TOPICAL HAZARD EVALUATION PROGRAM OF CANDIDATE INSECT REPELLENTS A13-3822. (U) ARMY ENVIRONMENTAL HYGIENE AGENCY ABERDEEN PROVING GROUND MD J V WADE ET AL.
TOPICAL HAZARD EVALUATION PROGRAM
OF
CANDIDATE INSECT REPELLENTS A13-38225a, A13-38192a, A13-38194a, A13-38599a, and A13-38427a
US DEPARTMENT OF AGRICULTURE PROPRIETARY CHEMICALS
STUDY NUMBERS 75-51-0334-84, 75-51-0336-84, 75-51-0344-84, 75-51-0355-84, and 75-51-0356-84
JUNE 1981 - NOVEMBER 1983

Approved for public release; distribution unlimited.
The Topical Hazard Evaluation Program of candidate insect repellent chemicals A13-38225a, A13-38192a, A13-38194a, A13-38599a, and A13-38427a, US Department of Agriculture Proprietary Chemicals, Study No. 75-51-0334-84, 75-51-0335-84, 75-51-0336-84, 75-51-0337-84, and 75-51-0338-84, Jun 81 - Nov 83.

Chemicals A13-38192a, A13-38599a, and A13-38427a produced no primary skin irritation. Chemicals A13-38225a and A13-38194a produced mild irritation of the intact skin and the skin surrounding an abrasion. Chemical A13-38599a was noninjurious to the eyes of rabbits. Chemical A13-38192a produced mild injury to the cornea; chemicals A13-38225a, A13-38427a, and A13-38194a produced mild injury to the cornea and, in addition, some injury to the conjunctiva upon application to the eyes of rabbits. Chemicals A13-38225a, A13-38192a, A13-38599a, and A13-38427a did not produce a sensitization reaction. Chemical...
AI3-383194a produced a slight sensitization reaction in 6 of the 10 guinea pigs tested. All chemicals were relatively nontoxic by ingestion and did not potentiate photoirritation. Recommend that chemicals AI3-38225a, AI3-38192a, AI3-38599a, and AI3-38427a be approved for further testing as candidate insect repellants. Recommend that chemical AI3-38194a be disapproved for further testing due to its sensitizing potential.
EXECUTIVE SUMMARY

The purpose, essential findings, and major recommendations of the enclosed report follow:

a. Purpose. The purpose of this program is to provide guidance for entomological testing of the candidate insect repellents A13-38225a, A13-38192a, A13-38194a, A13-38599a, and A13-38427a, by means of laboratory animal studies using New Zealand White rabbits, Sprague-Dawley rats, and albino Hartley guinea pigs.

b. Essential Findings. Chemicals A13-38192a, A13-38599a, and A13-38427a produced no primary skin irritation. Chemicals A13-38225a and A13-38194a produced mild irritation of the intact skin and the skin surrounding an abrasion. Chemical A13-38599a was noninjurious to the eyes of rabbits. Chemical A13-38192a produced mild injury to the cornea; chemicals A13-38225a, A13-38427a, and A13-38194a produced mild injury to the cornea and, in addition, some injury to the conjunctiva upon application to the eyes of rabbits. Chemicals A13-38225a, A13-38192a, A13-38599a, and A13-38427a did not produce a sensitization reaction. Chemical A13-38194a produced a slight sensitization reaction in 6 of the 10 guinea pigs tested. All chemicals were relatively nontoxic by ingestion and did not potentiate photoirritation.

c. Major Recommendations. Recommend that chemicals A13-38225a, A13-38192a, A13-38599a, and A13-38427a be approved for further testing as candidate insect repellents. Recommend that chemical A13-38194a be disapproved for further testing due to its sensitizing potential.
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1. AUTHORITY.


d. 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 Department of Agriculture, Agricultural Research, Science and Education Administrations; 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 A13-38225a, A13-38192a, A13-38599a, A13-38427a, and A13-38194a, US Department of Agriculture (USDA) Proprietary Chemicals.

4. SUMMARY OF FINDINGS. Hazard evaluations of the candidate insect repellents A13-38225a, A13-38192a, A13-38599a, A13-38427a, and A13-38194a, USDA Proprietary chemicals, were conducted by this Agency using New Zealand White rabbits, Sprague-Dawley rats and albino Hartley guinea pigs. A tabular presentation of animal toxicity data developed by this Agency follows:"†

* 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) 80-23, revised 1978.

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

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TABLE. PRESENTATION OF DATA

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<th>RESULTS</th>
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SKIN IRRITATION STUDIES

Rabbits

Single 24-hour application to intact and abraded skin of New Zealand White rabbits. 0.5 mL technical grade chemical applied to each of six rabbits.

Chemicals AI3-38192a, AI3-38599a, and AI3-38427a did not produce irritation of the intact skin or of the skin surrounding an abrasion.

Chemicals AI3-38225a and AI3-38194a produced mild primary irritation of the intact skin and of the skin surrounding an abrasion.

