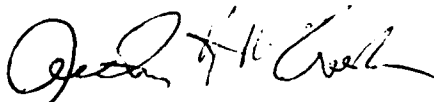


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TOPICAL HAZARD EVALUATION PROGRAM
DEFINITIONS OF CATEGORIES OF COMPOUNDS BEING
CONSIDERED FOR ACUTE SKIN APPLICATION

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.

Study Nos. 75-51-0193-81 and 75-51-0194-81, Oct 78 - Jan 81

APPENDIX B

CHEMICAL: AI3-37579, USDA Proprietary Chemical		USAHA TOXICITY CATEGORY				USAHA STUDY NO: 75-51-0193-81	
PRIMARY SKIN EFFECTS NEW ZEALAND WHITE RABBITS		II				CONDITIONS - 0.5 mL technical grade chemical applied to intact and abraded skin.	
	Time of Observation Hours	Response Rabbit No.				Mean Score	Comments
		103	104	105	106 107 108		
Erythema & Eschar							
Intact Skin	24	1	0	0	2	0.50	
Intact Skin	72	0	0	0	0		
Abraded Skin	24	0	0	0	1	0.16	
Abraded Skin	72	0	0	0	0		
					Subtotal	0.66	
Edema Formation							
Intact Skin	24	0	0	0	1	0.16	
Intact Skin	72	0	0	0	0	0	
Abraded Skin	24	0	0	0	0	0	
Abraded Skin	72	0	0	0	0	0	
					Subtotal	0.16	
					Total Avg	0.41	

HSE-LT Form 39-2, 1 Jun 80

Study Nos. 75-51-0193-81 and 75-51-0194-81, Oct 78 - Jan 81

APPENDIX C

CHEMICAL: AI3-37580, USDA Proprietary Chemical		USAEHA STUDY NO. 75-51-0194-81								
PRIMARY SKIN EFFECTS NEW ZEALAND WHITE RABBITS	USAEHA TOXICITY CATEGORY I	CONDITIONS - 0.5 mL technical grade chemical applied to intact and abraded skin.								
		Time of Observation Hours	Response Rabbit No.							
		103	104	105	106	107	108	Mean Score	Comments	
<u>Erythema & Eschar</u>										
Intact Skin		0	0	1	0	1	0	0.33		
Intact Skin		0	0	0	0	0	0			
Abraded Skin		1	0	1	0	2	0	0.67		
Abraded Skin		0	0	0	0	0	0			
		Subtotal							1.00	
<u>Edema Formation</u>										
Intact Skin		0	0	0	0	0	0			
Intact Skin		0	0	0	0	0	0			
Abraded Skin		0	0	0	0	2	0	0.33		
Abraded Skin		0	0	0	0	0	0			
		Subtotal							0.33	
		Total Avg							0.66	

HSE-LT Form 39-2, 1 Jun 80

Study Nos. 75-51-0193-81 and 75-51-0194-81, Oct 78 - Jan 81

APPENDIX D

CHEMICAL: AI3-37579, USDA Proprietary Chemical		USAEHA STUDY NO. 75-51-0193-81								
ACUTE EYE EFFECTS NEW ZEALAND WHITE RABBITS		USAEHA TOXICITY CATEGORY	CONDITIONS -							
		A	Single 24-hr application of 0.1 mL technical grade chemical to one eye of each of six rabbits.							
Time of Reading	Hrs-Days	Structure	Scores						Score	Comments
			Rabbit No.							
			1	2	3	4	5	6		
24		cornea iris conjunctivae	827 0 0 0	828 5 0 2	829 0 0 0	830 0 0 0	831 0 0 0	706 0 0 4	5 0 0 6	
48		cornea iris conjunctivae	0 0 0	0 0 0	0 0 0	0 0 0	0 0 0	0 0 0	0 0 0	
72		cornea iris conjunctivae	0 0 0	0 0 0	0 0 0	0 0 0	0 0 0	0 0 0	0 0 0	
7-days		cornea iris conjunctivae	0 0 0	0 0 0	0 0 0	0 0 0	0 0 0	0 0 0	0 0 0	

Study Nos. 75-51-0193-81 and 75-51-0194-81, Oct 78 - Jan 81

APPENDIX E

CHEMICAL: AI3-37580, USDA Proprietary Chemical		USAEHA STUDY NO. 75-51-0194-81					
ACUTE EYE EFFECTS NEW ZEALAND WHITE RABBITS		USAEHA TOXICITY CATEGORY	CONDITIONS				
A		A	Single 24-hr application of 0.1 mL technical grade chemical to one eye of six rabbits.				
				Structure	Score	Comments	
Time of Reading	Structure	Scores					
Days		Rabbit No.					
		19	20	21	22	23	24
24	cornea iris conjunctivae	0 0 0	0 0 2	0 0 0	0 0 0	0 0 0	0 0 2
48	cornea iris conjunctivae	0 0 0	0 0 0	0 0 0	0 0 0	0 0 0	0 0 0
72	cornea iris conjunctivae	0 0 0	0 0 0	0 0 0	0 0 0	0 0 0	0 0 0
7-days	cornea iris conjunctivae						

