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

OPP OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

SEP - 6 1996

MEMORANDUM

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

SUBJECT: **NAPTALAM (Alanap):** Review of an acute inhalation toxicity study in the rat.

EPA DP Barcode: D224427; EPA Submission No. S502492; MRID# 43936401; EPA Pesticide Chemical Code 030703, Toxicology Chemical No. 780A (Na salt); 592 (acid); Reregistration Case # 0183.

TO: Linda Propst/Susanne Cerrelli, PM 73
Special Review and Reregistration Division (7508W)

FROM: Stephen C. Dapson, Ph.D. Stephen C. Dapson 9/3/96
Senior Pharmacologist, Review Section I
Toxicology Branch II/HED (7509C)

THRU: Jess Rowland, M.S. Jess Rowland 9/3/96
Acting Section Head, Review Section I
and
Yiannakis M. Ioannou, Ph.D., D.A.B.T. Y.M. Ioannou 9/5/96
Acting Chief, Toxicology Branch II
Health Effects Division (7509C)

Registrant: Uniroyal Chemical Company, Inc.

Action Requested: Review of an acute inhalation toxicity study in the rat.

Recommendations: TBII reviewed the study, *AN ACUTE (4-HOUR) INHALATION TOXICITY STUDY OF NAPTALAM SODIUM IN THE RAT VIA NOSE-ONLY EXPOSURE* (Huntingdon Life Sciences for UNIROYAL CHEMICAL COMPANY, INC., Study No. 95-5256, February 22, 1996, EPA MRID# 43936401). The following are the conclusions from the study:

In an acute inhalation toxicity study (MRID# 43936401), Sprague Dawley derived Albino Rats ([CD®-Crl:CD®(SD)BR]) from Charles River Laboratories, Kingston, New York 12484 were exposed by the inhalation route (nose only) to Naptalam Sodium (91.6% a.i.; Lot/Batch No.: BFI 2781) for 4 hours and then observed for a period of 15 days.

The inhalation LC_{50} in rats for Naptalam Sodium is greater than 2.0 mg/L. This is Toxicity Category IV.

This study is Acceptable and satisfies the guideline requirement (§81-3) for an inhalation toxicity (LC_{50}) study in rats.

I. Toxicology Profile for Naptalam and Na-Naptalam (40 CFR §158.340)

Technical: Naptalam and Na-Naptalam
Use Pattern: food use

This compound is a registered active ingredient, a reregistration **List B** chemical; the following data are available for Naptalam and Na-Naptalam. Study requirements have been based on the use pattern for this chemical. **THE FOLLOWING DOES NOT NECESSARILY REFLECT REREGISTRATION REQUIREMENTS.**

	Required	Satisfied
§81-1 Acute oral toxicity in rats	Yes	Yes
§81-2 Acute dermal toxicity in rabbits	Yes	Yes
§81-3 Acute inhalation toxicity in rats	Yes	Yes[1]
§81-4 Primary eye irritation in rabbits	Yes	**NO**
§81-5 Primary dermal irritation in rabbits	Yes	**NO**
§81-6 Dermal sensitization - guinea pig	Yes	**NO**
§82-1(a) 90 day feeding - rat	Yes	NO[2]
§82-1(b) 90 day feeding - dog	Yes	NO[2]
§83-1(a) 2-year feeding - rodent	Yes	Yes
§83-1(b) 1 year feeding - nonrodent	Yes	Yes
§83-2(a) Carcinogenicity - rat	Yes	Yes
§83-2(b) Carcinogenicity - mouse	Yes	**NO[3]**
§83-3(a) Teratology - rat	Yes	Yes
§83-3(b) Teratology - rabbit	Yes	Yes
§83-4 Multigeneration reproduction-rat	Yes	Yes
§84-2(a) Mutagenicity-Gene Mutation	Yes	Yes
§84-2(b) Mutagenicity-Struct. Chromosome Aberr.	Yes	Yes
§84-4 Mutagenicity-Other Genotoxic Effects	Yes	Yes
§85-1 General metabolism - rat	Yes	**NO**

[1] = see discussion in this document.
[2] = satisfied by an acceptable chronic toxicity study.
[3] = a new study may be required if use patterns for this chemical change in the future.

