TOPICAL HAZARD EVALUATION PROGRAM
OF CANDIDATE INSECT REPELLENTS
AI3-34155, 1-(4-CHLOROPHENOXY)-2-(2-METHOXYETHOXY)-ETHANE AND
AI3-34156, 1-(4-CHLOROPHENOXY)-2-(2-ETHOXYETHOXY)-ETHANE
STUDY NOS. 75-51-0015-80 AND 75-51-0016-80
FEBRUARY 1977 - APRIL 1980

Approved for public release, distribution unlimited.
Preliminary hazard evaluations of A13-34155 and A13-34156 were performed by means of laboratory animal studies using rats, rabbits, and guinea pigs. The technical grade compounds did not cause skin, eye, or photo irritation. They did not prove to be skin sensitizers or to be acutely toxic by ingestion. It was recommended that both compounds be approved for further testing as candidate insect repellents.
SUBJECT: Topical Hazard Evaluation Program of Candidate Insect Repellents
AI3-34155, 1-(4-chlorophenoxy)-2-(2-methoxyethoxy)-ethane, and
AI3-34156, 1-(4-chlorophenoxy)-2-(2-ethoxyethoxy)-ethane, Study
Nos. 75-51-0015-80 and 75-51-0016-80, February 1977 - April 1980

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

Preliminary hazard evaluations of AI3-34155 and AI3-34156 were performed
by means of laboratory animal studies using rats, rabbits, and guinea pigs. The
technical grade compounds did not cause skin, eye, or photo irritation. They
did not prove to be skin sensitizers or to be acutely toxic by ingestion. It
was recommended that both compounds be approved for further testing as
candidate insect repellents.

FOR THE COMMANDER:

JOHN F. MAZUR
MAJ, MSC
Director, Laboratory Services

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<td>NTIS 340243</td>
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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 the candidate insect repellents A13-34155 and A13-34156.

4. SUMMARY OF FINDINGS. Hazard evaluations of the candidate repellents A13-34155 and A13-34156 were 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) 74-23, revised 1978.
† The experiments reported herein were performed in animal facilities fully accredited by the American Association for the Accreditation of Laboratory Animal Care.

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TABLE. PRESENTATION OF DATA

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<thead>
<tr>
<th>Test</th>
<th>Results</th>
<th>Interpretation</th>
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<tbody>
<tr>
<td><strong>SKIN IRRITATION STUDIES</strong></td>
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<tr>
<td>Rabbits</td>
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<tr>
<td>Single 24-hour application to intact and abraded skin of New Zealand White rabbits.</td>
<td>Compounds AI3-34155 and AI3-34156 did not cause any irritation of the intact skin or of the skin surrounding an abrasion.</td>
<td>USAHA Category I (ref Appendix).</td>
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<tr>
<td>0.5 mL technical grade compound applied to each of six rabbits.</td>
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<tr>
<td><strong>EYE IRRITATION STUDIES</strong></td>
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<td></td>
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<tr>
<td>Rabbits</td>
<td></td>
<td></td>
</tr>
<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>Compounds AI3-34155 and AI3-34156 did not cause any irritation to the eyes of rabbits.</td>
<td>USAHA Category A (ref Appendix).</td>
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<tr>
<td><strong>APPROXIMATE LETHAL DOSE (ALD)</strong></td>
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<td></td>
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<tr>
<td>Oral</td>
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<tr>
<td>Rats (male)-no diluent</td>
<td>For AI3-34155, the ALD was determined to be 1125 mg/kg. For AI3-34156, the ALD was 3300 mg/kg.</td>
<td>Neither compound presents much lethal hazard from accidental ingestion.</td>
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PHOTOCHEMICAL SKIN IRRITATION STUDIES

Rabbits

A single 0.05 mL application of a 25 percent (w/v) solution of each compound 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.

Neither compound in ethanol caused a photochemical irritation reaction under test conditions. Compounds AI3-34155 and AI3-34156 did not cause a photochemical irritation reaction under test conditions and are not expected to cause a photochemical irritation in humans.

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.

Positive control application and irradiation caused greater irritant effects than in unirradiated skin areas.
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#### SENSITIZATION STUDIES

**Guinea Pigs (Male)**

Intradermal injections of 0.1 mL of a 0.1 percent solution (w/v) of A13-34155, A13-34156 or of dinitrochloro-benzene (DNCB)* in a mixture containing 1 volume of propylene glycol and 29 volumes of saline.

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

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

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<td>Challenge doses of A13-34155 and A13-34156 did not produce sensitization reaction.</td>
<td>Compounds A13-34155 and A13-34156 did not produce sensitization reactions under test conditions and are not expected to produce sensitization reactions in man.</td>
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<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
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5. CONCLUSION. Technical grade compounds A13-34155 and A13-34156 did not cause any skin, eye, or photo irritation, no sensitization reaction, and did not prove to be an acute ingestion hazard.

6. RECOMMENDATION. Under the provisions of the Memorandum of Understanding (paragraph 1b), it is recommended that A13-34155 and A13-34156 be approved for further testing as candidate insect repellents.

ALLEN W. SINGER
CPT, VC
General Veterinary Officer
Toxicology Division

APPROVED:

ARthur H. McCreesh, Ph.D.
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.
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