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

#780A MAR - 3 1995

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: **NAPTALAM (Alanap):** Review of a metabolism "bridging" study protocol.
EPA DP Barcode: D210871; EPA Submission No. S479732;
MRID# none; EPA Pesticide Chemical Code 030703,
Toxicology Chemical No. 780A.

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

FROM: Stephen C. Dapson, Ph.D. Stephen C. Dapson 2/28/95
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THRU: Yiannakis M. Ioannou, Ph.D., D.A.B.T. Y M Ioannou 3/2
Section Head, Review Section I
and
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Chief, Toxicology Branch II M van Gemert 3/3/95
Health Effects Division (7509C)

Registrant: Uniroyal Chemical Company, World Headquarters,
Middlebury, CT 06749

Action Requested: Review a metabolism "bridging" study protocol to satisfy guideline requirement §85-1 for naptalam.

Recommendations: TB II has reviewed the metabolism "bridging" study protocol from the registrant and has determined that the study meets the basic requirements and is acceptable with minor modifications.

BACKGROUND:

The registrant requested a Low Volume/Minor Use Waiver for the General Metabolism Study (§85-1). They suggested to replace the §85-1 with a modified study. The following is from the MEMO of Dapson to Rossi/Cerrelli, dated January 25, 1994.

MRID # 402745-02, Analysis of Urine Samples From [^{14}C] Naptalam (ALANAP) Rat Metabolism Study, Uniroyal Chemical Co., Inc. and Biotek, Inc., Uniroyal Project No. 8660 and Biotek Study No, 8603B, 7/7/87 (7/10/87) for Guideline §85-1, General Metabolism, includes MRID # 418600-03, Analysis of Percent Active Ingredient of the Test Compound:

The absorption, distribution, metabolism, and excretion of naptalam were studied in groups of male and female CD rats administered a single oral dose of 250 or 1000 mg/kg [^{14}C] naptalam by gavage.

[^{14}C]Naptalam was rapidly absorbed, distributed, and excreted in rats at both dose levels. The 7-day recoveries were at least 84.85% of the administered dose for all dosing groups, with higher recoveries in the males. The elimination of radioactivity in the urine (39.39-45.30%) was almost comparable for all male and female dose groups. The radioactivity in the feces was 59.13-67.73% in male groups and 41.56-43.10% in the female groups. The elimination data suggest that absorption of naptalam is rapid, bioaccumulation is low, and excretion occurs in the feces and urine. The authors concluded that most radioactivity in the feces was due to unabsorbed test material because most of the fecal elimination occurred within 24 hours. This explanation could not be confirmed because intravenous dosing was not conducted to provide further information on the fecal and urinary elimination pattern. The urine contained one major radioactive band which was identified as the unmetabolized parent compound. No metabolites were identified in the urine. Since the metabolism of naptalam was not evaluated in the feces, the complete metabolite pattern of naptalam in rats cannot be determined. The study also indicated that naptalam and/or its metabolites do not bioaccumulate to an appreciable extent following oral exposure since all the tissues contained negligible levels of radioactivity at 7 days postexposure.

Based on the study results,no conclusion can be made regarding sex- or dose-related differences in the metabolism of naptalam since radioactivity in the feces was not analyzed. Furthermore, no metabolic pathway could be determined for naptalam. The study also showed that administration of 250 and 1000 mg/kg naptalam did not induce any apparent treatment-related clinical effects.

The study is classified as **Core-Supplementary Data** and **does not satisfy** the guideline requirement (§85-1) for a General Metabolism study in Rats. This study may be upgraded if the following additional data are provided:

1) identification of metabolites in the feces to evaluate sex-related differences in metabolism and determine metabolic pathway of naptalam;

2) intravenous dosing study to evaluate fecal elimination (i.e., unabsorbed test material and/or biliary excretion);

3) repeated dosing study to evaluate toxicokinetic differences with different dosing regimen.

COMPANY RESPONSE:

The dietary exposure to Alanap is very low. The only crops remaining on the Alanap-L label are minor crops, i.e. cucumbers, watermelons, cantaloupes and muskmelons. These crops do not contribute significantly to the total dietary exposure of the total population. For example, watermelons and cucumbers contribute only 0.08 and 0.07 g/kg/body weight/day, respectively[1]. Dietary contribution for cantaloupes and muskmelons were not obtained. The tolerance for Naptalam in cucurbits (whole fruit) is 0.1 ppm which is a neglible residue tolerance based on the limit of quantitation of the analytical method. Dietary exposure is further diminished by eliminating, in many cases, the peels from the fruit, although small amounts of cucumber and watermelon peels may be consumed. In a cucumber metabolism study conducted by Uniroyal (MRID #41790503), most of the radioactivity was found in the peels.

