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TOPICAL HAZARD EVALUATION PROGRAM OF CANDIDATE INSECT REPELLENT--ETC(U)  
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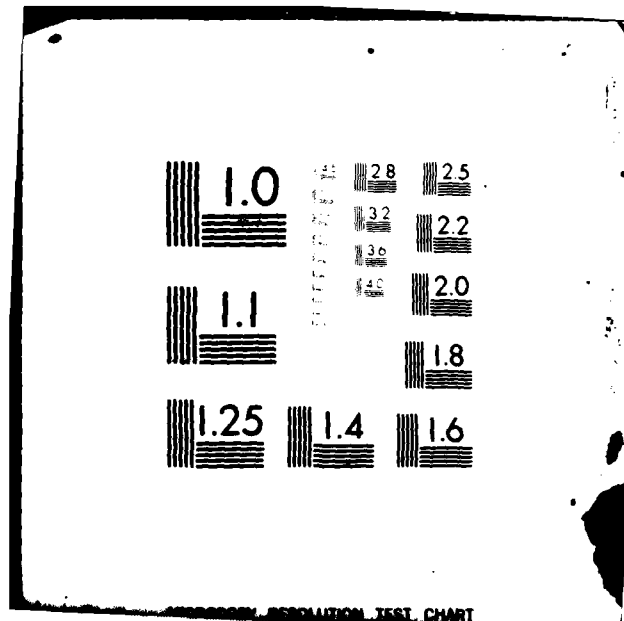
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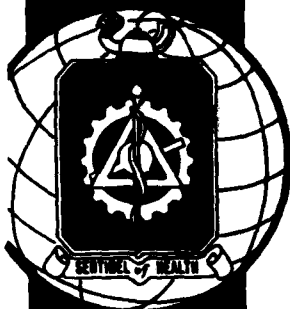
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**UNITED STATES ARMY  
ENVIRONMENTAL HYGIENE  
AGENCY**

**ABERDEEN PROVING GROUND, MD 21010**

TOPICAL HAZARD EVALUATION PROGRAM  
OF CANDIDATE INSECT REPELLENTS  
US DEPARTMENT OF AGRICULTURE PROPRIETARY CHEMICALS  
STUDY NOS. 75-51-0291-82, 75-51-0293-82 THRU 75-51-0297-82  
AND 75-51-0304-82  
FEBRUARY 1981 - APRIL 1982 .

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| REPORT DOCUMENTATION PAGE                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                  | READ INSTRUCTIONS<br>BEFORE COMPLETING FORM                  |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------|--------------------------------------------------------------|
| 1. REPORT NUMBER: 75-51-0291-82, 75-51-0293-82 thru 75-51-0297-82 and 75-51-0304-82                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | 2. GOVT ACCESSION NO. AD-A117453 | 3. RECIPIENT'S CATALOG NUMBER                                |
| 4. TITLE (and Subtitle) Topical Hazard Evaluation Program of Candidate Insect Repellents, US Department of Agriculture Proprietary Chemicals, Study No. 75-51-0291-82, 75-51-0293-82 thru 75-51-0297-82 and 75-51-0304-82, Feb 81 - Apr 82                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                  | 5. TYPE OF REPORT & PERIOD COVERED<br>Final, Feb 81 - Apr 82 |
| 7. AUTHOR(s)<br>Michael J. Topper, CPT, VC<br>John G. Harvey, Jr.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                  | 6. PERFORMING ORG. REPORT NUMBER                             |
| 9. PERFORMING ORGANIZATION NAME AND ADDRESS<br>US Army Environmental Hygiene Agency<br>Aberdeen Proving Ground, MD 21010                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                  | 8. CONTRACT OR GRANT NUMBER(s)                               |
| 11. CONTROLLING OFFICE NAME AND ADDRESS<br>Commander<br>US Army Health Services Command<br>Fort Sam Houston, TX 78234                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                  | 10. PROGRAM ELEMENT, PROJECT, TASK AREA & WORK UNIT NUMBERS  |
| 14. MONITORING AGENCY NAME & ADDRESS (if different from Controlling Office)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                  | 12. REPORT DATE<br>Feb 81 - Apr 82                           |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                  | 13. NUMBER OF PAGES<br>7                                     |
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| 17. DISTRIBUTION STATEMENT (of the abstract entered in Block 20, if different from Report)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                  |                                                              |
| 18. SUPPLEMENTARY NOTES                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                  |                                                              |
| 19. KEY WORDS (Continue on reverse side if necessary and identify by block number)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                  |                                                              |
| AI3-38266                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | AI3-38299a                       | ALD                                                          |
| AI3-38270a                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | AI3-38193                        | Guinea Pig Sensitization                                     |
| AI3-38272a                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Skin Irritation                  | Topical Hazard Evaluation Program                            |
| AI3-38293a                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Eye Irritation                   | USDA Proprietary Chemical                                    |
| AI3-38296a                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Photoirritation                  |                                                              |
| 20. ABSTRACT (Continue on reverse side if necessary and identify by block number)<br>Preliminary hazard evaluations of AI3-38266, 38270a, 38272a, 38293a, 38296a, and 38193 were performed by means of laboratory animal studies using rats, rabbits, and guinea pigs. Chemicals AI3-38266, 38270a, 38272a, 38293a, and 38299a caused mild skin irritation while AI3-38193 caused no skin irritation. Chemicals 38270a, 38272a, 38299a and 38193 produced mild corneal injury and in addition, AI3-38299a and 38193 produced injury to the conjunctiva of rabbits. Washing of the eyes reduced the severity of the injuries. Chemicals AI3-38266, 38293a and 38296a were noninjurious to the eyes. All tested chemicals did not produce a |                                  |                                                              |

