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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY  
WASHINGTON, D.C. 20460

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*NOV 18 1993*

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OFFICE OF  
PREVENTION, PESTICIDES AND  
TOXIC SUBSTANCES

MEMORANDUM

**SUBJECT:** Naphthalene Acetic Acid Acetamide - Review of acute toxicity studies

P.C. CODE: 056001  
DP Barcode: D195128  
Case: 818943  
Submission: S448419  
Accession Number: 247584

**FROM:** Virginia A. Dobozy, V.M.D., M.P.H., Veterinary Medical Officer *Virginia A. Dobozy 11/17/93*  
Review Section I, Toxicology Branch II  
Health Effects Division (H7509C)

**TO:** Larry Schnaubelt/Susan Jennings/PM 72  
Special Review & Reregistration Division  
(H7508C)

**THRU:** Yiannakis M. Ioannou, Ph.D., Section Head *Yiannakis M. Ioannou 11/17/93*  
Review Section I, Toxicology Branch II  
Health Effects Division (H7509C)

and

Marcia van Gemert, Ph.D., Branch Chief *Marcia van Gemert 11/18/93*  
Toxicology Branch II  
Health Effects Division (H7509C)

**Registrant:** Union Carbide Company

**Action Requested:** Review the acute toxicity studies in accession #247584.

**Recommendation:** Toxicology Branch II has reviewed the five acute toxicity studies. (A dermal sensitization study was not submitted.) Four were judged to be supplementary; one was minimum.

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DATA SUMMARY

All of the following studies were contained in accession number 247584.

Acute Oral Toxicity (81-1)

Acute oral LD<sub>50</sub> (95% confidence limits) for male and female rats combined was 1690 mg/kg (1408 - 2028 mg/kg).

Toxicity Category: III

Classification: Supplementary

Acute Dermal Toxicity (81-2)

The acute dermal LD<sub>50</sub> for male and female rabbits combined was greater than 2000 mg/kg.

Toxicity Category: III

Classification: Supplementary

Acute Inhalation Toxicity (81-3)

The study was grossly inadequate, and the acute inhalation LC<sub>50</sub> in rats could not be calculated.

Toxicity Category: Could not be assigned

Classification: Supplementary

Primary Eye Irritation (81-4)

Naphthalene acetic acid acetamide produced corneal changes in rabbits that were not reversible by 13 days.

Toxicity Category: Could not be assigned

Classification: Supplementary

Primary Dermal Irritation (81-5)

Naphthalene acetic acid acetamide was not a dermal irritant in rabbits.

Toxicity Category: IV

Classification: Minimum

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Reviewed by: Virginia A. Dobozy, V.M.D., M.P.H. *Virginia A. Dobozy 11/16/93*  
Section I, Toxicology Branch II (H7509C)  
Secondary Reviewer: Yiannakis M. Ioannou, Ph.D. *J.M.I. 11/16/93*  
Section I, Toxicology Branch II (H7509C)

DATA EVALUATION REPORT

**STUDY TYPE:** Acute Oral Toxicity/Rats (81-1)

**EPA I.D. NUMBERS:** P. C. CODE: 056001  
Accession Number: 247584

**TEST MATERIAL:** Naphthalene Acetic Acid Acetamide

**STUDY NUMBER:** PH 402-UC-002-82

**TESTING FACILITY:** Pharmakon Research International, Inc.  
Waverly, PA

**SPONSOR:** Union Carbide Company

**TITLE OF REPORT:** Acute Oral Toxicity in Rats (14 Day)

**AUTHOR(S):** Victor Mallory

**REPORT ISSUED:** March 22 - April 21, 1982 (Dates of Performance)

**CONCLUSIONS:** Five groups of five rats per sex were administered naphthalene acetic acid acetamide in methylcellulose by single-dose gavage at dosages of 1000, 1500, 2000, 2500, or 3000 mg/kg. The acute oral LD<sub>50</sub> (95% confidence interval) for males and females combined was 1690 mg/kg (1408 - 2028 mg/kg).

**TOXICITY CATEGORY:** III

**CLASSIFICATION:** Supplementary - This study does not satisfy the guideline requirements (81-1) for an acute oral toxicity study in rats.



<u>Dose (mg/kg)</u>	<u># Dead/# Per Group</u>	
	<u>Males</u>	<u>Females</u>
1000	0/5	0/5
1500	1/5	2/5
2000	3/5	5/5
2500	3/5	4/5
3000	5/5	5/5

All of the deaths occurred during the first two days of the study. Necropsies on the animals that died revealed fluid-filled and distended stomachs and small intestines. The oral LD<sub>50</sub> (95% confidence interval) for males and females combined was calculated as 1690 (1408 to 2028 mg/kg). Terminal necropsies revealed no lesions in those animals which survived until the end of the study.

