UNITED STATES ARMY
ENVIRONMENTAL HYGIENE
AGENCY

ABERDEEN PROVING GROUND, MD 21010-5422

TOPICAL HAZARD EVALUATION PROGRAM
OF
CANDIDATE INSECT REPELLENT AI36328-b
1-[(6-METHYL-3-CYCLOHEXEN-1-YL)CARBONYL] PYRROLIDINE
STUDY NO. 75-51-0434-87
MARCH 1987

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**Topical Hazard Evaluation Program of Candidate Insect Repellent A13-36328-b**

**Study No.** 75-51-0434-87, March 1987

**PERSONAL AUTHORS**
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**TYPE OF REPORT**
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**DATE COVERED**
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**ABSTRACT**
To provide guidance for further entomological testing of the Candidate Insect Repellent A13-36328-b, 1-[(6-methyl-3-cyclohexen-1-yl) carbonyl]pyrrolidine. HAZARDS, TOXICITY, skin irritation.

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SUBJECT: Topical Hazard Evaluation Program of Candidate Insect Repellent, A13-36328-b, 1-[(6-Methyl-3-cyclohexen-1-yl)carbonyl] pyrrolidine, Study No. 75-51-0434-87, March 1987

EXECUTIVE SUMMARY

The purpose and recommendations of the enclosed report follow:

a. Purpose. To provide guidance for further entomological testing of the Candidate Insect Repellent A13-36328-b by means of laboratory animal studies using New Zealand white rabbits. In addition, these data may be useful in developing preliminary safety guidelines for handling this compound.

b. Recommendations. Based on professional scientific judgment, the following recommendations are offered.

(1) A13-36328-b should be disapproved for further extensive entomological and toxicological testing.

(2) If chemical A13-36328-b is accidently introduced into the eyes, they should be flushed immediately with copious amounts of water.

(3) If efficacy data is felt to warrant further entomological studies of this chemical, it should be resubmitted in a repurified form and/or at the intended use concentration.

FOR THE COMMANDER:

Colonel, MC
Director, Occupational and Environmental Health

Encl

CF:
HQDA(DASG-PSP-E) (wo/encl)
Dir, Advisory Cen on TOX, NRC (2 cy) (w/encl)
Commdt, AMS (HSHA-IPM) (w/encl)
USDA, ARS (Dr. Terrence McGovern) (w/encl)
USDA, ARS-Southern Region (3 cy) (w/encl)
USDA, ARS-Southern Region (COL Moussa) (w/encl)
Cdr, USAMRDC (SGRD-DPM) (COL Reinert) (w/encl)
Topical Hazard Eval Program Study No. 75-51-0434-87, March 1987


3. PURPOSE. To provide guidance for further entomological testing of the Candidate Insect Repellent A13-36328-b.

4. MATERIALS AND METHODS. *†

   a. Testing for primary skin irritation and primary eye irritation was conducted using New Zealand white rabbits from Hazleton-Dutchland Laboratories, Denver, Pennsylvania.

   b. The sample tested in these studies was synthesized by Dr. Terrence P. McGovern, Organic Chemical Synthesis Laboratory, USDA, Beltsville, Maryland.

   c. Primary skin and eye irritation studies were performed as described in reference 2b on subject chemical.

5. SUMMARY OF FINDINGS. A tabular presentation of animal toxicity data developed by this Agency on the candidate insect repellent A13-36328-b is shown in the Table.

6. DISCUSSION. Previous studies have shown that this compound produced only mild primary skin irritation and that it was not a photoskin irritant or a potential sensitizer (ref 2d). Although these studies also showed moderate irritation to corneal tissues at 24 hours they did not report the results of resolution at 7 and 21 days. In the present study A13-36328-b produced mild primary irritation to the skin of rabbits as a technical grade compound and as a 25 percent ethanol solution (Appendix A, Category II). It also caused severe injury to the cornea of rabbit eyes developing into ulceration and vascuization (Appendix A, Category F). Caution should be exercised should this chemical ever be tested further.

