AD-A173 453 PRELIMINARY ASSESSMENT OF THE RELATIVE TOXICITY OF AI3-36174 IN ANIMALS M..(U) ARMY ENVIRONMENTAL HYGIENE AGENCY ABERDEEN PROVING GROUND MD G J LEACH SEP 86 1/1

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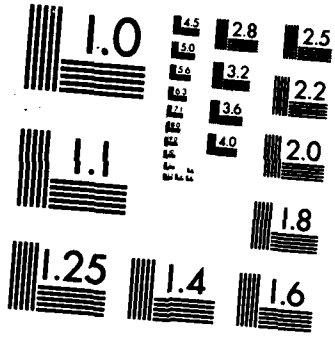

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UNITED STATES ARMY ENVIRONMENTAL HYGIENE AGENCY

ABERDEEN PROVING GROUND, MD 21010-5422

AEHA

PRELIMINARY ASSESSMENT OF THE RELATIVE TOXICITY OF
AI3-36174 IN ANIMALS
STUDY NO. 75-51-0531-86
MARCH 1985 - JULY 1986

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UNCLASSIFIED
SECURITY CLASSIFICATION OF THIS PAGE

AD-A173 453

REPORT DOCUMENTATION PAGE

1a. REPORT SECURITY CLASSIFICATION UNCLASSIFIED	1b. RESTRICTIVE MARKINGS
2a. SECURITY CLASSIFICATION AUTHORITY	3 DISTRIBUTION / AVAILABILITY OF REPORT Approved for Public Release; Distribution Unlimited
2b. DECLASSIFICATION / DOWNGRADING SCHEDULE	
4. PERFORMING ORGANIZATION REPORT NUMBER(S) 75-51-0531-86	5. MONITORING ORGANIZATION REPORT NUMBER(S)
6a. NAME OF PERFORMING ORGANIZATION US Army Environmental Hygiene Agency 6b OFFICE SYMBOL (If applicable) HSHB-MO-T	7a. NAME OF MONITORING ORGANIZATION
6c. ADDRESS (City, State, and ZIP Code) Aberdeen Proving Ground, MD 21010-5422	7b. ADDRESS (City, State, and ZIP Code)
8a. NAME OF FUNDING / SPONSORING ORGANIZATION 8b. OFFICE SYMBOL (If applicable)	9. PROCUREMENT INSTRUMENT IDENTIFICATION NUMBER
8c. ADDRESS (City, State, and ZIP Code)	10 SOURCE OF FUNDING NUMBERS PROGRAM ELEMENT NO. / PROJECT NO. / TASK NO. / WORK UNIT ACCESSION NO.

11. TITLE (Include Security Classification) Preliminary Assessment of the Relative Toxicity of AI3-36174 in Animals, Study No. 75-51-0531-86, March 1985 - July 1986

12. PERSONAL AUTHOR(S)
Glenn J. Leach

13a. TYPE OF REPORT	13b. TIME COVERED	14. DATE OF REPORT (Year, Month, Day)	15. PAGE COUNT
Study	FROM Mar 85 TO Jul 86	86/09	12

16. SUPPLEMENTARY NOTATION

17. COSATI CODES			18. SUBJECT TERMS (Continue on reverse if necessary and identify by block number)
FIELD	GROUP	SUB-GROUP	Candidate Cockroach Repellents, AI3-36174, Toxicity Screening Tests

19. ABSTRACT (Continue on reverse if necessary and identify by block number)

Preliminary toxicity data are presented for the candidate cockroach repellent AI3-36174. These data are intended to provide guidance in selecting compounds for further entomological and toxicological evaluation. The rat oral approximate lethal dose was found to be >5000 mg/kg. This compound produced moderate to severe skin and eye irritation in rabbits. When tested in both neat and dilute concentrations, AI3-36174 caused mild sensitization reactions in guinea pigs. It was not mutagenic in the Ames test and there were no statistically significant physiological changes in anesthetized rats. At room temperature, this compound was not an inhalation hazard; however, if heated, vapor concentrations may reach sufficient levels to cause skin, eye and respiratory irritation.