EYE IRRITATION STUDIES

Rabbits

Single 24-hour application of 0.1 mL technical grade chemical to one eye of each of nine New Zealand White rabbits. Three of the nine rabbits had the eye flushed with warm water for 1 minute, 25 seconds after application.

Chemical AI3-38599a was noninjurious to the eye.

Chemical AI3-38192a produced mild injury to the cornea.

Chemicals AI3-38225a, AI3-38427a and AI3-38194a produced mild injury to the cornea and, in addition, some injury to the conjunctiva.

Washing with warm water decreased the ocular injury noted on application of chemicals AI3-38225a and AI3-38194a.
Approximate Lethal Dose

**Oral**

| Rats (male) - no diluent | A13-38225a > 2871 mg/kg | These chemicals are relatively nontoxic by ingestion. |
| Rats (female) - no diluent | A13-38192a > 2871 mg/kg |
| A13-38194a > 6761 mg/kg |
| A13-38599a > 3333 mg/kg |
| A13-38427 > 5000 mg/kg |

Photocchemical Skin Irritation Studies

**Rabbits**

A single 0.05 mL application of a 25% (w/v) solution of each chemical and of a 10% (w/v) oil of Bergamot solution (positive control) in 95% ethyl alcohol was applied to the intact skin of six rabbits. Five minutes after application, the rabbits were exposed to ultraviolet (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 test chemicals, 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.

Positive control application and irradiation caused greater irritant effects than in unirradiated skin areas.
Study Nos. 75-51-0334-84, 75-51-0336-84, 75-51-0344-84, 75-51-0355-84, and 75-51-0356-84, Jun 81 - Nov 83

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<th>TEST</th>
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<tr>
<td>SENSITIZATION STUDIES</td>
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<tr>
<td>Guinea Pigs (Male)</td>
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<td>Intradermal (ID) injections of 0.1 mL of a 0.1% (w/v) solution of each tested chemical or of dinitrochlorobenzene (DNCB)* in a mixture containing 1 volume of propylene glycol and 29 volumes of saline:</td>
<td>Challenge doses of AI3-3825a, AI3-38192a, AI3-38599a, and AI3-38427a did not produce sensitization reactions.</td>
<td>These chemicals are not expected to produce a sensitization reaction in humans.</td>
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<td>Ten test guinea pigs for each chemical were given 10 sensitizing doses over a 3-week period. After a 2-week rest, they were challenged with ID injections of each test compound.</td>
<td>Chemical AI3-38194a produced slight sensitization reactions in 6 of 10 guinea pigs tested.</td>
<td>This chemical could produce a sensitization reaction in humans.</td>
</tr>
<tr>
<td>Control</td>
<td></td>
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<tr>
<td>Ten positive control guinea pigs were sensitized over 3-weeks with DNCB. After a 2-week rest, they were challenged with ID injections of DNCB.</td>
<td>Challenge dose of DNCB in positive control guinea pigs produced a marked sensitization reaction in 10 out of 10 guinea pigs.</td>
<td>DNCB produced a marked sensitization reaction, indicating that these guinea pigs respond to sensitizing agents.</td>
</tr>
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* A known skin sensitizer.
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5. CONCLUSION. Chemicals A13-38192a, A13-38599a, and A13-38427a produced no primary irritation. Chemicals A13-38225a and A13-38194a produced mild primary irritation of the intact skin and of the skin surrounding an abrasion. Chemical A13-38599a was noninjurious to the eyes of rabbits. Chemical A13-38192a produced mild injury to the cornea; chemicals A13-38225a, A13-38427a, and A13-38194a produced mild injury to the cornea and, in addition, some injury to the conjunctiva upon application to the eyes of rabbits. Chemicals A13-38225a, A13-38192a, A13-38599a, and A13-38427a did not produce a sensitization reaction. Chemical A13-38194a produced a slight sensitization reaction in 6 of the 10 guineas pigs tested. All chemicals were relatively nontoxic by ingestion and did not potentiate photoirritation. These studies were monitored by Analytical Quality Assurance Office (see Appendix B).

6. RECOMMENDATION. Recommend that chemicals A13-38225a, A13-38192a, A13-38599a, and A13-38427a be approved for further testing as candidate insect repellents. Recommend that chemical A13-38194a be disapproved for further testing due to its sensitizing potential.

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APPENDIX A

TOPOCAL 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.
APPENDIX B

ANALYTICAL QUALITY ASSURANCE

The Analytical Quality Assurance Office certifies the following with regard to this study:

a. This study was conducted in accordance with:

   (1) Standing Operating Procedures developed by the Toxicology Division, USAEHA.


b. Facilities were inspected during its operational phase to insure compliance with paragraph a above.

c. The information presented in this report accurately reflects the raw data generated during the course of conducting the study.

   PAUL V. SNEERING, Ph.D.
   Chief, Analytical Quality Assurance Office