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

TOPIC'S HAZARD EVALUATION PROGRAM
OF
CANDIDATE INSECT REPELLENTS AI3-38359a, AI3-38282,
AI3-38277a, AI3-38865a, and AI3-38866a
US DEPARTMENT OF AGRICULTURE PROPRIETARY CHEMICALS
STUDY NOS. 75-51-0375-84, 75-51-0423-84,
75-51-0440-84, 75-51-0446-84, and 75-51-0447-84
APRIL 1982 - MARCH 1984

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**Topical Hazard Evaluation Program of Candidate Insect Repellents A13-38359a, A13-38282, A13-38277a, A13-38865a, and A13-38866a, US Department of Agriculture Proprietary Chemicals, Study No. 75-51-0375-84, 75-51-0423-84, 75-51-0440-84, 75-51-0446-84, Apr 82 - Mar 84**

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**ABSTRACT**
These compounds produced no primary irritation of the intact skin and no greater than mild primary irritation of the skin surrounding an abrasion. Chemicals A13-38359a and A13-38866a produced mild injury to the cornea and, in addition, some injury to the conjunctiva. Chemicals A13-38277a, A13-38865a, and A13-38866a produced moderate injury to the cornea and, in addition, some injury to the conjunctiva. This injury had healed by 7 days post-application. Chemicals A13-38859a and A13-38282 produced moderate to marked sensitization in five of ten, and four of ten, guinea pigs, respectively. The other chemicals did not produce.
20. All tested chemicals did not cause a photosensitization reaction and demonstrated slight to moderate oral toxicity.
SUBJECT: Topical Hazard Evaluation Program of Candidate Insect Repellents
A13-38359a, A13-38282, A13-38277a, A13-38865a, and A13-38866a, US
Department of Agriculture Proprietary Chemicals, Study Nos.
75-51-0375-84, 75-51-0423-84, 75-51-0440-84, 75-51-0446-84, and
75-51-0447-84, April 1982 - March 1984

EXECUTIVE SUMMARY

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

a. Purpose.  The purpose of this program is to provide guidance for further entomological testing of the candidate insect repellents A13-38359a, A13-38282, A13-38277a, A13-38865a, and A13-38866a by means of laboratory animal studies using New Zealand White rabbits, Sprague-Dawley rats, and albino Hartley guinea pigs.

b. Essential Findings.  These compounds produced no primary irritation of the intact skin and no greater than mild primary irritation of the skin surrounding an abrasion.  Chemicals A13-38359a and A13-38866a produced mild injury to the cornea and, in addition, some injury to the conjunctiva.  Chemicals A13-38277a, A13-38865a, and A13-38282a produced moderate injury to the cornea and, in addition, some injury to the conjunctiva.  This injury had healed by 7 days post-application.  Chemicals A13-38359a and A13-38282a produced moderate to marked sensitization in 5 of 10 and 4 of 10 guinea pigs tested, respectively.  The other chemicals did not produce sensitization reactions.  All tested chemicals did not cause a photochemical irritation reaction and demonstrated slight to moderate oral toxicity.

c. Major Recommendations.  Recommend that chemical A13-38866a be approved for further testing as a candidate insect repellent.  Further testing should be conducted on chemicals A13-38277a, and A13-38865a only if their entomological efficacy is equivalent or superior to currently approved repellents due to their potential to produce ocular injury.  Recommend that chemicals A13-38359a and A13-38282 be disapproved for further testing due to their sensitizing potential.

FOR THE COMMANDER:

JOEL C. GUTOS, M.D.
Colonel, MC
Director, Occupational and Environmental Health

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Cdr, HSC (HSC-P)
Comdt, ANS (NSHA-P)
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USDA, ARS (Dr. Terrence McGovern)
USDA, ARS-Southern Region (3 cy)
Cdr, USAMRDC (SGRD-DPH/LTC(P) Reinert)
DEPARTMENT OF THE ARMY
U. S. ARMY ENVIRONMENTAL HYGIENE AGENCY
ABERDEEN PROVING GROUND, MARYLAND 21010

TOPICAL HAZARD EVALUATION PROGRAM
OF
CANDIDATE INSECT REPELLENTS A13-38359a, A13-38282,
A13-38277a, A13-38865a, and A13-38866a
US DEPARTMENT OF AGRICULTURE PROPRIETARY CHEMICALS
STUDY NOS. 75-51-0375-84, 75-51-0423-84,
75-51-0440-84, 75-51-0446-84, and 75-51-0447-84
APRIL 1982 - MARCH 1984

1. AUTHORITY.

a. Letter, US Department of Agriculture - Agricultural Research,
   Southern Region, Insects Affecting Man and Animals Research Laboratory,

b. Letter, US Department of Agriculture - Agricultural Research,
   Southern Region, Insects Affecting Man and Animals Research Laboratory,
   Gainesville, Florida, 10 February 1983.

c. Letter, US Department of Agriculture - Agricultural Research,
   Southern Region, Insects Affecting Man and Animals Research Laboratory,

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, Agriculture Research, Science and
   Education Administrations; titled Coordination of Biological and

2. REFERENCE. Toxicology Division Topical Hazard Evaluation Program
   Procedural Guide, US Army Environmental Hygiene Agency (USAEHA), January
   1982.

3. PURPOSE. The purpose of this program is to provide guidance for
   further entomological testing of the candidate insect repellents
   A13-38359a, A13-38282, A13-38277a, A13-38865a, and A13-38866a, US
   Department of Agriculture (USDA) Proprietary Chemicals.