(≥ or =)

20. DISTRIBUTION / AVAILABILITY OF ABSTRACT	21. ABSTRACT SECURITY CLASSIFICATION
☒ UNCLASSIFIED/UNLIMITED ☐ SAME AS RPT. ☐ DTIC USERS	UNCLASSIFIED

22a NAME OF RESPONSIBLE INDIVIDUAL	22b TELEPHONE (Include Area Code)	22c. OFFICE SYMBOL
Glenn J. Leach	(301) 671-3980	HSHB-MO-T

DD FORM 1473, 84 MAR 83 APR edition may be used until exhausted. All other editions are obsolete

SECURITY CLASSIFICATION OF THIS PAGE
UNCLASSIFIED

DEPARTMENT OF THE ARMY
U. S. ARMY ENVIRONMENTAL HYGIENE AGENCY
ABERDEEN PROVING GROUND, MARYLAND 21010-5422

REPLY TO ATTENTION OF

HSHB-MO-T

30 September 1986

SUBJECT: Preliminary Assessment of the Relative Toxicity of AI3-36174 in Animals, Study No. 75-51-0531-86, March 1985 - July 1986

Executive Director
Armed Forces Pest Management Board
Forest Glen Section, WRAMC
Washington, DC 20307-5001

EXECUTIVE SUMMARY

The purpose and a summary of the recommendations of the enclosed report follow:

a. Purpose. To provide preliminary toxicity data for the candidate cockroach repellent AI3-36174. These data are intended to provide guidance in selecting compounds for further entomological and toxicological evaluation. In addition, the data may be useful in developing preliminary safety guidelines for handling this compound.

b. Recommendations. Due primarily to the severity of skin and eye damage and its potential for producing skin sensitization, we recommend AI3-36174 be disapproved for additional developmental work as a candidate cockroach repellent. This recommendation is based on professional scientific judgment.

FOR THE COMMANDER:

Encl

N. [illegible] THOMPSON
Colonel, MC
Director, Occupational and [illegible]
Environmental Health

CF:
HQDA(DASG-PSP) (wo/encl)
Comdt, AHS (HSHA-IPM) (w/encl)
Dir, Advisory Cen on Tox, NRC (2 cy) (w/encl)
USDA, ARS (Dr. Terrence McGovern) (w/encl)
USDA, ARS - Southern Region (w/encl)
Cdr, USMRDC (SGRD-DPM/COL Reinert) (w/encl)

QUALITY INSPECTED 4

A-1

DEPARTMENT OF THE ARMY
U. S. ARMY ENVIRONMENTAL HYGIENE AGENCY
ABERDEEN PROVING GROUND, MARYLAND 21010-5422

REPLY TO ATTENTION OF

HSHB-MO-T

PRELIMINARY ASSESSMENT OF THE RELATIVE TOXICITY OF
AI3-36174 IN ANIMALS
STUDY NO. 75-51-0531-86
MARCH 1985 - JULY 1986

1. AUTHORITY.

a. Letter, US Department of Agriculture - Agricultural Research Service, Southern Region, Insects Affecting Man and Animals Research Laboratory, Gainesville, Florida, 5 December 1984.

b. Memorandum of Understanding between the US Army Environmental Hygiene Agency; the US Army Health Services Command; the Department of tne Army, Office of The Surgeon General; the Armed Forces Pest Control Board and the Department of Agriculture, Agricultural Research, Science and Education Administration; titled, Coordination of Biological and Toxicological Testing of Pesticides, effective 23 January 1979.