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20. sensitization reaction or photoirritation. Chemical AI3-38272a is moderately toxic while all other tested chemicals were relatively non-toxic from ingestion. It was recommended that all tested chemicals be approved for further testing as candidate insect repellents. In case of accidental eye exposure it was strongly recommended that the eye be thoroughly flushed with warm water to prevent serious eye injury.



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DEPARTMENT OF THE ARMY CPT Topper/mhb/AUTOVON  
U. S. ARMY ENVIRONMENTAL HYGIENE AGENCY 584-3980  
ABERDEEN PROVING GROUND, MARYLAND 21010

REPLY TO  
ATTENTION OF

HSB-LT-T/WP

16 JUL 1982

SUBJECT: Topical Hazard Evaluation Program of Candidate Insect Repellents,  
US Department of Agriculture Proprietary Chemicals, Study Nos.  
75-51-0291-82, 75-51-0293-82 thru 75-51-0297-82 and 75-51-0304-82,  
February 1981 - April 1982

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

EXECUTIVE SUMMARY

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

a. Purpose. The purpose of this report is to provide guidance for further entomological testing of the candidate insect repellents AI3-38266, -38270a, -38272a, -38293a, -38296a, -38299a, and -38193 by means of laboratory animal studies using rats, rabbits, and guinea pigs.

b. Essential Findings. Chemicals AI3-38266, -38270a, -38272a, -38293a, and -38299a caused mild skin irritation while AI3-38193 caused no skin irritation. Chemicals -38270a, -38272a, -38299a and -38193 produced mild corneal injury and, in addition, AI3-38299a and -38193 produced injury to the conjunctiva of rabbits. Washing of the eyes reduced the severity of the injuries. Chemicals AI3-38266, -38293a and -38296a were noninjurious to the eyes. None of the tested chemicals produced a sensitization or photoirritation reaction. Chemical AI3-38272a was moderately toxic, while all other tested chemicals were relatively nontoxic by oral administration.

c. Major Recommendations. It was recommended that all tested chemicals be approved for further testing as candidate insect repellents. In case of accidental eye exposure, it was strongly recommended that the eyes be thoroughly flushed with warm water to prevent serious eye injury.

