TOPICAL HAZARD EVALUATION OF CANDIDATE INSECT REPELLENT AI3-365-ETC(U)

MAY 77 M H WEEKS, B J DESENA

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TOPICAL HAZARD EVALUATION OF
CANDIDATE INSECT REPELLENT AI3-36558
3-METHYL-1-[ (2-METHYLCYCLOHEXYL)CARBONYL]PIPERIDINE
TOPICAL HAZARD EVALUATION PROGRAM
STUDY NO. 51-0820-77
OCTOBER 1975 - DECEMBER 1976

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US ARMY
ENVIRONMENTAL HYGIENE AGENCY
ABERDEEN PROVING GROUND, MD 21010
Topical Hazard Evaluation of Candidate Insect Repellent A13-36558 3-Methyl-1-((2-Methylcyclohexyl)carbonyl)Piperidine

A13-36558 eye irritation
Topical Hazard Evaluation sensitization
candidate repellent oral toxicity
Skin irritation Photochemical Skin irritation

A hazard evaluation of A13-36558 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 determination of oral toxicity. It was found that A13-36558 is a potential sensitizing chemical. Technical grade compound produced moderate injury to the cornea and to the conjunctiva of the rabbit and may cause similar damage if it should accidentally enter the eye of man. Based on these findings, it is recommended that A13-36558 not be approved for further testing as a candidate insect repellent.
ABSTRACT

A hazard evaluation of AI3-36558 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 determination of oral toxicity. It was found that AI3-36558 is a potential sensitizing chemical. Technical grade compound produced moderate injury to the cornea and to the conjunctiva of the rabbit and may cause similar damage if it should accidentally enter the eye of man. Based on these findings, it is recommended that AI3-36558 not be approved for further testing as a candidate insect repellent.
1. AUTHORITY.


   b. Memorandum of Understanding Between the US 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 December 1970 with Amendment No. 1, effective August 1974.


3. PURPOSE. The purpose of this study was to provide guidance for further entomological testing of the candidate insect repellent AI3-36558.

4. SUMMARY OF FINDINGS. A hazard evaluation of the candidate repellent AI3-36558, 3-methyl-1-[[2-methylcyclohexyl]carbonyl]piperidine, 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:


† 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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TABULAR PRESENTATION OF DATA

<table>
<thead>
<tr>
<th>Test</th>
<th>Results</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>SKIN IRRITATION STUDIES</td>
<td></td>
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<tr>
<td>Rabbits</td>
<td></td>
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<tr>
<td>Single 24-hour application to</td>
<td>AI3-36558 produced mild irritation to the</td>
<td>USAEHA Category II (reference</td>
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<td>intact and abraded skin of New</td>
<td>intact skin and to skin surrounding an</td>
<td>Appendix)</td>
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<tr>
<td>Zealand White rabbits.</td>
<td>abrasion.</td>
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<tr>
<td>0.5 ml technical grade</td>
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<tr>
<td>compound applied to each of</td>
<td></td>
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<td>six rabbits.</td>
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<td>EYE IRRITATION STUDIES</td>
<td></td>
<td></td>
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<tr>
<td>Rabbits</td>
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<td></td>
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<tr>
<td>Single 24-hour application of</td>
<td>AI3-36558 produced moderate injury to the</td>
<td>USAEHA Category E (reference</td>
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<tr>
<td>0.1 ml of technical grade</td>
<td>cornea and, in addition, some injury to the</td>
<td>Appendix)</td>
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<tr>
<td>compound to one eye of each of</td>
<td>conjunctiva in six of six rabbits at 24 hr</td>
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<tr>
<td>six New Zealand White rabbits.</td>
<td>after application and for 3 days thereafter.</td>
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<tr>
<td></td>
<td>No signs at seven days.</td>
<td></td>
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<tr>
<td>APPROXIMATE LETHAL DOSE (ALD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rats (male) - no diluent ALD</td>
<td>ALD = 3300 mg/kg</td>
<td>Presents little lethal hazard from</td>
</tr>
<tr>
<td></td>
<td>Dosages of 430 mg/kg and higher caused nasal</td>
<td>acute accidental ingestion.</td>
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<tr>
<td></td>
<td>discharge.</td>
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</table>
PHOTOCHEMICAL SKIN IRRITATION STUDIES

Rabbits

A single application (0.05 ml) of a 25-percent (w/v) solution of the compound (AI3-36558) 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.

CONTROL

Following UV exposure of the rabbits, 0.05 ml of the test compound, positive control and diluent were applied to additional skin areas to serve as unirradiated control sites. Application areas were checked for irritation at 24, 48 and 72 hours.

SENSITIZATION STUDIES

Guinea Pig (male)

Intradermal injections of 0.1 ml of a 0.1 percent suspension (w/v) of AI3-36558 or dinitrochlorobenzene (DNCB)* in a mixture containing 1 volume of propylene glycol and 29 volumes of saline.

* A known skin sensitizer.
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**Test Results and Interpretation**

**SENSITIZATION STUDIES (cont)**

**Guinea Pig (cont)**

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<tr>
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<tr>
<td>Ten test guinea pigs received and challenged with an 0.1 percent solution of AI3-36558</td>
<td>Challenge dose of test compound (last intradermal injection) produced a slight sensitization reaction in 2 out of 10 guinea pigs.</td>
<td>Compound AI3-36558 produced a slight sensitizing reaction under test conditions and may produce a sensitizing reaction in certain susceptible individuals.</td>
</tr>
<tr>
<td>Ten positive control guinea pigs received and challenged with 0.1 percent suspension of DNCB.</td>
<td>Positive control (DNCB) produced a marked sensitization reaction in 10 out of 10 guinea pigs.</td>
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<tr>
<td>Ten cage control guinea pigs; five receiving challenge dose of test compound without prior sensitizing dose of DNCB without prior sensitizing dose.</td>
<td>Cage control guinea pigs showed no greater reaction to test compound and DNCB than were seen in original test groups.</td>
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</table>
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5. CONCLUSION. AI3-36558 is a potential sensitizing chemical. Technical grade compound produced moderate injury to the cornea and to the conjunctiva of the rabbit and may cause similar damage if it should accidentally enter the eye of man.

6. RECOMMENDATION. Under the provisions of the Memorandum of Understanding (reference paragraph 1b), it is recommended that AI3-36558, 3-methyl-1-[(2-methylcyclohexyl)carbonyl]piperidine, not be approved for further testing as a candidate insect repellent.

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

Brendan 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.
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.