2. REFERENCES.

a. Topical Hazard Evaluation Program Procedure Guide, Toxicology Division, US Army Environmental Hygiene Agency (USAEHA), October 1985.

b. Standing Operating Procedures, HSHB-OT, Toxicology Division, USAEHA.

c. Final Report, Mutagenicity Evaluation of AI3-36174C in the Ames Salmonella/Microsome Reverse Mutation Assay, Hazleton Biotechnologies Company, HBC Project No. 20988, July 1986.

3. PURPOSE. To provide preliminary toxicity data for the candidate cockroach repellent AI3-36174. This report summarizes the toxicological data for USDA candidate cockroach repellent AI3-36174. These data are intended to be used in selecting compounds for more extensive entomological and toxicological testing. The data may also be used in establishing preliminary safety guidelines for handling the material.

4. BACKGROUND.

a. General. The preliminary toxicological evaluation of candidate cockroach repellents consists of a series of acute screening tests designed to assess potential hazards from single exposures by various routes of administration. The test battery included:

Use of company names does not imply endorsement by the US Army, but is intended only to assist in identification of a specific product.

(1) Rat oral approximate lethal dose (ALD).

(2) Primary irritation (skin and eye).

(3) Dermal sensitization.

(4) Saturated vapor (inhalation hazard).

(5) Physiological screen.

(6) Mutagenicity (Ames test).

b. Project Information.

(1) All raw data from this study may be found in project file number 75-51-0531-86 or USAEHA Laboratory Notebooks Numbered 101, 106, 114, and 115.

(2) In conducting the studies described in this report, the investigators adhered to reference 2a. In addition, these studies were performed in animal facilities fully accredited by the American Association for the Accreditation of Laboratory Animal Care.

5. PROCEDURES.

a. Test Compound. Two lots (b & c) of AI3-36174 were synthesized and supplied for use in the toxicological evaluations by Dr. Terrance McGovern, USDA, Beltsville, Maryland. AI3-36174 is a clear colorless liquid. It exhibits low solubility in water but is soluble in acetone and other organic solvents. It has a molecular weight of 181 and boils at 72 °C at 0.05 mm Hg.

b. Methods.

(1) Acute Toxicity Tests. Detailed descriptions of the methodology for tests a through d listed below are published in reference 2b. Methodology for test (e) is published in reference 2c.

(a) Rat ALD.

(b) Skin irritancy.

(c) Eye irritancy.

(d) Dermal sensitization (Buehler technique).

(e) Saturated vapor.

(2) Mutagenicity. Mutagenicity testing was performed by Hazleton Biotechnologies Company under contract DAAD05-86-M-L723 with USAEHA. A complete description of the methodology and results may be found in the final report (reference 2d).

(3) Physiological Screening. The physiological screening tests were designed to obtain basic information on the underlying mechanisms of action for this compound. Male Sprauge Dawley rats weighing between 270 - 380 gms were anesthetized with sodium pentabarbital (30 mg/kg). A heparinized cannula (15 cm length of PE50 tubing) was inserted into the left carotid artery for blood pressure monitoring. A similar catheter was inserted into the right external jugular vein for drug injection. A Statham P23-AC fluid filled pressure transducer (Gould Instruments) was used for blood pressure monitoring. The signals were processed by a Buxco Model 6 Pulmonary Function Analyzer (Buxco Electronics) and printed on a Texas Instruments® Silent 700 terminal. EKG's were monitored from LEAD II and fed through a pre-amplifier and Buxco EKG analyzer. A digital recording of wave heights and intervals was printed on a second Texas Instruments TI terminal. Following a short period of time, usually 10-15 minutes, stable physiological recordings were obtained and the animals were treated with challenge doses of standard pharmacological drugs including epinephrine, nor-epinephrine, acetylcholine and histamine. Saline injections served as a volume control. Preliminary experiments were performed in order to find optimum dosage levels. In most cases, the dosage chosen produced a marked change in blood pressure (10-50 mm Hg) lasting less than 5 minutes. Following the initial drug challenges, the test compound AI3-36174 was injected intraperitoneally, and the drug challenges were repeated 15 minutes post injection. For each drug, the maximum change from baseline condition was recorded and the pre- and post-dosing values compared. In this way, each animal served as its own control. The data were analyzed using a two-way analysis of variance with repeated measures program on an IBM® PC microcomputer. A least significant range test was used to compare pre and post-dosing values. A probability of less than 0.05 was used as the level of significance.