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APPENDIX F

PHOTOCHEMICAL IRRITATION-NEW ZEALAND WHITE RABBITS

CHEMICAL: AI3-37579, USDA Proprietary Chemical		USAEHA STUDY NO. 75-51-0193-81		
COMMENTS:				
PROCEDURE: 0.05 mL of a 25 percent solution of chemical and of a 10 percent solution of oil of Bergamot in 95 percent ethanol applied to intact skin of six rabbits. Rabbits were exposed to UV light for 30 minutes.				
MEAN SKIN IRRITATION SCORE				
Observation Time	Test Compound UV Exposure		Positive Control UV Exposure	
	Erythema	Edema	Erythema	Edema
24 Hours	7	5	20	19
48 Hours	10	9	19	22
72 Hours	8	6	13	14
TOTAL	25	20	52	55
Mean Irritant Responses	1.39	1.11	2.89	3.06
Net Score	Erythema 0.33	Edema 0.39	Erythema 1.83	Edema 2.50

Study Nos. 75-51-0193-81 and 75-51-0194-81, Oct 78 - Jan 81

APPENDIX G

PHOTOCHEMICAL IRRITATION-NEW ZEALAND WHITE RABBITS

CHEMICAL: AI3-37580, USDA Proprietary Chemical

USAEHA STUDY NO. 75-51-0194-81

COMMENTS:

PROCEDURE: 0.05 mL of a 25 percent of chemical and of a 10 percent solution of oil of Bergamot in 95 percent ethanol applied to intact skin of six rabbits. Rabbits were exposed to UV light for 30 minutes.

Observation Time	MEAN SKIN IRRITATION SCORE									
	Test Compound UV Exposure		Test Compound Non-UV Exposure		Positive Control UV Exposure		Positive Control Non-UV Exposure		Positive Control Edema	
	Erythema	Edema	Erythema	Edema	Erythema	Edema	Erythema	Edema	Erythema	Edema
24 Hours	8	2	9	3	21	22	13	9		
48 Hours	8	2	10	5	21	19	11	5		
72 Hours	10	1	10	2	19	11	7	1		
TOTAL	26	5	29	10	61	52	31	15		
Mean Irritant Responses	1.44	0.28	1.61	0.56	3.39	2.89	1.72	0.83		
Net Score	Erythema 0.17		Edema 0.28		Erythema 1.67		Edema 2.06			

Study Nos. 75-51-0193-81 and 75-51-0194-81, Oct 78 - Jan 81

APPENDIX H

CHEMICAL: AI3-37579, USDA Proprietary Chemical		USAEHA STUDY NO. 75-51-0193-81			
GUINEA PIG SENSITIZATION MALE HARTLEY STRAIN		Substance: AI3-37579			
		Identify: USDA Proprietary Chemical			
		Positive Control: Dinitrochlorobenzene			
Scoring Time 24 hours	Mean Body Wt (G)		Mean Irritation Scores		Comments
	Initial	Final	Diluent	Test Compound	
Test Compound	439	603	Initial: 0 Final: 0	Initial: 6.60 Final: 5.30	
Positive Control	441	601	Initial: 0 Final: 0	Initial: 10.4 Final: 3.44	
Test Compd 48 hours	Mean Body Wt (G)		Mean Irritation Scores		
	Initial	Final	Diluent	Test Compound	
Test Compound	-	-	Initial: - Final: -	Initial: 3.20 Final: 4.20	
Positive Control	-	-	Initial: - Final: -	Initial: 6.60 Final: 2.60	
					Final Scores >100 - Strong Sensitizing 25-100 - Mild Sensitizing <25 - No Sensitizing

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APPENDIX I

CHEMICAL: A13-37580, USDA Proprietary Chemical		USAEHA CONTROL NO. 75-51-0194-81			
GUINEA PIG SENSITIZATION MALE HARTLEY STRAIN		Substance: A13-37580			
		Identify: USDA Proprietary Chemical			
		Positive Control: Dinitrochlorobenzene			
Scoring Time 24 hours	Mean Body Wt (G)		Mean Irritation Scores		Comments
	Initial	Final	Diluent Initial	Test Compound Initial	
Test Compound	418	576	0	1.7	3.8
Positive Control	441	601	0	10.4	344
Test Compd 48 hours	Mean Body Wt (G)		Mean Irritation Scores		
	Initial	Final	Diluent Initial	Test Compound Initial	
Test Compound	-	-	0	0	1.6
Positive Control	-	-	0	6.60	260

Final Scores
 >100 - Strong Sensitizing
 25-100 - Mild Sensitizing
 <25 - No Sensitizing

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