#### IV. COMPLIANCE

A signed Quality Assurance statement was submitted indicating that the study was performed in accordance with the Good Laboratory Practices Regulation of FDA.

#### V. STUDY DEFICIENCIES

1. The lot number and purity of the test material were not provided.
2. The dosage volumes exceeded the recommendations of the Pesticide Assessment Guidelines which state that the volume should not exceed 1 ml/100 g body weight in rodents.

#### VI. CONCLUSIONS

Five groups of five rats per sex were administered naphthalene acetic acid acetamide in methylcellulose by single-dose gavage at dosages of 1000, 1500, 2000, 2500, or 3000 mg/kg. The acute oral LD<sub>50</sub> (95% confidence interval) for males and females combined was 1690 (1408 - 2028).

#### VI. TOXICITY CATEGORY: III

- #### VII. CORE CLASSIFICATION: Supplementary (See STUDY DEFICIENCIES) -
- The study may be upgraded if the lot number and purity of the test material are supplied.

Reviewed by: Virginia A. Dobozy, V.M.D., M.P.H.  
Section I, Toxicology Branch II (H7509C)  
Secondary Reviewer: Yiannakis M. Ioannou, Ph.D.  
Section I, Toxicology Branch II (H7509C)

*Virginia A. Dobozy 11/16/93*  
*J.M.I. 11/16/93*

DATA EVALUATION REPORT

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**STUDY TYPE:** Acute Dermal Toxicity/Rabbits (81-2)

**EPA I.D. NUMBERS:** P. C. CODE: 056001  
Accession Number: 247584

**TEST MATERIAL:** Naphthalene Acetic Acid Acetamide

**STUDY NUMBER:** PH 422-UC-002-82

**TESTING FACILITY:** Pharmakon Research International, Inc.  
Waverly, PA

**SPONSOR:** Union Carbide Company

**TITLE OF REPORT:** Acute Dermal Toxicity in Rabbits

**AUTHOR(S):** Victor Mallory

**REPORT ISSUED:** April 22 - May 6, 1982 (Dates of Performance)

**CONCLUSIONS:** A dose of 2 g/kg of naphthalene acetic acid acetamide was applied to the abraded skin of ten (five male and five female) New Zealand White rabbits for 24 hours. One female died on day 11 after dosing. There was evidence of dermal irritation (erythema and edema) in all the animals. The acute dermal LD<sub>50</sub> was greater than 2 g/kg.

**TOXICITY CATEGORY:** III

**CLASSIFICATION:** Supplementary - This study does not satisfy the guideline requirements (81-2) for an acute dermal toxicity study in rabbits.

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I. MATERIALS

A. Test Material

Name: Naphthalene Acetic Acid Acetamide  
Purity: Not provided  
Lot Number: Not provided  
Description: White powder  
Storage Conditions: Not provided

B. Vehicle: 0.9% NaCl

C. Test Animals

Species: New Zealand White rabbits  
Source: Perfection Breeders, Douglassville, PA and Marland Breeders, Hewitt, NJ  
Age: Not provided  
Weight: At Initiation - 2 to 3 kg  
Housing: Individually in cages sized in accordance with the "Guide for the Care and Use of Laboratory Animals"  
Environmental Conditions: Temperature: 20 ± 3°C  
Humidity: 30 - 70%  
Photoperiod: 12 hours light/dark

Acclimation Period: Five days

II. METHODS

One day before the application of the test chemical, the entire trunk of 5 male and 5 female rabbits was clipped. The next day, the skin was abraded with a clean needle and then 2 gm/kg of test material (moistened with physiological saline) was applied to the skin. The area was covered with gauze and then wrapped with rubber dam and an ace bandage. After 24 hours, the bandages were removed, and the skin was washed. Evaluations of a topical response were made at 2 and 4 hours after the exposure period and twice daily thereafter. Body weights were recorded initially, weekly and at study termination. At the end of the observation period, all the animals were sacrificed and gross necropsies were performed.

III. RESULTS

One female rabbit died on Day 11 of the study. The postmortem gross examination revealed brown foci on the lungs, discoloration of the intestines, heart and oral cavity. All of the animals exhibited moderate erythema and edema two hours after the bandages were removed. The signs of irritation were present until Day 3 when scaling started to appear. Three animals (including the one which died) lost weight during the study. There were no treatment-related gross necropsy changes in the animals that were sacrificed at the

end of the study. The dermal LD<sub>50</sub> was greater than 2 g/kg.

