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CASWELL FILE

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

MAY 23 1996

MEMORANDUM

SUBJECT: **NAPTALAM (Alanap)**: Review of a company response to a rereview of a rat teratology study.
EPA DP Barcodes: D219086 and D219228; EPA Submission No.s S493497 and S493823; EPA MRID No.s 43767101 and 43774401; EPA Pesticide Chemical Code 030703 (Na salt); 030702 (acid); 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 5/17/96
Senior Pharmacologist, Review Section I
Toxicology Branch II/HED (7509C)

THRU: Yiannakis M. Ioannou, Ph.D., D.A.B.T. J.M. Ioannou 5/17/96
Section Head, Review Section I
and
Stephanie R. Irene, Ph.D. Stephanie R. Irene 5/23/96
Acting Chief, Toxicology Branch II
Health Effects Division (7509C)

Registrant: Uniroyal Chemical Company, Inc.

Action Requested: Review a company response to a rereview of a rat teratology study with Naptalam.

Recommendations: Based on additional data/clarifications submitted by the Registrant, TBII has determined that the rat teratology study with Naptalam is now acceptable and satisfies the guideline requirement (§83-3a) for a developmental toxicity (teratology) study in the rat.

I. Background

MRID# 00106320: *Teratologic Evaluation of Alanap S Technical in Sprague-Dawley Rats* (Food and Drug Research Laboratories, Inc for Uniroyal Inc., Study No. 5888a, December 22, 1978), the following is the Executive Summary from the review:

In a developmental toxicity (teratology) study (MRID# 00106320), sexually mature Sprague-Dawley rats of the BLU: (SD) BR strain from Blue Spruce Farms, Inc., Altamont, NY received either 0, 15, 115, or 500 mg/kg/day Alanap S Technical (Na Salt; unknown purity; Batch No. B19062, CC4035) by oral gavage in corn oil. The study originally had a high dose of 900 mg/kg/day of which all animals died after the first few doses; a new group was substituted using 500 mg/kg/day.

Maternal toxicity was noted at 115 mg/kg/day and above in the form of reduced body weight gain during the dosing period (gestation days 6-15), the post dosing period (gestation days 15-20), for the combined dosing plus post dosing period (gestation days 6-20) and for the entire gestation period (except 115 mg/kg/day). The 900 mg/kg/day dose group had complete deaths and there was increased maternal wastage at 500 mg/kg/day. The Maternal Toxicity LOEL is 115 mg/kg/day and the Maternal Toxicity NOEL is 15 mg/kg/day based on reduced body weight gain.

Developmental toxicity was noted in the 500 mg/kg/day dose group as lower mean fetal weight compared to the control group and there was an increased incidence of unspecified missing sternebrae, incomplete ossification of unspecified vertebrae, unspecified skull bones, unspecified extremities and increased missing or reduced hyoid bone in the 500 mg/kg/day dose group. The Developmental Toxicity LOEL is 500 mg/kg/day and the Developmental Toxicity NOEL is 115 mg/kg/day based on reduced mean fetal weight and increased skeletal observations.

The study is classified as Core Supplementary Data and does not satisfy the guideline requirement for a developmental toxicity (teratology) study (§83-3a) in the rat. The study may be upgraded if the deficiencies listed below are addressed to the Agency's satisfaction.

Study Deficiencies: The percent active ingredient of the test compound was not provided. No analysis of dosing solutions was performed (however, toxicity was noted so the animals did receive compound). Bones that were affected in the fetuses were not identified. Limited data were provided for maternal effects; however, this study was conducted prior to the 1984 Guidelines.

II. Company Response

1. EPA Comment:

The percent active ingredient of the test compound was not provided.

Company Response:

The percent active ingredient for Lot #C465 (Batch BL9062-CC4035) is 91.6 - 92.8% Na Alanap (MRID# 43767101).

EPA Response:

The response is acceptable to the Agency.

2. EPA Comment:

No analysis of dosing solutions was performed (however, toxicity was noted so the animals did receive compound).

Company Response:

The following data were provided (MRID# 43774401): *Dosing formulations were found to be homogenous and accurately prepared. The calculated mean test article concentrations of the dosage preparations were 98 and 111% of the nominal levels for the 1.5 and 90 mg/ml concentrations, respectively. Dosage formulations held for 7 days contained 72 and 92% of the day 0 levels, for the 1.5 and 90 mg/ml concentrations, respectively.*

EPA Comment:

The response is acceptable to the Agency. The range for homogeneity for the 1.5 mg/ml solution was 1.32-1.59 (mean - 1.47±0.111) mg/ml and for the 98 mg/ml solution was 92.3-108 (mean - 100±5.08) mg/ml. The low level for the stability measurement for the 1.5 mg/ml solution may be due to the low concentration since it was not stated if a stock solution was made and dilutions made from this.

