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

FEB 81  M J TOPPER  M H WEEKS

UNCLASSIFIED

USAHEA-75-51-0134-81

END

DATE FILMED 3-81

DTC
UNITED STATES ARMY
ENVIRONMENTAL HYGIENE
AGENCY
ABERDEEN PROVING GROUND, MD 21010

TOPICAL HAZARD EVALUATION PROGRAM
OF CANDIDATE INSECT REPELLENT AI3-37429-B,
US DEPARTMENT OF AGRICULTURE PROPRIETARY CHEMICAL
STUDY NO. 75-M-0134-81

Approved for public release, distribution unlimited.
Preliminary hazard evaluations of the candidate insect repellent A13-37429-a were performed by means of laboratory animal studies using rats, rabbits, and guinea pigs. The technical grade chemical showed a potential for producing mild primary irritation of the intact skin and the skin surrounding an abrasion, causing mild injury to the cornea and, in addition, some injury to the conjunctiva, and some skin irritation from ethanol solutions. It caused no other irritation reactions from photochemical or sensitization testing and does not present an acute ingestion hazard. It is recommended that A13-37429-a.
20. ABSTRACT (continued)

US Department of Agriculture Proprietary Chemical, be approved for further testing as a candidate insect repellent.
SUBJECT: Topical Hazard Evaluation Program of Candidate Insect Repellent A13-37429-a, US Department of Agriculture Proprietary Chemical, Study No. 75-51-0134-81, September 1978 - November 1980

A summary of the pertinent findings and recommendations of the inclosed report follows:

Preliminary hazard evaluations of the candidate insect repellent A13-37429-a was performed by means of laboratory animal studies using rats, rabbits, and guinea pigs. The technical grade chemical showed a potential for producing mild primary irritation of the intact skin and the skin surrounding an abrasion, causing mild injury to the cornea and, in addition, some injury to the conjunctiva, and some skin irritation from ethanol solutions. It caused no other irritation reactions from photochemical or sensitization testing and does not present an acute ingestion hazard. It is recommended that A13-37429-a, US Department of Agriculture Proprietary Chemical, be approved for further testing as a candidate insect repellent.

FOR THE COMMANDER:

JOHN F. MAZUR
MAJ, MSC
Director, Laboratory Services

CF:
HQDA (DASG-PSP)
Cdr, HSC (HSPA-P)
Dir, Advisory Cen on Tox, NRC
Comdt, AMS (HSA-1PM)
USDA, ARS (Dr. Terrence McGovern)
USDA, ARS-Southern Region
TOPICAL HAZARD EVALUATION PROGRAM
OF CANDIDATE INSECT REPELLENT A13-37429-a
US DEPARTMENT OF AGRICULTURE PROPRIETARY CHEMICAL
STUDY NO. 75-51-0134-81
SEPTEMBER 1978 - NOVEMBER 1980

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 candidate insect repellent A13-37429-a.

4. SUMMARY OF FINDINGS. Hazard evaluation of the candidate repellent A13-37429-a 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 rats for determination of oral toxicity. 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) 78-23, revised 1978.
† The experiments reported herein were performed in animal facilities fully accredited by the American Association for the Accreditation of Laboratory Animal Care.

Approved for public release, distribution unlimited.
TABLE. PRESENTATION OF DATA

<table>
<thead>
<tr>
<th>Test</th>
<th>Results</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SKIN IRRITATION STUDIES</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rabbits</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single 24-hour application to intact and abraded skin of New Zealand White rabbits.</td>
<td>Chemical A13-37429-a</td>
<td>USAEHA Category II (ref Appendix A)</td>
</tr>
<tr>
<td></td>
<td>produced mild erythematous irritation of the intact skin and of the skin surrounding an abrasion without edema.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.5 mL technical grade chemical applied to each of six rabbits.</td>
<td>(See Appendix B for details.)</td>
</tr>
<tr>
<td><strong>EYE IRRITATION STUDIES</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rabbits</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single 24-hour application of 0.1 mL technical grade chemical to one eye of each of six New Zealand White rabbits.</td>
<td>Chemical A13-37429-a produced mild injury to the cornea and in addition mild injury to the conjunctiva of rabbits in four out of six rabbits at 24 hrs but showed no irritation at 48 hrs.</td>
<td>USAEHA Category C (ref Appendix A). (See Appendix C for details)</td>
</tr>
<tr>
<td><strong>APPROXIMATE LETHAL DOSE (ALD)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rats (male)-no diluent</td>
<td>ALD&gt;2900 mg/kg</td>
<td>Presents little lethal hazard from accidental ingestion.</td>
</tr>
</tbody>
</table>
PHOTOCHEMICAL SKIN IRRITATION STUDIES

