Topical Hazard Evaluation Program of Candidate Insect Repellent A13-36436, US Department of Agriculture Proprietary Amide

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A preliminary hazard evaluation of A13-36436 was performed by means of laboratory animal studies using rats, rabbits and guinea pigs. The technical grade compound did not produce eye or skin irritation, or cause a photochemical irritation in rabbits, did not sensitize guinea pigs and did not demonstrate an acute ingestion hazard. It was recommended that A13-36436 be approved for further testing as a candidate insect repellent.
SUBJECT: Topical Hazard Evaluation Program of Candidate Insect Repellent
A13-36436, US Department of Agriculture Proprietary Amide, Study

Executive Secretary
Armed Forces Pest Control Board
Forest Glen Section, WRAMC
Washington, DC 20012

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

A preliminary hazard evaluation of A13-36436 was performed by means of
laboratory animal studies using rats, rabbits and guinea pigs. The technical
grade compound did not produce eye or skin irritation, or cause a
photochemical irritation in rabbits, did not sensitize guinea pigs and did
not demonstrate an acute ingestion hazard. It was recommended that A13-36436
be approved for further testing as a candidate insect repellent.

FOR THE COMMANDER:

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1. AUTHORITY.
   
a. Letter, US Department of Agriculture - Agricultural Research Service, 
   Southern Region, Insects Affecting Man-Research Laboratory, Gainesville, 
   
b. Memorandum of Understanding between the Department of the Army, 
   Office of The Surgeon General; the US Army Health Services Command; the US 
   Army Environmental Hygiene Agency; the Armed Forces Pest Control Board; and 
   the US Department of Agriculture, effective 1970 with Amendment No. 1 
   effective August 1974.

2. REFERENCE. Toxicology Division Procedural Guide, USAEHA, 1972, revised 
   1976.

3. PURPOSE. The purpose of this program is to provide guidance for further 
   entomological testing of the candidate insect repellent A13-36436.

4. SUMMARY OF FINDINGS. A hazard evaluation of the candidate repellent 
   A13-36436, USDA Proprietary Amide, 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:*

* 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, 
† 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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**SKIN IRRITATION STUDIES**

**Rabbits**

<table>
<thead>
<tr>
<th>Test</th>
<th>Results</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single 24-hour application to intact and abraded skin of New Zealand White rabbits.</td>
<td>Compound AI3-36436 produced no primary irritation of the intact skin or to the skin surrounding an abrasion.</td>
<td>USAEHA Category I (ref Appendix).</td>
</tr>
<tr>
<td>0.5 ml technical grade compound applied to each of six rabbits.</td>
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**EYE IRRITATION STUDIES**

**Rabbits**

<table>
<thead>
<tr>
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<th>Results</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Single 24-hour application of 0.1 ml technical grade compound to one eye of each of six New Zealand White rabbits.</td>
<td>Compound AI3-36436 did not produce any injury to the cornea, and, in addition, no injury to the conjunctiva in six out of six rabbits.</td>
<td>USAEHA Category A (ref Appendix).</td>
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**APPROXIMATE LETHAL DOSE (ALD)**

**Oral**

<table>
<thead>
<tr>
<th>Test</th>
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<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rats (male) - no diluent</td>
<td>ALD&gt;7400 mg/kg</td>
<td>Presents little lethal hazard from accidental ingestion.</td>
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</table>
PHOTOCHEMICAL SKIN IRRITATION STUDIES

Rabbits

A single application (0.05 ml) of a 25 percent (w/v) solution of the compound (AI3-36436) 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 AI3-36436 in ethanol did not cause a photochemical irritation reaction under test conditions. Positive control application and irradiation caused greater irritant effects than in unirradiated skin areas.

Control

Following UV exposures of the rabbits, 0.05 ml of test compound, 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.
**SENSITIZATION STUDIES**

**Guinea Pigs (Male)**

<table>
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</tr>
</thead>
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<tr>
<td>Intradermal injections of 0.1 ml of a 0.1 percent suspension (w/v) of AI3-36436 or of dinitrochlorobenzene (DNCB)* in a mixture containing 1 volume of propylene glycol and 29 volumes of saline.</td>
<td>Challenge dose of test compound (last intradermal injection) did not produce a sensitization reaction.</td>
<td>Compound AI3-36436 did not produce a sensitization reaction under these test conditions and is not expected to produce a sensitization reaction in man.</td>
</tr>
<tr>
<td>Ten test guinea pigs received and challenged with a 0.1 percent solution of AI3-36436.</td>
<td></td>
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<tr>
<td>Ten positive control guinea pigs received and challenged with a 0.1 percent solution of DNCB.</td>
<td>Positive controls (DNCB) produced a marked sensitization reaction in 10 out of 10 guinea pigs.</td>
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</tr>
</tbody>
</table>

* A known skin sensitizer.
5. CONCLUSION. Technical grade compound A13-36436 presents no acute hazard from eye, skin, photochemical or sensitization contact or from acute ingestion.

6. RECOMMENDATION. Under the provision of the Memorandum of Understanding (para 1b), it is recommended that A13-36436, USDA Proprietary Amide, be approved for further testing as a candidate insect repellent.

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General Veterinary Officer
Toxicology Division

APPROVED:

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Chief, Toxicology Division
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.