4. SUMMARY OF FINDINGS. Hazard evaluations of the candidate insect
   repellents A13-38359a, A13-38282, A13-38277a, A13-38865a, and A13-38866a,
   USDA Proprietary Chemicals, were conducted by this Agency using New Zealand
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White rabbits, Sprague-Dawley rats, and albino Hartley guinea pigs. A tabular presentation of animal toxicity data developed by this Agency follows:†

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>
</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>All tested chemicals did not produce primary irritation of the intact skin and no greater than mild primary irritation of the skin surrounding an abrasion.</td>
<td>USAEHA Category I (ref Appendix A)</td>
</tr>
<tr>
<td>0.5 mL technical grade chemical applied to each of six rabbits.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EYE IRRITATION STUDIES</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 nine New Zealand White rabbits. Three of the nine rabbits had the eye flushed with warm water for 1 minute, 25 seconds after application.</td>
<td>Chemical A13-38359a and AI3-38666a produced mild injury to the cornea and, in addition, some injury to the conjunctiva. Chemicals A13-38282, A13-38277a, and A13-38865a produced moderate injury to the cornea and, in addition, some injury to the conjunctiva. Occular injury had healed by 7 days post-application. Washing did not significantly decrease ocular injury.</td>
<td>USAEHA Category C (ref Appendix A) USAEHA Category E (ref Appendix A)</td>
</tr>
</tbody>
</table>

† 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>
<thead>
<tr>
<th>Test</th>
<th>Results</th>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>APPROXIMATE LETHAL DOSE</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Oral</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rats (male) – no diluent</td>
<td>A13-38359a &gt;3,333 mg/kg</td>
<td>These chemicals</td>
</tr>
<tr>
<td></td>
<td>A13-3866a &gt;5,000 mg/kg</td>
<td>demonstrated</td>
</tr>
<tr>
<td></td>
<td>A13-38282 987 mg/kg</td>
<td>slight to</td>
</tr>
<tr>
<td></td>
<td>A13-38277a 2,222 mg/kg</td>
<td>moderate toxicity</td>
</tr>
<tr>
<td></td>
<td>A13-3885a 987 mg/kg</td>
<td>upon ingestion.</td>
</tr>
<tr>
<td></td>
<td>A13-3886a &gt;1,480 mg/kg</td>
<td></td>
</tr>
<tr>
<td><strong>PHOTOCHEMICAL SKIN IRRITATION STUDIES</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Rabbits</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>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.</td>
<td>These chemicals did not produce photo-chemical irritation under test conditions.</td>
<td>These chemicals are not expected to produce a photo-chemical irritation reaction in humans.</td>
</tr>
<tr>
<td><strong>Control</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Following UV exposure of the rabbits, 0.05 mL of test chemical, positive control and diluent were applied to additional skin areas to serve as un-irradiated control sites. Application areas were checked for skin irritation at 24, 48 and 72 hours.</td>
<td>Positive control application and irradiation caused greater irritant effects than in un-irradiated skin areas.</td>
<td></td>
</tr>
</tbody>
</table>
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<thead>
<tr>
<th>Test</th>
<th>Results</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>SENSITIZATION STUDIES</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Guinea Pigs (Female)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intradermal (ID) injections of 0.1 mL of a minimally irritating concentration of each tested chemical or of dinitrochlorobenzene (DNCB)* in a mixture containing 1 volume of propylene glycol and 29 volumes of saline:</td>
<td></td>
<td></td>
</tr>
<tr>
<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 chemical.</td>
<td>Challenge doses of A13-38277a, A13-38865a, and A13-38866a did not produce sensitization reactions.</td>
<td>These chemicals are not expected to produce a sensitization reaction in humans.</td>
</tr>
<tr>
<td></td>
<td>Chemicals A13-38359a and A13-38282 produced moderate to marked sensitization reactions in 5 of 10 and 4 of 10 guinea pigs, respectively.</td>
<td>These chemicals could produce sensitization reactions in humans.</td>
</tr>
<tr>
<td>Control</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>These guinea pigs responded to sensitizing agents</td>
</tr>
</tbody>
</table>

* A known skin sensitizing agent.

5. CONCLUSION. These compounds produced no primary irritation of the intact skin and no greater than mild primary irritation of the skin surrounding an abrasion. Chemicals A13-38359a and A13-38866a produced mild injury to the cornea and, in addition, some injury to the conjunctiva. Chemicals A13-38277a, A13-38865a, and A13-38282a produced moderate injury to the cornea and, in addition, some injury to the conjunctiva. This
Injury had healed by 7 days post-application. Chemicals A13-38359a and A13-38282 produced moderate to marked sensitization in 5 of 10, and 4 of 10, guinea pigs, respectively. The other chemicals did not produce sensitization reactions. All tested chemicals did not cause a photo-chemical irritation reaction and demonstrated slight to moderate oral toxicity. These studies were monitored by the Analytical Quality Assurance Office (see Appendix B).

6. RECOMMENDATION. Recommend that chemical A13-38866a be approved for further testing as a candidate insect repellent. Further testing should be conducted on chemicals A13-38277a and A13-38865a only if their entomological efficacy is equivalent or superior to currently approved repellents due to their potential to produce ocular injury. Recommend that chemicals A13-38359a and A13-38282 be disapproved for further testing due to their sensitizing potential.
APPENDIX A

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

ANALYTICAL QUALITY ASSURANCE

The Analytical Quality Assurance Office certifies the following:

a. These studies were conducted in accordance with:

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

   (2) Title 21, Code of Federal Regulations (CFR), 1983 rev, Part 58, Good Laboratory Practice for Nonclinical Laboratory Studies.

   (3) Final Rule, Pesticide Programs; Good Laboratory Practice Standards; 48 Federal Register (FR) 53963-53969, 29 November 1983.

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

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

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