IV. COMPLIANCE

A signed Quality Assurance statement was submitted indicating that the study was performed in accordance with the Good Laboratory Practices Regulation of FDA.

IV. STUDY DEFICIENCIES

1. The lot number and purity of the test material was not provided.
2. The Pesticide Assessment Guidelines, Subdivision F, indicate that the skin should not be abraded prior to the application of the test material.

V. CONCLUSIONS

A dose of 2 g/kg of naphthalene acetic acid acetamide was applied to the abraded skin of ten (five male and five female) New Zealand White rabbits for 24 hours. One female died on day 11 after dosing. There was evidence of dermal irritation (erythema and edema) in all the animals. The acute dermal LD<sub>50</sub> was greater than 2 g/kg.

VI. TOXICITY CATEGORY: III

VII. CORE CLASSIFICATION: Supplementary (See STUDY DEFICIENCIES) - The study may be upgraded if the lot number and purity of the test material are supplied.

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DATA EVALUATION REPORT

STUDY TYPE: Acute Inhalation/Rats (81-3)

EPA I.D. NUMBERS: P. C. CODE: 056001  
Accession Number: 247584

TEST MATERIAL: Naphthalene Acetic Acid Acetamide

PROJECT NUMBER: MB 75-850

TESTING FACILITY: MB Research Laboratories, Inc.  
Spinnerstown, PA

SPONSOR: Union Carbide Agricultural

TITLE OF REPORT: Report on Inhalation Toxicity in Rats

AUTHOR(S): Oscar M. Moreno, Ph.D.

REPORT ISSUED: August 25, 1975

CONCLUSIONS: One group of ten male Wistar rats was exposed to an atmosphere of "at least 20,000 ppm" of naphthalene acetamide for one hour. There were no deaths or no clinical signs of toxicity.

TOXICITY CATEGORY: Cannot be assigned

CLASSIFICATION: Supplementary - This study does not satisfy the guideline requirements (81-3) for an acute inhalation study in rats. A new study is required.

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**I. MATERIALS**

**A. Test Material**

Chemical Name: naphthalene acetamide  
Purity: Not provided  
Lot Number: Not provided  
Description: White powder  
Storage Conditions: Not provided

**B. Test Animals**

Species: Male Wistar rats  
Source: Not provided  
Age: Not provided  
Weight: 269 - 325 g  
Date Received: Not provided  
Acclimation Period: Not provided

No information about housing or environmental conditions was provided in the study report.

**II. METHODS**

The Methods section of the study report reads, " Ten male Wistar rats were placed in a closed chamber of 51 liters. The animals were exposed to a nominal concentration of at least 20,000 ppm for a period of 1 hour. The rats were removed from the chamber at 60 minutes and were observed daily for 14 days for signs of toxicity. Body weights were recorded prior to and 14 days after treatment." No information was provided on atmosphere generation, chamber conditions or atmosphere monitoring.

**III. RESULTS**

According to the study report, there were no deaths and no signs of toxicity. All the animals gained weight during the study.

**IV. COMPLIANCE**

No compliance information was submitted.

**V. STUDY DEFICIENCIES**

The study is grossly inadequate in most respects. Another acute inhalation study should be conducted in accordance with 81-3 of the Pesticide Assessment Guidelines, Subdivision F, Hazard Evaluation: Human and Domestic Animals.

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VI. CONCLUSIONS

One group of ten male Wistar rats was exposed to an atmosphere of "at least 20,000 ppm" of naphthalene acetamide for one hour. There were no deaths or no clinical signs of toxicity.

VII. CORE CLASSIFICATION: Supplementary - The study is grossly inadequate. Another acute inhalation study should be conducted in accordance with 81-3 of the Pesticide Assessment Guidelines, Subdivision F, Hazard Evaluation: Human and Domestic Animals.