Previous studies conducted by Uniroyal Chemical Co. have shown that Naptalam and/or its metabolites do not bioaccumulate to an appreciable extent following oral exposure and that absorption, distribution and elimination of Naptalam do not appear to be dose related (MRID #402745-02). Finally, this study showed that the administration of 250 and 1000 mg/kg Naptalam to rats did not induce any apparent treatment-related clinical effects.

In light of the information already available on rat metabolism of Naptalam along with its low level of dietary exposure, Uniroyal Chemical Co. suggests that the requirement for additional rat metabolism studies be replaced by a bridging study in which radiolabeled ^{14}C-Alanap would be administered intravenously to male and female rats followed by identification of the urinary and fecal metabolites. This study would be completed within six months following approval of the proposed bridging study. A detailed study protocol would be submitted for Agency approval prior to start of the study.

EPA RESPONSE:

The Agency has no objections to the conduct of a bridging study in male and female rats for resolving several issues including the identification of metabolites in urine and feces. The protocol for such a study should be approved by the Agency. For the present time, however, the rat metabolism study remains classified as **Core-Supplementary Data.**

II. Comments on the Proposed Metabolism "Bridging" Study Protocol:

In the proposed study, 14C-Naptalam will be administered to 5 male and 5 female CD rats at the dose level of 5 mg/kg by intravenous injection. Urine and feces will be collected at different time points and analyzed for radioactivity content. At sacrifice, specific tissues will also be collected and their radioactivity content will be determined.

Representative samples of urine and feces will be analyzed by isolating, purifying and identifying metabolites and/or parent material.

The protocol, as presented, appears to be acceptable for the purpose for which it is intended. The following minor modifications are suggested:

1. If at all feasible, identify metabolites ≥ 5% (instead of ≥ 10%) of the administered dose.

2. For better accountability of the administered radioactivity, the site of injection should be analyzed at sacrifice for unabsorbed radioactivity.

III. 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	**NO**
§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[1]
§82-1(b)90 day feeding - dog	Yes	NO[1]
§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**[2]
§83-3(a)Teratology - rat	Yes	**NO**
§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] = **satisfied by an acceptable chronic toxicity study.**
[2] = **discussed below**

Formulation: Alanap L

	Required	Satisfied
§81-1 Acute oral toxicity in rats	Yes	**NO**
§81-2 Acute dermal toxicity in rabbits	Yes	**NO**
§81-3 Acute inhalation toxicity in rats	Yes	**NO**
§81-4 Primary eye irritation in rabbits	Yes	Yes
§81-5 Primary dermal irritation in rabbits	Yes	Yes
§81-6 Dermal sensitization - guinea pig	Yes	Yes

IV. Data Gaps

The following are data gaps for technical Naptalam and Na-Naptalam (see discussion in this document):

§81-3 Acute inhalation toxicity in rats
§81-4 Primary eye irritation in rabbits
§81-5 Primary dermal irritation in rabbits
§81-6 Dermal sensitization - guinea pig
§83-3(a)Teratology - rat (additional data required)
§83-2(b)Carcinogenicity - mouse
§85-1 General metabolism - rat

Also, the Neurotoxicity Guidelines study requirements are still reserved at this time until more information of the toxicity of this chemical is available.

The following are the data gaps for the formulation Alanap L:

§81-1 Acute oral toxicity in rats
§81-2 Acute dermal toxicity in rabbits
§81-3 Acute inhalation toxicity in rats

V. Actions Being Taken to Obtain Additional Information or Clarification

None at this time.

VI. 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.

VII. Pending Regulatory Actions

None.

VIII: Toxicological Issues Pertinent to this Request

A. New toxicology Data on Naptalam and Na-Naptalam

No new studies were submitted with this action.

B. Carcinogenicity and Mutagenicity

The RfD/QA Peer Review 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.

The RfD/QA Peer Review 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.

13544

R063035

Chemical:	**Naptalam, sodium salt**
PC Code:	**030703**
HED File Code	**13000 Tox Reviews**
Memo Date:	**03/03/95**
File ID:	**DPD210871**
Accession Number:	**000-00-0048**

HED Records Reference Center
09/16/2003