FOR THE COMMANDER:

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*John F. Mazur*  
JOHN F. MAZUR  
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Director, Laboratory Services

CF:  
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Cdr, HSC (HSPA-P)  
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USDA, ARS (Dr. Terrence McCovern)  
USDA, ARS-Southern Region (2 cy)



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

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TOPICAL HAZARD EVALUATION PROGRAM  
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US DEPARTMENT OF AGRICULTURE PROPRIETARY CHEMICALS  
STUDY NOS. 75-51-0291-82, 75-51-0293-82 THRU 75-51-0297-82  
AND 75-51-0304-82  
FEBRUARY 1981 - APRIL 1982

1. AUTHORITY.

a. Letter, US Department of Agriculture - Agricultural Research, Southern Region, Insects Affecting Man and Animals Research Laboratory, Gainesville, Florida, 12 February 1981 (AI3-38266, -38270a, -38272a, -38293a, -38296a, and -38299a).

b. Letter, US Department of Agriculture - Agricultural Research, Southern Region, Insects Affecting Man and Animals Research Laboratory, Gainesville, Florida, 9 April 1981 (AI3-38193).

c. 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 Administrations; titled, Coordination of Biological and Toxicological Testing of Pesticides, effective 23 January 1979.

2. REFERENCE. Toxicology Division Standing Operating Procedures, US Army Environmental Hygiene Agency (USAEHA), 1981.

3. PURPOSE. The purpose of this program is to provide guidance for further entomological testing of the candidate insect repellents AI3-38266, -38270a, -38272a, -38293a, -38296a, -38299a, and -38193.

4. SUMMARY OF FINDINGS. Hazard evaluations of the above candidate repellents, US Department of Agriculture (USDA) Proprietary Chemicals 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:\*†

\* 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) 80-23, revised 1978.

† 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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February 1981 -- April 1982

TABLE. PRESENTATION OF DATA

| Test                                                                                                                | Results                                                                                                                                                  | Interpretation                                                                           |
|---------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------|
| <u>SKIN IRRITATION STUDIES</u>                                                                                      |                                                                                                                                                          |                                                                                          |
| <u>Rabbits</u>                                                                                                      |                                                                                                                                                          |                                                                                          |
| Single 24-hour application to intact and abraded skin of New Zealand White rabbits.                                 | Chemical AI3-38193 did not cause any irritation of the intact skin or of the skin surrounding an abrasion.                                               | USAEHA Category I<br>(ref Appendix A)                                                    |
| 0.5 mL technical grade chemical applied to each of six rabbits.                                                     | Chemicals AI3-38266, -38270a, -38272a, -38293a, -38296a, -38299a caused mild primary irritation of the intact skin and the skin surrounding an abrasion. | USAEHA Category II<br>(ref Appendix A)                                                   |
| <u>EYE IRRITATION STUDIES</u>                                                                                       |                                                                                                                                                          |                                                                                          |
| <u>Rabbits</u>                                                                                                      |                                                                                                                                                          |                                                                                          |
| Single 24-hour application of 0.1 mL technical grade chemical to one eye of each of nine New Zealand White rabbits. | Chemicals AI3-38266, -38293a, and -38296a were noninjurious to the eyes of rabbits.                                                                      | USAEHA Category A<br>(ref Appendix A)                                                    |
| Three of the nine rabbits had the eye flushed with warm water for 1 minute 25 seconds after application.            | Chemicals AI3-38270a and -38272a produced mild injury to the cornea of rabbits.                                                                          | USAEHA Category B<br>(ref Appendix A)                                                    |
|                                                                                                                     | Chemicals AI3-38299a and -38193 produced mild injury to the cornea and, in addition, some injury to the conjunctiva of rabbits.                          | USAEHA Category C<br>(ref Appendix A)                                                    |
|                                                                                                                     | All tested chemicals which were flushed from the eye with water after application were noninjurious to the eyes of rabbits.                              | Washing of the eyes after an accidental exposure should prevent injury to the human eye. |

Study Nos. 75-51-0291-82, 75-51-0293-82 thru 75-51-0297-82, and 75-51-0304-82,  
February 1981 -- April 1982

| Test | Results | Interpretation |
|------|---------|----------------|
|------|---------|----------------|

#### APPROXIMATE LETHAL DOSE (ALD)

##### Oral

|                        |            |              |                                                                   |
|------------------------|------------|--------------|-------------------------------------------------------------------|
| Rats (male)-no diluent | AI3-38266  | > 4311 mg/kg | These chemicals are relatively nontoxic if accidentally ingested. |
|                        | AI3-38270a | > 4311 mg/kg |                                                                   |
|                        | AI3-38298a | > 4311 mg/kg |                                                                   |
|                        | AI3-38296a | > 4311 mg/kg |                                                                   |
|                        | AI3-38299a | > 4311 mg/kg |                                                                   |
|                        | AI3-38193  | ≥ 6460 mg/kg |                                                                   |
|                        | AI3-38272a | = 1272 mg/kg | Chemical AI3-38272a is moderately toxic if accidentally ingested. |

#### PHOTOCHEMICAL SKIN IRRITATION STUDIES

##### Rabbits

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

The tested chemicals did not cause a photochemical irritation reaction under test conditions.

