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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(11)
DEC 81 M J TOPPER, J G HARVEY

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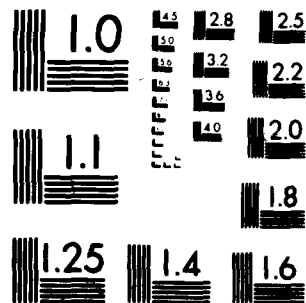
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**UNITED STATES ARMY
ENVIRONMENTAL HYGIENE
AGENCY**

ABERDEEN PROVING GROUND, MD 21010

TOPICAL HAZARD EVALUATION PROGRAM OF CANDIDATE INSECT REPELLENTS,
US DEPARTMENT OF AGRICULTURE PROPRIETARY CHEMICALS,
STUDY NUMBERS 75-51-0182-82 thru 75-51-0189-82, 75-51-0192-82,
and 75-51-0242-82
OCTOBER 1978 - SEPTEMBER 1981,

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REPORT DOCUMENTATION PAGE		READ INSTRUCTIONS BEFORE COMPLETING FORM																
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17. DISTRIBUTION STATEMENT (of the abstract entered in Block 20, if different from Report)																		
18. SUPPLEMENTARY NOTES																		
19. KEY WORDS (Continue on reverse side if necessary and identify by block number) <table border="0"> <tr> <td>AI3-37565</td> <td>AI3-37571</td> <td>Skin Irritation</td> <td rowspan="5">USDA Proprietary Chemicals Topical Hazard Evaluation Program</td> </tr> <tr> <td>AI3-37566</td> <td>AI3-37572</td> <td>Eye Irritation</td> </tr> <tr> <td>AI3-37567</td> <td>AI3-37574</td> <td>ALD</td> </tr> <tr> <td>AI3-37569</td> <td>AI3-37578</td> <td>Photo Irritation</td> </tr> <tr> <td>AI3-37570</td> <td>AI3-38010</td> <td>Guinea Pig Sensitization</td> </tr> </table>			AI3-37565	AI3-37571	Skin Irritation	USDA Proprietary Chemicals Topical Hazard Evaluation Program	AI3-37566	AI3-37572	Eye Irritation	AI3-37567	AI3-37574	ALD	AI3-37569	AI3-37578	Photo Irritation	AI3-37570	AI3-38010	Guinea Pig Sensitization
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20. ABSTRACT (Continue on reverse side if necessary and identify by block number) Preliminary hazard evaluations of the above candidate insect repellent chemicals were performed by means of laboratory animal studies using rats, rabbits, and guinea pigs. Chemicals AI3-37565, 37567, 37569, 37570, 37571, 37572, 37574 and 38010 did not cause any skin irritation. Chemical AI3-37566 and 37578 caused mild primary skin irritation. Chemical AI3-37574 was noninjurious to the eyes of rabbits. Chemicals AI3-37565 and 37572 caused mild injury to the cornea and chemicals AI3-37566, 37567, 37569, 37570, 37571, 37578, and 38010 caused mild injury to the cornea and, in addition, some injury to the conjunctiva.																		

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All chemicals were relatively nontoxic by ingestion and did not cause photo-irritation or prove to be skin sensitizers. Chemicals AI3-37570 and 37574 demonstrated some skin irritation from ethanol solutions during photoirritation studies. It was recommended that all chemicals be approved for further testing as candidate insect repellents.

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

CPT Topper/ldr/AUTOVON
584-3980

REPLY TO
ATTENTION OF
HSE-LT-T/WP

9 DEC 1981

SUBJECT: Topical Hazard Evaluation Program of Candidate Insect Repellents,
US Department of Agriculture Proprietary Chemicals, Study Numbers
75-51-0182-82 thru 75-51-0189-82, 75-51-0192-82, and 75-51-0242-82,
October 1978 - September 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 the above candidate insect repellent chemicals were performed by means of laboratory animal studies using rats, rabbits, and guinea pigs. Chemicals AI3-37565, 37567, 37569, 37570, 37571, 37572, 37574, and 38010 did not cause any skin irritation. Chemicals AI3-37566 and 37578 caused mild primary skin irritation. Chemical AI3-37574 was noninjurious to the eyes of rabbits. Chemicals AI3-37565 and 37572 caused mild injury to the cornea, and chemicals AI3-37566, 37567, 37569, 37570, 37571, 37578, and 38010 caused mild injury to the cornea and, in addition, some injury to the conjunctiva. All chemicals were relatively nontoxic by ingestion and did not cause photoirritation or prove to be skin sensitizers. Chemicals AI3-37570 and 37574 demonstrated some skin irritation from ethanol solutions during photoirritation studies. It was recommended that all chemicals be approved for further testing as candidate insect repellents.

FOR THE COMMANDER:

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as (5 cy)

John F. Mazur
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USDA, ARS-Southern Region (2 cy)



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
US DEPARTMENT OF AGRICULTURE PROPRIETARY CHEMICALS
STUDY NUMBERS 75-51-0182-82 thru 75-51-0189-82, 75-51-0192-82,
and 75-51-0242-82
OCTOBER 1978 - SEPTEMBER 1981

1. AUTHORITY.

a. Letter, US Department of Agriculture - Agricultural Research Service, Southern Region, Insects Affecting Man and Animal Research Laboratory, Gainesville, FL, 13 October 1978 (AI3-37565, 37566, 37567, 37569, 37570, 37571, 37572, 37574, and 37578).

b. Letter, US Department of Agriculture - Agricultural Research Service, Southern Region, Insects Affecting Man and Animal Research Laboratory, Gainesville, FL, 23 November 1978 (AI3-38010).