Rabbits

A single 0.05 mL application of a 25-percent (w/v) solution of each chemical 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 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 AI3-37429-a in ethanol did not cause a photochemical irritation reaction under test conditions and is not expected to cause a photochemical irritation in humans. Ethanol solutions of AI3-37429-a caused moderate irritation at both UV- and non-UV skin sites. (See Appendix D for details)

Control

Following UV exposures of the rabbits, 0.05 mL of test chemical, 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 No. 75-51-0134-81, Sep 78 - Nov 80**

**SENSITIZATION STUDIES**

**Guinea Pigs (Male)**

Intradermal injections of 0.1 mL of a 0.1-percent solution (w/v) of A13-37429-a or of dinitrochlorobenzene (DNCB)* in a mixture containing 1 volume of propylene glycol and 29 volumes of saline.

Ten test guinea pigs for each chemical were given 10 sensitizing doses over a 3-week period. After 2 weeks' rest, they were challenged with ID injections of each test chemical.

Ten positive control guinea pigs were sensitized over 3 weeks with DNCB. After 2 weeks' rest, they were challenged with ID injections of DNCB.

<table>
<thead>
<tr>
<th>Test Results</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Challenge doses of A13-37429-a did not produce a sensitization reaction. (See Appendix E for details.)</td>
<td>Chemical A13-37429-a did not produce sensitization reactions under test conditions and is not expected to produce sensitization reactions in man.</td>
</tr>
<tr>
<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 reaction, indicating the guinea pigs respond to sensitizing agents.</td>
</tr>
</tbody>
</table>

* A known skin sensitizer
5. CONCLUSION. Technical grade chemical AI3-37429-a showed a potential for producing mild primary irritation of the intact skin and the skin surrounding an abrasion, causing mild injury to the cornea and, in addition, some injury to the conjunctiva, and some skin irritation from ethanol solutions. It caused no other irritation reactions from photochemical or sensitization testing and does not present an acute ingestion hazard.

6. RECOMMENDATIONS. Under the provisions of the Memorandum of Understanding (paragraph 1b), it is recommended that AI3-37429-a, USDA Proprietary Chemical, be approved for further testing as a candidate insect repellent. Ethanol solutions of this chemical may cause skin irritation in sensitive individuals and, if experienced, the site should be washed with copious amounts of water.

MICHAEL J. TOPPER, DVM
CPT, VC
General Veterinary Officer
Toxicology Division

MAURICE H. WEEKS
Chief, Toxicity Evaluation Branch
Toxicology Division

APPROVED:

ARTHUR H. MCCREESH, Ph.D.
Chief, Toxicology Division
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.
APPENDIX B