6. RESULTS.

a. ALD. The rat oral ALD was found to be $\geq$5000 mg/kg (Appendix A, Table A-1). This was the only dose that produced lethalities. This rat exhibited ataxia within 2 minutes of dosing and died overnight. Post mortem examination indicated hemorrhagic areas in the stomach and lungs. None of the other animals showed any toxic effects and all appeared normal when necropsied 14 days after dosing.

b. Skin Irritation. Compound AI3-36174 produced a total irritancy score of 7.5 in the Draize rabbit skin irritancy test. A description of the scoring system employed in these tests is provided at Appendix B. Based on this scoring system, AI3-36174 would be considered a moderate to severe skin irritant. Severe eschars were produced in all rabbits by 72 hours post application.

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c. Eye Irritation. Based on our Draize eye test in rabbits, this compound is a moderate to severe eye irritant with a total irritancy score of 30. It produced injury to both cornea and conjunctiva and the majority of the animals tested exhibited delayed healing, corneal opacity and circumcorneal vascularization. Washing did not appear to reduce the injury or healing time; however, all but one rabbit was healed by 7 days post application.

d. Skin Sensitization. When tested in neat concentrations, AI3-36174 was found to be a mild sensitizer. Due to the skin irritancy exhibited by this compound however, the data were equivocal. The sensitization test was repeated using non-irritating concentrations of compound. A 75 percent solution was used for induction and a 50 percent concentration for the challenge dose (80 percent ethanol diluent). Results from this second sensitization assay again indicated that AI3-36174 was a mild sensitizer.

e. Saturated Vapor. Data from the saturated vapor test are summarized in Tables A-1 and A-2 (Appendix A). The test protocol was modified resulting in 5 animal exposure groups in two separate tests. During the initial test (control, room temperature, high temperature groups) the high temperature bubbler was held at 50 °C rather than 100 °C. In the second test, a group was exposed using a 100 °C bubbler system and there was a concurrent air exposed group. Nominal exposure concentrations for the room temperature, 50 °C and 100 °C bubblers were 0.021 mg/L, 1.902 mg/L and 13.97 mg/L, respectively. Rats exposed to the highest concentration exhibited excessive salivation and rapid breathing, indicative of a respiratory irritant. Twenty four hours post exposure, all animals appeared normal. No rats died during the 8 hour exposure period however, during the 14 day post exposure period one rat from the control and 50 °C groups died.

f. Physiological Studies. Table A-3 (Appendix A) illustrates the cardiovascular effects of exposure to sublethal intraperitoneal injections of AI3-36174. The values presented represent the maximum change from resting or baseline levels in response to injections of the challenge drug. IP injections of AI3-36174 at dosages of 0.5 and 0.25 x ALD were lethal within 15 minutes to the anesthetized rats. We therefore chose 0.1 x ALD for the physiology experiments. At this dose, there were no statistically significant differences in the individual parameters measured however, there was a trend toward decreased blood pressure, heart rate, Rwave height and Pwave height. Responsiveness to the drug challenges also tended to be reduced in the compound treated rats. Additional physiological studies with this compound would be required to better elucidate the cardiovascular effects.

g. Mutagenicity. AI3-36174 did not exhibit mutagenic activity under the test conditions employed. It was negative in all test strains used (Salmonella typhimurium strains TA-1535, TA-1537, TA-1538, TA-98 and TA-100) and at dosages ranging from .1 µl to 25 µl per plate both activated and nonactivated test systems (reference 2c).