The tested chemicals 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 chemical, 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.

Study Nos. 75-51-0291-82, 75-51-0293-82 thru 75-51-0297-82, and 75-51-0304-82,  
February 1981 - April 1982

| Test                                                                                                                                                                                           | Results                                                                                                                      | Interpretation                                                                                                                                     |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------|
| <b><u>SENSITIZATION STUDIES</u></b>                                                                                                                                                            |                                                                                                                              |                                                                                                                                                    |
| <b><u>Guinea Pigs (Male)</u></b>                                                                                                                                                               |                                                                                                                              |                                                                                                                                                    |
| <b>Intradermal (ID)</b>                                                                                                                                                                        |                                                                                                                              |                                                                                                                                                    |
| injections of 0.1 mL of a 0.1 percent solution (w/v) of the tested chemicals or of dinitrochlorobenzene (DNCB)* in a mixture containing 1 volume of propylene glycol and 29 volumes of saline. |                                                                                                                              |                                                                                                                                                    |
| Ten test guinea pigs for each chemical were given 10 sensitizing doses over a 3-week period. After 2-weeks rest, they were challenged with ID injections of each test chemical.                | Challenge doses of the tested chemicals did not produce a sensitization reaction.                                            | The tested chemicals did not produce sensitization reactions under test conditions and are not expected to produce sensitization reactions in man. |
| Ten positive control guinea pigs were sensitized over 3 weeks with DNCB. After 2-weeks rest, they were challenged with ID injections of DNCB.                                                  | Challenge dose of DNCB in positive control guinea pigs produced a marked sensitization reaction in 10 out of 10 guinea pigs. | DNCB produced a marked reaction, indicating the guinea pigs respond to sensitizing agents.                                                         |

\* A known skin sensitizer.

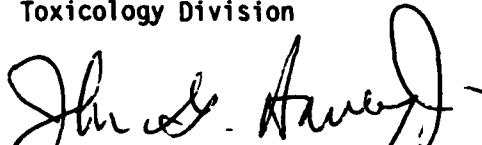
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5. CONCLUSION. Technical grade chemicals AI3-38266, -38270a, -38272a, -38293a, -38296a, and -38299a caused mild skin irritation. Chemical AI3-38193 did not cause any skin irritation. Chemicals AI3-38266, -38293a, and -38296a were noninjurious to the eyes of rabbits. Chemicals AI3-38270a and -38272a produced mild injury to the cornea and chemicals -38299a and -38193 produced mild injury to the cornea and, in addition, some injury to the conjunctiva of rabbits. All tested chemicals which were washed after application were noninjurious to the eyes of rabbits. All tested chemicals did not produce a sensitization reaction or photoirritation. Chemical AI3-38282a, is moderately toxic from ingestion but all other chemicals did not prove to be an acute ingestion hazard. The Analytical Quality Assurance review appears as Appendix B.

6. RECOMMENDATION. Under the provisions of the Memorandum of Understanding (paragraph 1c), it is recommended that all tested chemicals be approved for further testing as candidate insect repellents. In case of accidental eye exposure, it is strongly recommended that the eyes be thoroughly flushed with warm water to prevent serious eye injury.

  
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Study Nos. 75-51-0291-82, 75-51-0293-82 thru 75-51-0297-82, and  
75-51-0304-82, February 1981 - April 1982

## 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.

Study Nos. 75-51-0291-82, 75-51-0293-82, thru 75-51-0297-82, and  
75-51-0304-82, February 1981 - April 1982

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.

Study No. 75-51-0291-82, 75-51-0293-82 thru 75-51-0297-82, and 75-51-0304-82,  
February 1981 - April 1982

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, 1981 rev, Part 58, Good Laboratory Practice for Nonclinical Laboratories Studies.

b. Facilities were inspected during its operational phase to insure 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.



PAUL V. SNEERINGER, Ph.D.  
Chief, Analytical Quality  
Assurance Office

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