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 Secondary Reviewer: Yiannakis M. Ioannou, Ph.D. *Y M I* 11/17/93  
 Section I, Toxicology Branch II (H7509C)

DATA EVALUATION REPORT

**STUDY TYPE:** Primary Eye Irritation/Rabbits (81-4)

**EPA I.D. NUMBERS:** P. C. CODE: 056001  
 Accession Number: 247584

**TEST MATERIAL:** Naphthalene Acetic Acid Acetamide

**STUDY NUMBER:** PH 421-UC-001-82

**TESTING FACILITY:** Pharmakon Research International, Inc.  
 Waverly, PA

**SPONSOR:** Union Carbide Company

**TITLE OF REPORT:** Acute Eye Irritation Test in Rabbits

**AUTHOR (S):** Victor Mallory

**REPORT ISSUED:** April 27 - May 10, 1982 (Dates of Performance)

**CONCLUSIONS:** A dose of 100 mg of naphthalene acetic acid acetamide was instilled into the lower right eyelid of nine New Zealand albino rabbits. The eyes of three rabbits were rinsed with water immediately after the instillation; the other six eyes were not washed. The animals were then observed for signs of ocular irritation for 13 days. All of the animals showed signs of conjunctival irritation (redness, chemosis and/or discharge) that either partially or totally subsided over the course of the study. Three animals (two in the unrinsed group and one in the rinsed group) had corneal opacity that persisted in two animals (unrinsed group) through the end of the study. The study demonstrates that naphthalene acetic acid acetamide is an ocular irritant in rabbits, however the study duration does not comply with the Pesticide Assessment Guidelines.

**TOXICITY CATEGORY:** Cannot be assigned

**CLASSIFICATION:** Supplementary - This study does not satisfy the guideline requirements (81-4) for a primary eye irritation study in rabbits.

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I. MATERIALS

A. Test Material

Name: Naphthalene Acetic Acid Acetamide  
Purity: Not provided  
Lot Number: Not provided  
Description: White powder  
pH: 5.99  
Storage Conditions: Not provided

B. Test Animals

Species: Albino New Zealand White rabbits  
Source: Perfection Breeders, Douglassville, PA  
Age: Not provided  
Weight: 2 - 3 kg  
Housing: Individually in cages sized in accordance with the  
"Guide for the Care and Use of Laboratory Animals"  
Food and Water: Wayne Rabbit Ration® and tap water  
Environmental Conditions: Temperature: 20 ± 3° C  
Humidity: 30 to 70%  
Photoperiod: 12 hours light/dark  
Acclimation Period: Five days

II. METHODS

Twenty-four hours prior to treatment, the eyes of the nine (six male and three female) rabbits were examined and found to be normal. On the treatment day, 100 mg of naphthalene acetic acid acetamide was instilled into the right conjunctival sac of each of the animals. The left eye served as an untreated control. The treated eyes of three rabbits were rinsed with lukewarm water for one minute immediately following the administration of the test chemical. The eyes of the other six animals were not washed. Examinations for signs of irritancy were made at 24, 48 and 72 hours and 4, 7, 10 and 13 days after the instillation. A copy of the grading system used in the study is attached to the DER.

III. RESULTS

All of the animals (rinsed and unrinsed) showed evidence of conjunctival irritation (redness, chemosis and/or discharge) at 24 hours post-application. Two animals in the unrinsed group and one in the rinsed group also had corneal opacity (scores of 1-4). While the conjunctival reactions either partially or totally subsided during the course of the study, the corneal damage persisted to the end of the study in the two animals in the unrinsed group. One of the animals in the unrinsed group with corneal damage also had involvement of the iris beginning on Day 4 post-application and continuing through Day 10.

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IV. COMPLIANCE

A signed Quality Assurance statement was submitted indicating that the study was performed in accordance with the Good Laboratory Practices Regulation of FDA.

V. STUDY DEFICIENCIES

1. The lot number and purity of the test chemical were not provided.

2. The Pesticide Assessment Guidelines, Subdivision F, require that eye examinations are made for 21 days post-dosing. Additionally, the assignment of toxicity categories is based on the findings at 21 days. In this study, it is difficult to predict if the corneal irritation would have persisted in the two animals which had positive scores at 13 days. One of the animals that originally had a positive corneal score did heal before the end of the study.

VI. CONCLUSIONS

A dose of 100 mg of naphthalene acetic acid acetamide was instilled into the right lower eyelid of nine New Zealand albino rabbits. The eyes of three rabbits were rinsed with water immediately after the instillation; the other six eyes were not washed. The animals were then observed for signs of ocular irritation for 13 days. All of the animals showed signs of conjunctival irritation (redness, chemosis and/or discharge) that either partially or totally subsided over the course of the study. Three animals (two in the unrinsed group and one in the rinsed group) had corneal opacity that persisted in two animals (unrinsed group) through the end of the study. The study demonstrates that naphthalene acetic acid acetamide is an ocular irritant in rabbits, however the study duration does not comply with the Pesticide Assessment Guidelines.

