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

JUL 80  A W SINGER

UNCLASSIFIED USAEHA-75-51-0028-80
UNITED STATES ARMY
ENVIRONMENTAL HYGIENE
AGENCY
ABERDEEN PROVING GROUND, MD 21010

TOPICAL HAZARD EVALUATION PROGRAM
OF CANDIDATE INSECT REPELLENTS AI3-37221 and AI3-37225
1-(3-CYCLOHEXEN-1-YLCARBONYL)-3-METHYLPYPERIDINE AND
1-(3-CYCLOHEXEN-1-YLCARBONYL)-4-METHYLPYPERAZINE
STUDY NOS. 75-51-0028-80 and 75-51-0032-80
MAY 1977 to MAY 1980

Approved for public release; distribution unlimited.
Preliminary hazard evaluations of A13-37221 and A13-37225 were performed by means of laboratory animal studies using rabbits and guinea pigs. Both technical grade compounds caused moderate corneal and conjunctival irritations. A13-37221 caused mild primary skin irritation; A13-37225 caused no such reaction. A13-37225 was tested for skin sensitization and found to be negative.
HSE-LT/WP

SUBJECT: Topical Hazard Evaluation Program of Candidate Insect Repellents A13-37221 and A13-37225, 1-(3-cyclohexen-1-ylcarbonyl)-3-methylpiperidine and 1-(3-cyclohexen-1-ylcarbonyl)-4-methylpiperazine, Study Nos. 75-51-0028-80 and 75-51-0032-80, May 1977 to May 1980

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 A13-37221 and A13-37225 were performed by means of laboratory animal studies using rabbits and guinea pigs. Both technical grade compounds caused moderate corneal and conjunctival irritations. A13-37221 caused mild primary skin irritation; A13-37225 caused no such reaction. A13-37225 was tested for skin sensitization and found to be negative. Based upon the ocular injuries, it was recommended that both compounds be disapproved for further testing as candidate insect repellents.

FOR THE COMMANDER:

[Signature]

JOHN E. MAZUR
MAJ, MSC
Director, Laboratory Services

1 Incl
as (5 cy)

CF:
HQDA (DASG-PSP)
Cdr, HSC (HSPA-P)
Dir, Advisory Ctr on Tox, NRC
Supt, AHS (HSA-IPM)
USDA, ARS (Dr. Terrence McGovern)
USDA, ARS-Southern Region
DEPARTMENT OF THE ARMY
U.S. ARMY ENVIRONMENTAL HYGIENE AGENCY
ABERDEEN PROVING GROUND, MARYLAND 21010

HSE-LT/MP

TOPICAL HAZARD EVALUATION PROGRAM
OF CANDIDATE INSECT REPELLENTS A13-37221 and A13-37225
1-(3-CYCLOHEXEN-1-YLCARBONYL)-3-METHYLPiperidine and
1-(3-CYCLOHEXEN-1-YLCARBONYL)-4-METHYLPiperazine
STUDY NOS. 75-51-0028-80 and 75-51-0032-80
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1. AUTHORITY.


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


3. PURPOSE. The purpose of this program is to provide guidance for further entomological testing of the candidate insect repellents A13-37221 and A13-37225.

4. SUMMARY OF FINDINGS. Hazard evaluations of the candidate repellents A13-37221 and A13-37225 were 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:*t

* 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 experiments 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. 75-51-0028-80 and 75-51-0032-80, May 77 to May 80

TABLE. 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>
<td></td>
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<tr>
<td>Rabbits</td>
<td></td>
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<tr>
<td>Single 24-hour application to intact and abraded skin of New Zealand White rabbits.</td>
<td>Compound AI3-37225 did not cause any irritation of the intact skin or of the skin surrounding an abrasion.</td>
<td>USAEHA Category I (ref Appendix).</td>
</tr>
<tr>
<td>0.5 ml of each technical grade compound applied to each of six rabbits.</td>
<td>Compound AI3-37221 caused mild irritation of both the intact and abraded skin.</td>
<td>USAEHA Category II (ref Appendix).</td>
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<tr>
<td>EYE IRRITATION STUDIES</td>
<td></td>
<td></td>
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<tr>
<td>Rabbits</td>
<td></td>
<td></td>
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<tr>
<td>Single 24-hour application of 0.1 ml of each technical grade compound to one eye of each of six New Zealand White rabbits.</td>
<td>Both compounds caused moderate corneal and conjunctival injuries. This injury was still present in all eyes at 72 hrs. Evidence of corneal injury was detectable at 7 days in two rabbits for each compound.</td>
<td>USAEHA Category E (ref Appendix).</td>
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<table>
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<tr>
<th>Test</th>
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<tr>
<td><strong>SENSITIZATION STUDIES</strong></td>
<td></td>
<td></td>
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<tr>
<td>Guinea Pigs (Male)</td>
<td></td>
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<tr>
<td>Intradermal injections</td>
<td></td>
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<tr>
<td>of 0.1 ml of a 0.1 percent solution (w/v) of AI3-37225 or of dinitrochlorobenzene (DNCB)* in a mixture containing 1 volume of propylene glycol and 29 volumes of saline.</td>
<td>Challenge dose of AI3-37225 did not produce a sensitization reaction.</td>
<td>Compound AI3-37225 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 test guinea pigs</td>
<td>Challenge dose of DNCB</td>
<td>DNCB produced a marked reaction, indicating the guinea pigs respond to sensitizing agents.</td>
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<td>were given 10 sensiti-</td>
<td>in positive control</td>
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<tr>
<td>zing doses of AI3-37225</td>
<td>guinea pigs produced a marked sensitization reaction in 10 out of 10 guinea pigs.</td>
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<tr>
<td>over a 3-week period.</td>
<td>reaction in 10 out of 10</td>
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<td>After 2 weeks rest, they</td>
<td>guinea pigs.</td>
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<tr>
<td>were challenged with ID</td>
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<td>injections of test</td>
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<tr>
<td>compounds.</td>
<td></td>
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<tr>
<td>Ten positive control</td>
<td>Challenge dose of DNCB</td>
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<td>guinea pigs were</td>
<td>in positive control</td>
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<td>sensitized over 3 weeks</td>
<td>guinea pigs produced a marked sensitization reaction in 10 out of 10 guinea pigs.</td>
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<td>with DNCB. After 2 weeks</td>
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<td>injections of DNCB.</td>
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* A known skin sensitizer
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5. CONCLUSION. Both technical grade compounds caused moderate corneal injuries lasting longer than 72 hours in all rabbits, and longer than 7 days in two of six rabbits. These compounds do not qualify as nonhazardous repellents.

6. RECOMMENDATION. Under the provisions of the Memorandum of Understanding (paragraph 1b), it is recommended that A13-37221 and A13-37225 not be approved for further testing as candidate insect repellents.

[Signature]
ALLEN W. SINGER
CPT, VC
Laboratory Animal Veterinary Officer
Toxicology Division

APPROVED:

[Signature]
ARTHUR H. MCREESEH, Ph.D.
Chief, Toxicology Division
Study Nos. 75-51-0028-80 and 75-51-0032-80, May 77 to May 80

APPENDIX

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.