7. CONCLUSIONS. Compound AI3-36174 is moderately toxic by the oral route of exposure. It is a moderate to severe eye and skin irritant. This compound presents no acute inhalation hazard at room temperatures though at higher temperatures or if the repellent is atomized as an aerosol, it may cause skin, eye and respiratory irritation. It appears to be a mild sensitizer in both neat and diluted concentrations. It was not mutagenic in the Ames test. When administered at approximately 0.1 x the ALD to anesthetized, catherized rats, it did not produce any statistically significant cardiovascular effects, however, there was a tendency toward decreased blood pressure as well as an altered ECG.

8. RECOMMENDATIONS. Due primarily to the severity of the skin and eye damage and its potential for sensitizing skin, we recommend AI3-36174 be disapproved for additional developmental work as a cockroach repellent. This recommendation is based on professional scientific judgement.

9. ACKNOWLEDGEMENT. The project personnel shown in Appendix C assisted in the experiments.

Glenn J. Leach

GLENN J. LEACH
Biologist
Toxicology Division

APPROVED:

Maurice N. Weeks

MAURICE H. WEEKS
Chief, Toxicology Division

APPENDIX A

RESULTS

TABLE A-1. SUMMARY OF TOXICITY DATA CANDIDATE COCKROACH REPELLENT AI3-36174

ALD (Mg/Kg)	Skin Category	Eye Category	Sensitization	Sat Vapor	Physio	Ames
≥5000	IV	E	Positive	No deaths High conc- irritant	No signif- icant CV* effects	Negative

* Cardiovascular - Parameters monitored included blood pressure, heart rate and electrocardiogram in anesthetized rats.

TABLE A-2. SUMMARY OF SATURATED VAPOR RESULTS COMPOUND AI3-36174

Parameter/ Test Group	BW (grams)	$\frac{LW}{BW} \times 100$	$\frac{KW}{BW} \times 100$	$\frac{HW}{BW} \times 100$	$\frac{LGW}{BW} \times 100$	$\frac{TW}{BW} \times 100$	$\frac{BRW}{BW} \times 100$	$\frac{SW}{BW} \times 100$
Control	230 ± 8	5.734 ± 0.347	1.198 ± 0.098	0.494 ± 0.031	0.751 ± 0.041	0.947 ± 0.066	0.755 ± 0.038	0.498 ± 0.036
Room Temp	227 ± 3	5.460 ± 0.104	1.043 ± 0.044	0.474 ± 0.016	0.745 ± 0.048	0.964 ± 0.027	0.732 ± 0.028	0.358 ± 0.031
50 °C	228 ± 3	5.784 ± 0.290	1.160 ± 0.053	0.495 ± 0.020	0.692 ± 0.037	0.977 ± 0.023	0.725 ± 0.020	0.460 ± 0.038
Control-2	233 ± 3	5.830 ± 0.207	1.120 ± 0.028	0.467 ± 0.025	0.564 ± 0.065	0.914 ± 0.025	0.792 ± 0.008	0.347 ± 0.052
100 °C	231 ± 5	5.790 ± 0.115	1.161 ± 0.033	0.490 ± 0.014	0.694 ± 0.032	0.942 ± 0.038	0.808 ± 0.016	0.547 ± 0.058

Body weight (BW) and organ to body weight ratios, saturated vapor test, compound AI3-36174. Organ weights abbreviated as follows: Liver weight (LW), kidney weight (KW), heart weight (HW), lung weight (LGW), testes weight (TW), brain weight (BRW), spleen weight (SW). Numbers presented represent the mean ± standard error of the mean for six animals. There were no statistically significant differences among the three groups in any of the measured parameters.