II. Data Gaps

The following are data gaps for technical Naptalam and Na-Naptalam:

§81-4 Primary eye irritation in rabbits
§81-5 Primary dermal irritation in rabbits
§81-6 Dermal sensitization - guinea pig
§83-2(b) Carcinogenicity in the mouse - not required at present but may be required in the future if use patterns change
§85-1 General metabolism - rat

III. Actions Being Taken to Obtain Additional Information or Clarification

None at this time.

IV. Reference Dose

An RfD of 0.053 mg/kg/day based on a 1 year feeding study in the dog with a NOEL of 5.3 mg/kg/day (body weight changes were observed at the next higher dose of 25.8 mg/kg/day) and an uncertainty factor of 100, has been established.

V. Pending Regulatory Actions

None.

VI: Toxicological Issues Pertinent to this Request

A. New toxicology Data on Naptalam and Na-Naptalam

New data has been discussed in this memo.

B. Carcinogenicity and Mutagenicity

Recommendations made by the HED RfD/QA Peer Review Committee

Naptalam and Na-naptalam was presented to the RfD/Peer Review Committee on August 25, 1994 in order to determine if the available data and the additional information on the cancer risk provided by the registrant are adequate to satisfy the chronic toxicity and carcinogenicity guideline requirements. The following are the conclusions of the committee for the chronic/carcinogenicity studies:

The Committee considered the chronic toxicity studies in rats (MRID No. 00077053, 41838801, 42784001) and dogs (MRID No. 41057501) to be acceptable and the data evaluation records (HED Doc. 009801, 010741; 009801) to be adequate.

The Committee recommended upgrading of the chronic toxicity phase of the rat study from Core-supplementary to a Core-minimum status.

The Committee considered the carcinogenicity phase of the chronic toxicity/carcinogenicity study in rats (MRID No. 00077053, 41838801, 42784001) to be marginally acceptable. The highest dose level tested in rats caused 7-9% reduction of body weight gain. The Committee concluded that the treatment did not alter the spontaneous tumor profile in this strain of rats under the testing conditions.

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The Committee considered the carcinogenicity study in mice (MRID No. 00119003) to be unacceptable because of major deficiencies in the study conduct and reporting. Deficiencies observed in this study included mixing of dietary concentrations in the first few months of the study, lack of purity information about the technical used, and possible technical problems in the histopathological evaluation (the slides were read by two pathologists raising questions about the uniformity of criteria used in reading of these slides). The data provided a suggestive evidence of positive carcinogenic response in mice, but on the other hand was hard to analyze statistically because of the uncertainty arising from all deficiencies existed in this study. The Committee debated the question of whether a new mouse study would be required. Based on the current use and/or exposure profile, the consensus was that a new study would not be necessary at this time. The chemical is currently registered as a low volume/minor use chemical. Should the exposure or use profile change (expand) in the future, a new mouse study should be requested. **The chemical was classified as a "Group D" based on inadequacy of the data available.** It was also suggested that a surrogate risk analysis based on the worst case scenario may be performed if needed.

There are one positive and one possible positive mutagenicity studies.

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Primary Review by: Stephen C. Dapson, Ph.D. Stephen C. Dapson 9/3/96
Senior Pharmacologist, Review Section I, TBII/HED 7509C

Secondary Review by: Jess Rowland, M.S. Jess Rowland 9/3/96
Acting Section Head, Review Section I, TBII/HED 7509c

DATA EVALUATION RECORD

Study Type: Acute Inhalation Toxicity; Species: Rat
Guideline: §81-3

EPA ID No.s: EPA MRID# 43936401
EPA DP Barcode D224427
EPA Submission No. S502492
EPA Pesticide Chemical Code 030703
Toxicology Chemical Code 780A
Reregistration Case# 0183

Test Material: Naptalam Sodium
Synonyms: Sodium Alanap Technical

Sponsor: UNIROYAL CHEMICAL COMPANY, INC., 74 Amity Road, Bethany, CT 06524-3402

Testing Facility: Huntingdon Life Sciences, P.O. Box 2360, Mettlers Road, East Millstone, New Jersey 08875-2360

Title of Report: AN ACUTE (4-HOUR) INHALATION TOXICITY STUDY OF NAPTALAM SODIUM IN THE RAT VIA NOSE-ONLY EXPOSURE

Study Number(s): 95-5256

Author(s): Gary M. Hoffman, B.A., D.A.B.T.