COMPOUND: AI3-37429-a USDA Proprietary Chemical  USAEHA STUDY NO. 75-51-0134-81

<table>
<thead>
<tr>
<th>PRIMARY SKIN EFFECTS</th>
<th>AEHA TOXICITY CATEGORY</th>
<th>CONDITIONS - 0.5 mL applied to intact and abraded skin sites. Sites covered with 2&quot; by 2&quot; gauze for 24 hours.</th>
</tr>
</thead>
<tbody>
<tr>
<td>NEW ZEALAND WHITE RABBITS</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Time of Observation (Hours)</th>
<th>Response Rabbit No. 465</th>
<th>466</th>
<th>467</th>
<th>468</th>
<th>469</th>
<th>470</th>
<th>Mean Score</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythema &amp; Eschar</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intact Skin 24</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td>0.67</td>
<td></td>
</tr>
<tr>
<td>Intact Skin 72</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td>0.67</td>
<td></td>
</tr>
<tr>
<td>Abraded Skin 24</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td></td>
<td></td>
<td>2</td>
<td>1.33</td>
<td></td>
</tr>
<tr>
<td>Abraded Skin 72</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
<td>1</td>
<td>0.33</td>
<td></td>
</tr>
<tr>
<td>Edema Formulation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intact Skin 24</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Intact Skin 72</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Abraded Skin 24</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Abraded Skin 72</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Intact Score 0.55
Abrased Score 0.63
Total Score 9.75
<table>
<thead>
<tr>
<th>Time of Reading</th>
<th>Scores</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hrs-Days</strong></td>
<td><strong>Rabbit No.</strong></td>
<td><strong>288</strong></td>
</tr>
<tr>
<td>24</td>
<td>cornea</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>iris</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>conjunctivae</td>
<td>0</td>
</tr>
<tr>
<td>48</td>
<td>cornea</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>iris</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>conjunctivae</td>
<td>0</td>
</tr>
<tr>
<td>72</td>
<td>cornea</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>iris</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>conjunctivae</td>
<td>0</td>
</tr>
<tr>
<td>7-days</td>
<td>cornea</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>iris</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>conjunctivae</td>
<td>0</td>
</tr>
</tbody>
</table>

**Total**: 89
**Average**: 14.9
APPENDIX D

<table>
<thead>
<tr>
<th>Compound: AI3-37429-a, USDA Proprietary Chemical</th>
<th>USAEHA Study No. 75-51-0134-81</th>
</tr>
</thead>
</table>

**Photochemical Irritation**

Comments: Non-photochemical irritation but ethanol solutions caused moderate irritation at both UV and non-UV skin sites.

**New Zealand White Rabbits**

Procedure: 0.05 mL of a 25% solution of compound and a 10% solution of Oil of Bergamot (positive control) in 95% ethyl alcohol were applied to intact skin of six rabbits. Half the sites were then exposed to UV light for 30 minutes.

<table>
<thead>
<tr>
<th>Observation Time</th>
<th>Test Compound UV Exposure</th>
<th>Test Compound Non-UV Exposure</th>
<th>Positive Control UV Exposure</th>
<th>Positive Control Non-UV Exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Erythema</td>
<td>Edema</td>
<td>Erythema</td>
<td>Edema</td>
</tr>
<tr>
<td>24 Hours</td>
<td>11</td>
<td>14</td>
<td>9</td>
<td>12</td>
</tr>
<tr>
<td>48 Hours</td>
<td>12</td>
<td>6</td>
<td>12</td>
<td>4</td>
</tr>
<tr>
<td>72 Hours</td>
<td>12</td>
<td>7</td>
<td>11</td>
<td>4</td>
</tr>
<tr>
<td>Total Mean Irritant Responses</td>
<td>1.94</td>
<td>1.50</td>
<td>1.78</td>
<td>1.11</td>
</tr>
</tbody>
</table>
APPENDIX E

COMPOUND: AI3-37429-a, USDA Proprietary Chemical

USAHEA STUDY NO. 75-51-0134-81

GUINEA PIG SENSITIZATION

Substance: AI3-37429-a

Identify: 0.1 mL of a 0.1% solution intradermally

Positive Control: Dinitrochlorobenzene

<table>
<thead>
<tr>
<th>Scoring Time</th>
<th>Mean Body Wt (G)</th>
<th>Mean Irritation Scores</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>24 hours</td>
<td>Initial</td>
<td>Final</td>
<td>Diluent</td>
</tr>
<tr>
<td>Test Compound</td>
<td>464</td>
<td>642</td>
<td>0</td>
</tr>
<tr>
<td>Positive Control</td>
<td>491</td>
<td>736</td>
<td>0</td>
</tr>
</tbody>
</table>

Final Scores
>100 - Strong Sensitizing
25-100 - Mild Sensitizing
<25 - No Sensitizing

USAHEA FORM 26-4, 9 JUL 79 (HSE-LT)