TABLE A-3. SUMMARY OF PHYSIOLOGICAL DATA, COMPOUND AI3-36174

	BP		HR		QRS		QT		PW		RW		PH		RH	
	PRE	POST	PRE	POST	PRE	POST	PRE	POST	PRE	POST	PRE	POST	PRE	POST	PRE	POST
EPI	178 ± 6	155 ± 10	415 ± 14	355 ± 14	31 ± 2	31 ± 2	62 ± 1	62 ± 1	22 ± 2	23 ± 2	17 ± 2	18 ± 3	0.12 ± 0.02	0.10 ± 0.02	0.88 ± 0.07	0.76 ± 0.10
ACH	94 ± 5	62 ± 6	401 ± 12	323 ± 28	28 ± 2	29 ± 3	58 ± 3	58 ± 1	25 ± 1	18 ± 3	15 ± 2	16 ± 3	0.11 ± 0.02	0.06 ± 0.02	0.73 ± 0.08	0.66 ± 0.08
NE	161 ± 5	119 ± 15	408 ± 12	351 ± 19	30 ± 2	30 ± 2	61 ± 2	59 ± 1	24 ± 2	23 ± 2	17 ± 2	17 ± 3	0.14 ± 0.02	0.09 ± 0.02	0.80 ± 0.07	0.70 ± 0.09
HIST	96 ± 4	60 ± 9	384 ± 11	301 ± 26	28 ± 1	28 ± 2	58 ± 2	58 ± 2	26 ± 2	20 ± 3	15 ± 2	16 ± 2	0.11 ± 0.02	0.06 ± 0.02	0.71 ± 0.07	0.64 ± 0.07
SAL	116 ± 4	74 ± 8	367 ± 13	297 ± 21	30 ± 2	30 ± 2	61 ± 2	61 ± 2	27 ± 2	20 ± 3	17 ± 2	18 ± 3	0.13 ± 0.01	0.08 ± 0.02	0.76 ± 0.07	0.68 ± 0.08

Values presented are the mean ± the standard error of the mean for five animals. Maximum changes in response to drug challenges were recorded. Data were analyzed with a two way analysis of variance for repeated values. Table abbreviations are as follows: BP - blood pressure (mm HG), HR - heart rate (beats/min), WRS - width of QRS complex (msec), PW - P width (msec), RW - R - width (msec), PH - P height (millivolts), RH - R height (millivolts), PRE - pre-treatment response, Post - response to drug challenge 15 min post injection, EPI - epinephrine, ACH - acetylcholine, NE - nor epinephrine, HIST - histamine, SAL - saline. *Indicates significant difference when compared to pre exposure results. ($P < 0.05$)

Study No. 75-51-0331-86, March 1985 - July 1986

APPENDIX B

DEFINITIONS OF CATEGORIES OF SKIN AND EYE IRRITANTS

1. Skin irritants.

a. Category I - Compounds producing no irritation of intact skin or no greater than mild primary irritation of the skin surrounding an abrasion.

b. Category II - Compounds producing mild primary irritation of the intact skin and the skin surrounding an abrasion.

c. Category III - Compounds producing moderate primary irritation of the intact skin and the skin surrounding an abrasion.

d. 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.

e. Category V - Compounds impossible to classify because of staining of the skin or other masking effects owing to physical properties of the compound.

2. Eye irritants.

a. Category A - Compounds noninjurious to the eye.

b. Category B - Compounds producing mild injury to the cornea.

c. Category C - Compounds producing mild injury to the cornea and in addition some injury to the conjunctiva.

d. Category D - Compounds producing moderate injury to the cornea.

e. Category E - Compounds producing moderate injury to the cornea and in addition, some injury to the conjunctiva.

f. Category F - Compounds producing severe injury to the cornea and to the conjunctiva.

APPENDIX C

PROJECT PERSONNEL

The experiments described in this report were performed by a multidisciplinary group under the direction of Glenn Leach. The group included the following:

1. Lynn M. Balczewski, SGT, Lab Animal Care Specialist.
2. John G. Harvey, Bio Lab Tech.
3. John T. Houpt, Bio Lab Tech.
4. R. David Russell, CPT, VC.

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