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ARMY ENVIRONMENTAL HYGIENE AGENCY ABERDEEN PROVING GR--ETC F/G 6/6  
TOPICAL HAZARD EVALUATION OF CANDIDATE INSECT REPELLENT AI3-365--ETC(U)

JUN 77 M H WEEKS, B J DESENA  
USAEHA-51-0824-77

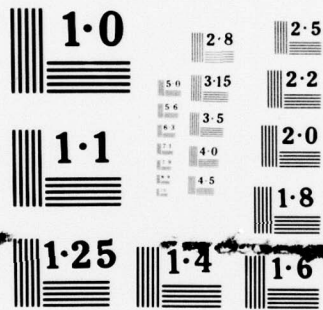
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TOPICAL HAZARD EVALUATION  
OF CANDIDATE INSECT REPELLENT AI3-36562  
4-METHYL-1-[(2-METHYLCYCLOHEXYL)CARBONYL] PIPERAZINE  
STUDY NO. 51-0824-77  
OCTOBER 1975 - MARCH 1977

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DEPARTMENT OF THE ARMY

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

10 Maurice H. Weeks  
Brenda J. Wehner

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ABSTRACT

A hazard evaluation of AI3-36562 was conducted using New Zealand White rabbits for skin and eye studies; Hartley guinea pigs for a skin sensitization study; and Sprague-Dawley, Wistar-derived rats for acute oral toxicity. AI3-36562 caused mild skin and eye irritation reactions in rabbits and should be used with caution around the eyes and mucosa. It was recommended that AI3-36562 be approved for further testing as a candidate insect repellent

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

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TOPICAL HAZARD EVALUATION  
OF CANDIDATE INSECT REPELLENT AI3-36562  
4-METHYL-1-[(2-METHYLCYCLOHEXYL)CARBONYL] PIPERAZINE  
STUDY NO. 51-0824-77  
OCTOBER 1975 - MARCH 1977

1. AUTHORITY.

a. Letter, US Department of Agriculture - Agricultural Research Service, Southern Region, Insects Affecting Man Research Laboratory, Gainesville, Florida, 17 October 1975.

b. Memorandum of Understanding between the US Army Environmental Hygiene Agency; the US Army Health Services Command; the US Department of the Army, Office of The Surgeon General; the Armed Forces Pest Control Board; and the US Department of Agriculture, effective December 1970 with Amendment No. 1, effective August 1974.

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

3. PURPOSE. The purpose of this program is to provide guidance for further entomological testing of the candidate insect repellent AI3-36562.

4. SUMMARY OF FINDINGS. A hazard evaluation of the candidate repellent AI3-36562, 4-methyl-1-[(2-methylcyclohexyl)carbonyl] piperazine 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, Wistar-derived 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 1972 - second printing 1974.

† 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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<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.	Compound AI3-36562 produced mild irritation to the intact skin and of the skin surrounding an abrasion.	USAEHA Category II (ref Appendix).
0.5 ml technical grade compound to each of six rabbits.		
<u>EYE IRRITATION STUDIES</u>		
<u>Rabbits</u>		
Single 24-hour application of 0.1 ml technical grade compound to one eye of each of six New Zealand White rabbits.	Compound AI3-36562 produced mild injury to the cornea and some injury to the conjunctiva in six of six rabbits lasting up to 3 days. No signs at 7 days.	USAEHA Category C (ref Appendix).
<u>APPROXIMATE LETHAL DOSE (ALD)</u>		
<u>ORAL</u>		
Rats (Male) - no diluent	ALD 3300 mg/kg	Presents little lethal hazard from acute accidental ingestion.

TEST	RESULTS	INTERPRETATION
<u>PHOTOCHEMICAL SKIN IRRITATION STUDIES</u>		
<u>Rabbits</u>		
A single application (0.05 ml) of a 25 percent (w/v) solution of the compound (AI3-36562) and of 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 AI3-36562 in ethanol did not cause a photochemical irritation reaction under test conditions. However, this solution caused a very mild irritation reaction for up to 3 days after application, on both irradiated and unirradiated skin areas.	Compound AI3-36562 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 exposure of the rabbits 0.05 ml of test compound, positive control and diluent were applied to additional skin areas to serve as unirradiated control sites. Application areas were checked for skin irritation reactions at 24, 48 and 72 hours.	Positive control application and irradiation caused greater irritant effects than in unirradiated skin areas.	

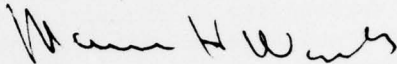
TEST	RESULTS	INTERPRETATION
<u>SENSITIZATION STUDIES</u>		
<u>Guinea Pigs (Male)</u>		
Intradermal injections of 0.1 ml of a 0.1 percent suspension (w/v) of AI3-36562 or of dinitrochlorobenzene (DNCB)* in a mixture containing 1 volume of propylene glycol and 29 volumes of saline.		
Ten test guinea pigs received and challenged with a 0.1 percent solution of AI3-36562.	Challenge dose of test compound (last intradermal injection) did not produce a sensitization reaction.	Compound AI3-36562 did not produce a sensitization reaction under these tests conditions and is not expected to produce a sensitization reaction in man.
Ten positive control guinea pigs received and challenged with 0.1 percent suspension of DNCB.	Positive control (DNCB) produced a marked sensitization reaction in ten out of ten guinea pigs.	
Ten cage control guinea pigs	Cage control guinea pigs showed no greater reaction to test compound and DNCB than were seen in original test groups.	
Five receiving challenge dose of test compound without prior sensitizing doses.		
Five receiving challenge dose of DNCB without prior sensitizing doses.		

\* A known skin sensitizer.

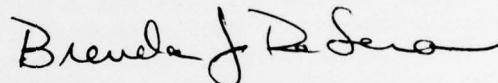
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5. CONCLUSION. Technical grade and 25 percent ethanol solutions of AI3-36562 cause mild skin irritation reactions in rabbits. Eye irritation injury was mild and reversible after 7 days.

6. RECOMMENDATION. Under the provisions of the Memorandum of Understanding (reference paragraph 1b) it is recommended that AI3-36562, 4-methyl-1-[(2-methylcyclohexyl)carbonyl] piperazine, be approved for further testing as a candidate insect repellent. It is to be used with caution around the eyes and mucosa.



MAURICE H. WEEKS  
Chief, Toxicity Evaluation Branch  
Toxicology Division

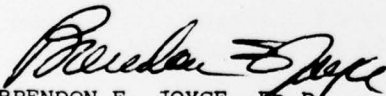


BRENDA J. DeSENA  
PFC  
Veterinary Specialist  
Toxicology Division

APPROVED:



ARTHUR H. McCREESH, Ph.D.  
Chief, Toxicology Division



BRENDON E. JOYCE, Ph.D.  
LTC, MSC  
Director, Laboratory Services

**APPENDIX**

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

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, prior to human testing.

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.