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TOPICAL HAZARD EVALUATION PROGRAM OF CANDIDATE INSECT REPELLENT--ETC(U)
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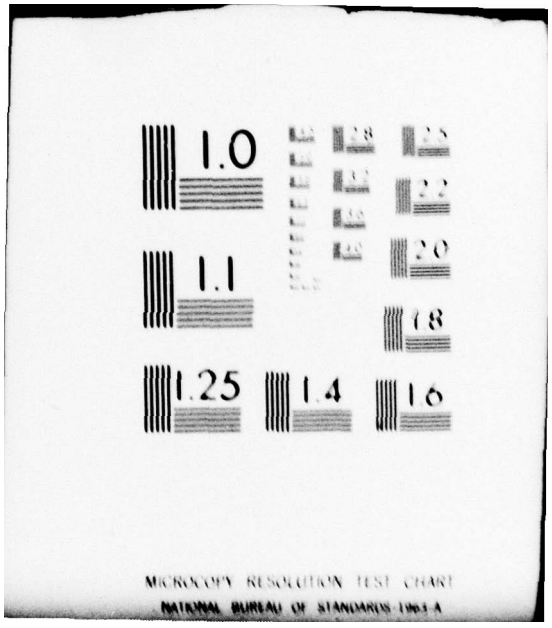
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UNITED STATES ARMY ENVIRONMENTAL HYGIENE AGENCY

ABERDEEN PROVING GROUND, MD 21010

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TOPICAL HAZARD EVALUATION PROGRAM
OF CANDIDATE INSECT REPELLENTS AI3-35765 AND AI3-35765E,
US DEPARTMENT OF AGRICULTURE PROPRIETARY COMPOUNDS
~~STUDY NUMBERS 75-51-0837-79 AND 75-51-0116-79~~
NOVEMBER 1975 - MAY 1979.

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eye irritation

20. ABSTRACT (Continue on reverse side if necessary and identify by block number)

A preliminary hazard evaluation of AI3-35765 was performed by means of laboratory animal studies using rats, rabbits, and guinea pigs. The technical grade compound caused mild primary skin irritation in rabbits and severe ocular damage in rabbits, but no photoirritation. It did not sensitize guinea pigs and did not demonstrate an acute ingestion hazard. A charcoal purified sample of this compound was supplied (AI3-35765e) and retested. AI3-35765e caused a mild injury to the cornea and conjunctiva of rabbits, but did not cause any primary skin irritation, photoirritation, skin sensitization, or demonstrate an ingestion hazard.

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

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17 AUG 1979

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SUBJECT: Topical Hazard Evaluation Program of Candidate Insect Repellents AI3-35765 and AI3-35765e, US Department of Agriculture Proprietary Compounds, Study Nos. 75-51-0837-79 and 75-51-0116-79, November 1975 - May 1979

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

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

A preliminary hazard evaluation of AI3-35765 was performed by means of laboratory animal studies using rats, rabbits, and guinea pigs. The technical grade compound caused mild primary skin irritation in rabbits and severe ocular damage in rabbits, but no photoirritation. It did not sensitize guinea pigs and did not demonstrate an acute ingestion hazard. A charcoal purified sample of this compound was supplied (AI3-35765e) and retested. AI3-35765e caused a mild injury to the cornea and conjunctiva of rabbits, but did not cause any primary skin irritation, photoirritation, skin sensitization, or demonstrate an ingestion hazard. It was recommended that AI3-35765e be approved for further testing as a candidate insect repellent.

FOR THE COMMANDER:

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

HSE-LT-T/WP

TOPICAL HAZARD EVALUATION PROGRAM OF CANDIDATE INSECT REPELLENTS AI3-35765 AND AI3-35765E US DEPARTMENT OF AGRICULTURE PROPRIETARY COMPOUNDS STUDY NUMBERS 75-51-0837-79 AND 75-51-0116-79 NOVEMBER 1975 - MAY 1979

1. AUTHORITY.

a. Letters, US Department of Agriculture - Agricultural Research Service, Southern Region, Insects Affecting Man and Animal Research Laboratory, Gainesville, Florida, 3 November 1975 and 16 August 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, effective 1970 with Amendment No. 1 effective August 1974.

2. REFERENCE. Toxicology Division Procedural Guide, USAEHA, 1972, revised 1976.

3. PURPOSE. The purpose of this study is to provide guidance for further entomological testing of the candidate insect repellents AI3-35765 and AI3-35765e.

4. SUMMARY OF FINDINGS. Hazard evaluations of the candidate repellents AI3-35765 and AI3-35765e, USDA Proprietary Compounds, 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:*†

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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," US Department of Health, Education and Welfare Publication No. (NIH) 74-23, revised in 1972, and in 1978.
† The experiments reported herein were performed in animal facilities fully accredited by the American Association for the Accreditation of Laboratory Animal Care.