† The studies reported herein were performed in animal facilities fully accredited by the American Association for the Accreditation of Laboratory Animal Care.
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</td>
<td>Chemical AI3-36328-b,</td>
<td>USAEHA Category II</td>
</tr>
<tr>
<td>to intact and abraded skin</td>
<td>produced mild primary</td>
<td>(ref App A)</td>
</tr>
<tr>
<td>of New Zealand White rabbits</td>
<td>skin irritation of the</td>
<td></td>
</tr>
<tr>
<td></td>
<td>intact skin and the skin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>surrounding an abrasion.</td>
<td></td>
</tr>
<tr>
<td>0.5 mL technical grade</td>
<td>Chemical AI3-36328-b</td>
<td>USAEHA Category II</td>
</tr>
<tr>
<td>chemical applied to each</td>
<td>produced mild to moderate</td>
<td>(ref App A)</td>
</tr>
<tr>
<td>of six rabbits.</td>
<td>primary skin irritation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>of the intact skin of</td>
<td></td>
</tr>
<tr>
<td></td>
<td>rabbits. Irritation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>had resolved 3 days after</td>
<td></td>
</tr>
<tr>
<td></td>
<td>application.</td>
<td></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>
</tr>
<tr>
<td>Single 24-hour application</td>
<td>Chemical AI3-36328-b,</td>
<td>USAEHA Category B</td>
</tr>
<tr>
<td>of 0.1 mL technical grade</td>
<td>produced pathological</td>
<td>(ref Appendix A)</td>
</tr>
<tr>
<td>chemical to one eye of each</td>
<td>changes to the cornea, i.e.</td>
<td>To be used with extreme caution</td>
</tr>
<tr>
<td>of nine New Zealand White</td>
<td>corneal ulceration with</td>
<td>around the eyes and mucose. Keep</td>
</tr>
<tr>
<td>rabbits. Three of the nine</td>
<td>vascularization was</td>
<td>away from all ocular areas.</td>
</tr>
<tr>
<td>rabbits had the eye flushed</td>
<td>observed after 14 and 21 days.</td>
<td></td>
</tr>
<tr>
<td>with warm water for 1 minute,</td>
<td></td>
<td></td>
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<tr>
<td>25 seconds after application.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
7. RECOMMENDATIONS. Based on professional scientific judgment, the following recommendations are offered. Recommend chemical AI3-36328-b be disapproved for further entomological and toxicological studies. If efficacy data of this chemical warrants further study, it should be resubmitted in a further purified form and/or at the intended use concentration.

Maurice H. Weeks
Chief, Toxicology Division

William T. Muehsam
SGT, USA
Animal Care Specialist
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. (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 or compounds producing necrosis, vesiculation, or eschars. (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 (e.g., nose and mouth).
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.

   (2) Title 21, Code of Federal Regulations (CFR), 1986 rev, Part 58, Good Laboratory Practice for Nonclinical Laboratory Studies.

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 the study.

TIMOTHY L. FISHER
Chief, Analytical Quality Assurance Office
SUPPLEMENTARY INFORMATION
MEMORANDUM FOR: ADMINISTRATOR, DEFENSE TECHNICAL INFORMATION MANAGEMENT CENTER, CAMERON STATION, ALEXANDRIA, VA 22304-6145

SUBJECT: Topical Hazard Evaluation Program of Candidate Insect Repellent, AI3-36328-b, 1-[(6-Methyl-3-cyclohexen-1-yl)carbonyl] pyrrolidine, Study No. 75-51-0434-87, March 1987

The following pen and ink changes should be made to the subject report.

a. Cover Sheet, line 3, change A136328-b to A13-36328-b.

b. Page 3, Column 3, last entry, line 1, change USAEHA Category B to USAEHA Category F.

FOR THE COMMANDER:

N. JOE THOMPSON
Colonel, MC
Director, Occupational and Environmental Health
END

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