Report Issued: February 22, 1996

Executive Summary: In an acute inhalation toxicity study (MRID# 43936401), Sprague Dawley derived Albino Rats ([CD®-Crl:CD®(SD)BR]) from Charles River Laboratories, Kingston, New York 12484 were exposed by the inhalation route (nose only) to Naptalam Sodium (91.6% a.i.; Lot/Batch No.: BFI 2781) for 4 hours and then observed for a period of 15 days.

The inhalation LC_{50} in rats for Naptalam Sodium is greater than 2.0 mg/L. This is Toxicity Category IV.

This study is Acceptable and satisfies the guideline requirement (§81-3) for an inhalation toxicity (LC_{50}) study in rats.

Compliance: A signed and dated Statement of No Data Confidentiality Claim, a GLP Statement, and a Quality Assurance Statement was provided. A signed and dated FIFRA Flagging Statement **was not** provided; however, it is the opinion of this reviewer that this study neither meets not exceeds any of the applicable criteria.

A. Materials and Methods

Test Compound: Purity: 91.6% a.i.
Description: Light purple powder
Lot/Batch No.: BFI 2781
Receipt date: 9/13/95
Other provided information: stored at room temperature
Contaminants: no data provided

Vehicle(s): none used

Test Animal(s): Species: Albino Rat (Outbred)
Strain: Sprague Dawley - derived [CD®-Crl:CD®(SD)BR]
Source: Charles River Laboratories
Kingston, New York 12484
Age: 10 weeks at start of study
Body Weight: mean: 228 g-females; 310 g-males

B. Study Design

This study was designed to assess the acute inhalation toxicity (LC_{50}) in rats.

Animal Husbandry

Animals were acclimated to the laboratory conditions for approximately 1 week and singly caged under standard animal care conditions. The animals received Certified Rodent Diet, No. 5002 (meal) (PMI Feeds, Inc., St. Louis, MO) and water (automated system) *ad libitum.*

Dose Administration:

Five males and 5 females were exposed by nose only application to the test material which was previously ...*sieved and then packed into cups, using a laboratory press,* using a dust feeder for 4 hours.

Observations

According to the investigators: *All animals were observed individually immediately prior, and as a group at approximately fifteen-minute intervals during the first hour of exposure and hourly for the remainder of the exposure period. body surface temperature was measured every thirty minutes for one male and one females rat throughout the exposure. All animals were observed individually upon removal from the chamber (approximately one half-hour after exposure was completed) and hourly for two hour post-exposure. Detailed physical observation were recorded at*

each interval...and for all animals once daily for days 2 through 15 post-exposure. Body weights were recorded on day 1, 8, and 15. Complete postmortem examination were conducted on all animals at study termination.

Statistical analysis

No statistical analysis methods were employed.

C. Results

1. Chamber Monitoring

The average analytical exposure concentration was 2.0 mg/L with a range of 1.9 to 2.1 mg/L (or ±0.05). The gravimetric concentration was 2.0 ±0.21. The particle sizes were as follows (from Table 1, page 25 of the investigators report):

MMAD (μm)	GSD	≤1.0μm	≤4.0μm	≤10.0μm
2.4±0.3	1.6-1.9	6.9±2.9%	82±6.2%	99±0.5%

The average chamber temperature 22±0.53°C; average relative humidity 33±7.8%; average airflow rate 25 Lpm. The animal body surface for the males was 32±2.1°C and for females 31±2.9°C.

2. Mortality

No mortality was reported.

3. Body Weights

Group summary and individual animal data were provided by the investigators, no treatment related effects were noted.

4. Physical Observations

During exposure there was labored breathing, chromodacryorrhea, and red nasal discharge. The secretory signs were noted for 2 hours after removal from the chamber. No treatment related observations were noted during the 14 day post-exposure period.

5. Necropsy Observations

No treatment related effects were noted.

D. Discussion/Conclusions

The inhalation LC_{50} in rats for Naptalam Sodium is greater than 2.0 mg/L.

E. Study Deficiencies:

No specific deficiencies.

F. Core Classification: Acceptable.

TOXICITY CATEGORY IV

13544

033815

Chemical:	**Benzoic acid, 2-((1-naphthalenylamino)ca**
PC Code:	**030703**
HED File Code	**13000 Tox Reviews**
Memo Date:	**09/06/96**
File ID:	**TX012040**
Accession Number:	**412-02-0280**

HED Records Reference Center
04/10/2002