Topical Hazard Eval Study No. 75-51-0837-79 and 75-51-0116-79, Nov 75-May 79

TABULAR PRESENTATION OF DATA

Test	Results	Interpretation
SKIN IRRITATION STUDIES		
Rabbits		
Single 24-hour application to intact and abraded skin of New Zealand White rabbits.	Compound AI3-35765 produced mild primary irritation of the intact skin and the skin surrounding an abrasion.	USAEHA Category II (ref Appendix)
0.5 ml technical grade compound applied to each of six rabbits.	Purified compound AI3-35765e produced no primary irritation of intact skin or of skin surrounding an abrasion.	USAEHA Category I (ref Appendix)
EYE IRRITATION STUDIES		
Rabbits		
Single 24-hour application of 0.1 ml technical grade compound to one eye of each of six New Zealand White rabbits.	Compound AI3-35765 produced severe corneal and conjunctival injury to all eyes. Corneal insult was detectable at 7 days in 3 of 6 rabbits.	USAEHA Category F (ref Appendix).
	Compound AI3-35765e produced mild corneal irritation and ulceration in 5 of 6 rabbits which persisted at 72 hours, in addition to mild conjuctival irritation in all six rabbits. All corneas had healed by 7 days.	USAEHA Category C (ref Appendix)
Single 24-hour application of 0.1 ml of 10 percent AI3-35765e (w/v) in propylene glycol to one eye of each of six rabbits.	Mixture produced mild corneal irritation in 3 of 6 rabbits which persisted at 72 hours, in addition to mild conjuctival irritation in all six rabbits. All corneas had healed by 7 days.	USAEHA Category C (ref Appendix)

Test	Results	Interpretation
APPROXIMATE LETHAL DOSE (ALD)		
Oral dosing of rats by stomach tube with technical grade AI3-35765 or or AI3-35765e (no diluent).	ALD>4300 mg/kg	Presents little lethal hazard from accidental ingestion.
PHOTOCHEMICAL SKIN IRRITATION STUDIES		
Rabbits		
A single application (0.05 ml) of a 25 percent (w/v) solution of the compounds 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 distance of 10-15 cm.	A 25 percent solution of AI3-35765 in ethanol did not cause a photochemical irritation reaction under test conditions. A 25 percent solution of AI3-35765e in ethanol did not cause a photochemical irritation reaction under test conditions. Positive control application and irradiation caused greater irritant effects than in unirradiated skin areas.	Compounds AI3-35765 and AI3-35765e did not cause a photochemical irritation reaction under test conditions and are not expected to cause a photochemical irritation in humans.
Control		
Following UV exposures of the rabbits, 0.05 ml of test compounds, 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.	Ethanol solutions of AI3-35765 caused slight primary skin irritation. The ethanol solutions of the purified AI3-35765e did not cause irritation.	

Topical Hazard Eval Study No. 75-51-0837-79 and 75-51-0116-79, Nov 75-May 79

Test	Results	Interpretation
SENSITIZATION STUDIES		
Guinea Pigs		
Intradermal injections of 0.05 ml of a 0.1 percent suspension (w/v) of AI3-35765, AI3-35765e, or of dinitrochlorobenzene (DNCB)* in a mixture containing 1 volume of propylene glycol and 29 volumes of saline.		
Ten test guinea pigs received ten sensitizing injections over 3 weeks, and were challenged 2 weeks later with 0.1 ml of 0.1 percent AI3-35765. Procedure was later repeated using AI3-35765e.	Challenge dose of either test compound (last intradermal injection) did not produce a sensitization reaction.	Both compounds AI3-35765 and AI3-35765e did not produce a sensitization reaction under these test conditions and are not expected to produce a sensitization reaction in man.
Ten positive control guinea pigs received ten sensitizing injections over 3 weeks with DNCB, and were challenged 2 weeks later with 0.1 percent DNCB.	Positive controls produced a marked sensitization reaction in 10 of 10 guinea pigs.	

* A known skin sensitizer.

5. DISCUSSION. Technical grade AI3-35765 causes severe ocular injury and mild skin irritation. Ethanol solutions of AI3-35765 also cause slight skin irritation. These properties could render AI3-35765 as a poor candidate repellent. In an effort to reduce the observed irritations, this compound was charcoal purified to eliminate contaminates and resubmitted as AI3-35765e. Retesting resulted in a reduction of all previously observed irritations.

6. CONCLUSION. Organic synthesis of AI3-35765 apparently results in small amounts of irritating byproducts as contaminates. Charcoal purification (AI3-35765e) provides a compound which causes mild corneal and conjunctival irritation in rabbits, but no primary skin or photochemical irritation. It does not sensitize guinea pigs, and is not an acute ingestion hazard in rats.

7. RECOMMENDATION. Further testing of this candidate should be after charcoal purification. Caution should be used when working near the eyes, and if eye contact occurs, they should be immediately flushed with water. Under the provisions of the Memorandum of Understanding (paragraph 1b), it is recommended that AI3-35765e be approved for further testing as a candidate insect repellent.

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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.