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 Department of Agriculture, Agricultural Research, Science and Education Administrations, titled, Coordination of Biological and Toxicological Testing of Pesticides, effective 23 January 1979.

2. REFERENCE. Toxicology Division Standing Operating Procedures, US Army Environmental Hygiene Agency (USAEHA), 1981.

3. PURPOSE. The purpose of this program is to provide guidance for further entomological testing of the candidate insect repellents: AI3-37565, 37566, 37567, 37569, 37570, 37571, 37572, 37574, 37578, and 38010, US Department of Agriculture (USDA) Proprietary Chemicals.

4. SUMMARY OF FINDINGS. Hazard evaluations of the above-named candidate repellents 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 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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Study Nos. 75-51-0182-82 thru 75-51-0189-82, 75-51-0192-82, and 75-51-0242-82

TABLE. PRESENTATION OF DATA

Test	Results	Interpretation
<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.	Chemicals AI3-37565, 37567, 37569, 37570, 37571, 37572, 37574, and 38010 did not cause any irritation of the intact skin or of the skin surrounding an abrasion.	USAEHA Category I (ref Appendix A)
	Chemicals AI3-37566 and 37578 produced mild primary irritation of the intact skin and the skin surrounding an abrasion.	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 AI3-37574 did not cause any irritation to the eyes of rabbits.	USAEHA Category A (ref Appendix A)
	Chemicals AI3-37565 and 37572 caused mild injury to the cornea.	USAEHA Category B (ref Appendix A)
	Chemicals AI3-37566, 37567, 37569, 37570, 37571, 37578, and 38010 caused mild injury to the cornea and, in addition, some injury to the conjunctiva.	USAEHA Category C (ref Appendix A)

Study Nos. 75-51-0182-82 thru 75-51-0189-82, 75-51-0192-82, and 75-51-0242-82

Test	Results	Interpretation
<u>APPROXIMATE LETHAL DOSE (ALD)</u>		
<u>Oral</u>		
Rats (male)-no diluent	AI3-37565 4300 mg/kg AI3-37566 9700 mg/kg AI3-37567 9700 mg/kg AI3-37569 9700 mg/kg AI3-37570 6500 mg/kg AI3-37571 6500 mg/kg AI3-37572 2900 mg/kg AI3-37574 2900 mg/kg AI3-37578 2900 mg/kg AI3-38010 6400 mg/kg	These chemicals are relatively nontoxic by ingestion.

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 each tested chemical in ethanol did not cause a photochemical irritation reaction under test conditions.

Ethanol solutions of AI3-37570 and 37574 caused slight irritation at both UV and non-UV skin sites.

All tested chemicals did not cause a photochemical irritation reaction under test conditions and are not expected to cause a photochemical irritation in humans.

Ethanol solutions of AI3-37570 and 37574 may cause skin irritation in some sensitive individuals. Personnel experiencing this reaction should wash off the solution as soon as possible.

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Test	Results	Interpretation
<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.	
<u>SENSITIZATION STUDIES</u>		
<u>Guinea Pigs (Male)</u>		
Intradermal injections of 0.1 mL of a 0.1-percent solution (w/v) of the tested 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 ten sensitizing doses over a 3-week period. After 2 weeks rest, they were challenged with intradermal (ID) injections of each test chemical.	Challenge doses of the tested chemicals did not produce a sensitization reaction.	The tested chemicals did not produce sensitization reactions under test conditions and are 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 responded to sensitizing agents.

* A known skin sensitizer.

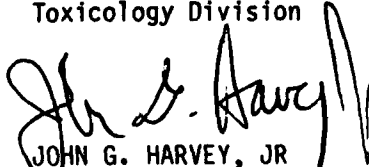
Study Nos. 75-51-0182-82 thru 75-51-0189-82, 75-51-0192-82, and 75-51-0242-82

5. CONCLUSION. Chemicals AI3-37565, 37567, 37569, 37570, 37571, 37572, 37574, and 38010 did not cause any skin irritation. Chemicals AI3-37566 and 37578 caused mild primary skin irritation. Chemical AI3-37574 was noninjurious to the eyes of rabbits. Chemicals AI3-37565 and 37572 caused mild injury to the cornea, and chemicals AI3-37566, 37567, 37569, 37570, 37571, 37578, and 38010 caused mild injury to the cornea and, in addition, some injury to the conjunctiva. All chemicals were relatively nontoxic by ingestion and did not cause photoirritation or prove to be skin sensitizers. Chemicals AI3-37570 and 37574 demonstrated some skin irritation from ethanol solutions during photoirritation studies.

6. RECOMMENDATION. Under the provisions of the Memorandum of Understanding (paragraph 1c), it is recommended that the following USDA proprietary chemicals be approved for further testing as candidate insect repellents: AI3-37565, 37566, 37567, 37569, 37570, 37571, 37572, 37574, 37578, and 38010. Ethanol solutions of chemicals AI3-37570 and 37574 may cause skin irritation in sensitive individuals and, if experienced, the site should be washed with copious amounts of water.



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APPROVED:



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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.

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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.

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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, 1981.

(2) Title 21, Code of Federal Regulations (CFR), 1981 rev, Part 58, Good Laboratory Practice for Nonclinical Laboratory Studies.

b. Facilities were inspected during its operational phase to insure compliance with paragraph 6.

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



PAUL V. SNEERINGER, Ph.D.
Chief, Analytical Quality
Assurance Office

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