TOPICAL HAZARD EVALUATION OF
CANDIDATE INSECT REPELLENT A13-36559
4-METHYL-1-[2-METHYLCYCLOHEXYL]CARBONYL]PIPERIDINE
TOPICAL HAZARD EVALUATION PROGRAM
STUDY NO. 51-0821-77
OCTOBER 1975 - DECEMBER 1976
Topical Hazard Evaluation Program of Candidate Insect Repellent A13-36559 4-Methyl-1-(2-Methylcyclohexyl)Carbonyl)Piperidine

Technical grade compound caused in rabbits moderate eye injury. Ethanol solutions of A13-36559 caused primary skin irritation and may be irritating to the skin of man. Based on these findings, it is recommended that A13-36559 not be approved for further testing as a candidate topical insect repellent. However, should the insect repellent qualities indicate that it presents a substantial improvement over standard repellents, it should be resubmitted in the form and concentration intended for usage.
ABSTRACT

A hazard evaluation of AI3-36559 was conducted using New Zealand White rabbits for skin and eye studies and Hartley guinea pigs for a skin sensitization study. Technical grade compound caused in rabbits moderate eye injury. Ethanol solutions of AI3-36559 caused primary skin irritation and may be irritating to the skin of man. Based on these findings, it is recommended that AI3-36559 not be approved for further testing as a candidate topical insect repellent. However, should the insect repellent qualities indicate that it presents a substantial improvement over standard repellents, it should be resubmitted in the form and concentration intended for usage.
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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 A13-36559.

4. SUMMARY OF FINDINGS. A hazard evaluation of the candidate repellent A13-36559, 4-methyl-1-[2-methylicyclohexyl]carbonyl]piperidine, was conducted by this Agency using New Zealand White rabbits for skin and eye studies and Hartley guinea pigs for a skin sensitization study. A tabular presentation of animal toxicity data developed in this Agency follows:

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† The experiments reported herein were performed in animal facilities fully accredited by the American Association for Accreditation of Laboratory Animal Care.

Approved for public release; distribution unlimited.
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TABULAR PRESENTATION OF DATA

<table>
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<th>Test</th>
<th>Results</th>
<th>Interpretation</th>
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**SKIN IRRITATION STUDIES**

**Rabbits**

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

0.5 ml technical grade compound applied to each of six rabbits.

AI3-36559 produced no primary irritation of the intact skin and only very slight erythema to abraded skin at 24 hr.

No signs at 72 hr and 7 days.

**USAHA Category I** (reference Appendix)

**EYE IRRITATION STUDIES**

**Rabbits**

Single 24-hr application 0.1 ml technical grade compound to one eye of each of six New Zealand White rabbits.

AI3-36559 produced mild injury to the cornea and moderate injury to the conjunctiva.

No signs at 7 days.

**USAHA Category E** (reference Appendix)

**SENSITIZATION STUDIES**

**Guinea Pigs (male)**

Intradermal injection of 0.1 ml of a 0.1 percent suspension (w/v) of AI3-36559 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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<tbody>
<tr>
<td>Ten test guinea pigs received and challenged with 0.1 percent suspension of AI3-36559.</td>
<td>Challenge dose of test compound (last intradermal injection) did not produce a sensitization reaction.</td>
<td>Compound AI3-36559 did not produce a sensitization reaction under test conditions and is not expected to produce a sensitization reaction in man.</td>
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<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>
<td></td>
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<tr>
<td>Ten cage control guinea pigs; five receiving challenge dose of test compound without prior sensitizing doses; five receiving challenge dose of DNCB without prior sensitizing doses.</td>
<td>Cage control guinea pigs showed no greater reaction to test compound and DNCB than was seen in original test groups.</td>
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**PHOTOCHENICAL SKIN IRRITATION STUDIES**

**Rabbits**

A single application (0.05 ml) of 25-percent (w/v) solution of the compound 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 New Zealand White rabbits. Five minutes after application, the rabbits were exposed to UV light (365 nm) for 30 minutes from a distance of 10 to 15 cm.

Application areas were checked for irritation at...
5. CONCLUSION. Technical grade AI3-36559 caused moderate eye injury, as 25 percent solutions in ethyl alcohol skin irritation and may cause similar adverse reactions in man.

6. RECOMMENDATIONS. Under the provisions of the Memorandum of Understanding (reference paragraph 1b), it is recommended that AI3-36559, 4-methyl-1- [(2-methylcyclohexyl)carbonyl]piperidine not be approved for further testing as a candidate topical insect repellent. However, should the insect repellent qualities indicate that it presents a substantial improvement over standard repellents, it should be resubmitted in the form and concentration intended for usage.

MAURICE H. WEEKS
Chief, Toxicity Evaluation Branch
Toxicology Division

BRENDA J. DeSENA
PFC
Veterinary Specialist
Toxicology Division

APPROVED:

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

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