VI. TOXICITY CATEGORY: Cannot be assigned

VI. CORE CLASSIFICATION: Supplementary (see STUDY DEFICIENCIES)

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Page 15 is not included in this copy.

Pages \_\_\_\_\_ through \_\_\_\_\_ are not included in this copy.

The material not included contains the following type of information:

\_\_\_\_\_ Identity of product inert ingredients.

\_\_\_\_\_ Identity of product impurities.

\_\_\_\_\_ Description of the product manufacturing process.

\_\_\_\_\_ Description of quality control procedures.

\_\_\_\_\_ Identity of the source of product ingredients.

\_\_\_\_\_ Sales or other commercial/financial information.

\_\_\_\_\_ A draft product label.

\_\_\_\_\_ The product confidential statement of formula.

\_\_\_\_\_ Information about a pending registration action.

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\_\_\_\_\_ The document is a duplicate of page(s) \_\_\_\_\_.

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The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.

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Secondary Reviewer: Yiannakis M. Ioannou, Ph.D. *YMI 11/17/93*  
Section I, Toxicology Branch II (H7509C)

DATA EVALUATION REPORT

STUDY TYPE: Primary Dermal Irritation/Rabbits (81-5)

EPA I.D. NUMBERS: P. C. CODE: 056001  
Accession Number: 247584

TEST MATERIAL: Naphthalene Acetic Acid Acetamide

STUDY NUMBER: 45-47

TESTING FACILITY: Bushy Run Research Center  
Export, PA

SPONSOR: Union Carbide Company

TITLE OF REPORT: Rabbit Skin Irritancy Study

AUTHOR(S): Roy C. Myers

REPORT ISSUED: April 20, 1982

CONCLUSIONS: A dose of 0.5 g of naphthalene acetic acid acetamide was applied to each of four intact and abraded skin sites of six female New Zealand White rabbits for 24 hours. There was no evidence of a dermal reaction in any of the treated animals. The study demonstrates that naphthalene acetic acid acetamide is not a dermal irritant in rabbits.

TOXICITY CATEGORY: IV

CLASSIFICATION: Minimum - This study satisfies the guideline requirements (81-5) for a primary dermal irritation study in rabbits.



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**I. MATERIALS**

**A. Test Material**

Name: Naphthalene acetic acid acetamide  
Purity: 98%  
Lot Number: 1M1407  
Description: White powder  
Storage Conditions: Not provided

**B. Test Animals**

Species: New Zealand white rabbit  
Source: Three Springs Kennels, Jackson Center, PA  
Age: 12 to 18 weeks  
Weight: 2.0 to 3.0 kg  
Housing: Individually in cages  
Food and Water: Big Red Maintenance Diet (Agway) and tap water  
*ad libitum*  
Environmental Conditions: Temperature: 75 to 76° F  
Humidity: 37 to 49%  
Photoperiod: 12 hours light/dark  
Acclimation Period: At least 5 days

**II. METHODS**

A few days before dosing, the entire trunk of six female rabbits was clipped. On the day of dosing, 500 mg of naphthalene acetic acid acetamide moistened with physiological saline was applied to each of four sites on the rabbits. The skin of two sites had been abraded. The test chemical was covered with a gauze patch and plastic sheeting was placed loosely around the trunk of the rabbits. The animals were placed in a restraining device for 24 hours, after which the bandages were removed. The application sites were examined for signs of dermal irritation at 24 and 72 hours after the contact period and graded using the Draize scale.

**III. RESULTS**

There were no dermal reactions in any of the animals at 24 or 72 hours.

**IV. COMPLIANCE**

A signed Quality Assurance statement was submitted.

**V. STUDY DEFICIENCIES**

1. The Pesticide Assessment Guidelines, Subdivision F, indicate that the skin should not be abraded prior to the application of the test material.

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2. The dosing duration specified in the Guidelines is 4 hours rather than 24.

3. The recommended dose in the Guidelines is 0.5 g; in this study, 0.5 g was applied to each of four sites.

VI. CONCLUSIONS

A dose of 0.5 g of naphthalene acetic acid acetamide was applied to each of four intact and abraded skin sites of six female New Zealand White rabbits for 24 hours. There was no evidence of a dermal reaction in any of the treated animals. The study demonstrates that naphthalene acetic acid acetamide is not a dermal irritant in rabbits.

VI. TOXICITY CATEGORY: IV

VII. CLASSIFICATION: Minimum - See STUDY DEFICIENCIES

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