3. EPA Comment:

Bones that were affected in the fetuses were not identified.

Company Response:

(MRID# 43767101) Admittedly, the study was performed many years ago, and the laboratory did not record findings of individual bones, but nevertheless, this study shows quite clearly, adequacy to assessing developmental toxicity in this species. Maternal toxicity was evident at doses of 115 and 500 mg/kg (NOEL = 15) and developmental toxicity was observed at 500 mg/kg (NOEL = 115), values in agreement with the reviewers.

Morphologically, it is not important *which* bones of the skull, vertebrae, and extremities are incompletely ossified. This is because the whole process of ossification has been retarded indirectly in the fetus through maternal toxicity elicited by the test article at the dose of 500 mg/kg/day. Typically, the process is generalized and it would be redundant and a meaningless exercise to list which of the 175 bones of each specimen in this species are incompletely ossified. In the present study, this high dose level retarded fetal growth, resulting in a statistically significant reduction in fetal body weight, and this was accompanied as expected, by incomplete ossification of skeletal systems (skull, vertebrae, extremities). When the fetus is retarded somatically, so is the skeleton too in the developmental retardation process.

Since ossification occurs normally on gestation days 15 to 20 and continues on postnatally in the rat, retardation of development would be manifested by incomplete ossification. The portions of the skeleton termed "missing" (sternebrae, hyoid bone) represent an earlier stage of the same process: They have been retarded to the extent that the bone has not yet ossified to any extent at all.

Finally, since ossification is a continuous process from gestation day 15 through day 23 or so in the postnatal period, and the animals are sacrificed one day (day 20) prior to normal delivery, some fetuses, control and treated alike, have incompletely ossified skeletons as one might expect, in this "window of opportunity" related to time of conception. In the present study, the maternal toxicity induced by compound administration secondarily caused the developmental retardation to a greater extent among treated fetuses than among the controls.

EPA Response:

It is important *which* bones of the skull, vertebrae, and extremities are incompletely ossified and it would **not** be redundant and a meaningless exercise to list which of the 175 bones of each specimen in this species are incompletely ossified. The guidelines require identification of the bones involved, not a generalized "reduced ossification of the skeleton". Although maternal toxicity may be the cause of the reduced ossification noted, this **cannot** be stated with certainty. The individual bones involved allow patterns of effects to be discerned and can enforce or discount toxic effects. As stated in the DER, there was a slightly increased number of resorptions and postimplantation loss in the 115 and 500 mg/kg/day dose groups along with slightly reduced litter sizes. Also, there was reduced mean fetal weight in the 500 mg/kg/day dose group (statistically significantly reduced). Further, there was increased incidence of missing sternebrae (slight; which sternebrae not specified), incomplete ossification of the vertebrae (which vertebrae not specified), skull (which bones not specified), extremities (which bones not specified) and increased missing or reduced hyoid bone in the 500 mg/kg/day dose group.

4. EPA Comment:

Limited data were provided for maternal effects; however, this study was conducted prior to the 1984 Guidelines.

Company Response:

(MRID# 43767101) In response to the statement by the reviewers that "limited data were provided for maternal effects", it seems obvious to me, even with the absence of food consumption data, the statistically significant body weight decrement of 27% over gestation in the 500 mg/kg group compared to the control and the dose-related mortality in the 115 and 500 mg/kg groups demonstrate clearly the toxic effect on the mothers.

EPA Response:

The EPA Pesticide Assessment Guidelines state maternal toxicity reporting requirements. The only data reported in this study were mortality, body weights and limited cesarean section data (no corpora lutea counts, a requirement), no clinical signs of toxicity or gross pathological examinations. Food consumption data are not required under the 1984 guidelines (but has proven helpful in those studies measuring it). As stated in the DER, maternal systemic toxicity was noted at 115 mg/kg/day and above in

the form of reduced body weight gain during the dosing period (gestation days 6-15), the post dosing period (gestation days 15-20) and for the combined dosing plus post dosing period (gestation days 6-20) and for the entire gestation period. All animals in the 900 mg/kg/day dose group died and there was increased maternal wastage at 500 mg/kg/day.

5. Company Conclusions:

The additional data submitted should allow the upgrade of the study to Acceptable.

EPA Conclusions:

Based on additional data/clarifications submitted by the Registrant, TBII has determined that the rat teratology study with Naptalam is now **Acceptable** and satisfies the guideline requirement (§83-3a) for a developmental toxicity (teratology) study in the rat. The Executive summary for MRID# 00106320 with MRID# 43767101, 43774401: *Teratologic Evaluation of Alanap S Technical in Sprague-Dawley Rats* (Food and Drug Research Laboratories, Inc for Uniroyal Inc., Study No. 5888a, December 22, 1978) should read as follows:

In a developmental toxicity (teratology) study (MRID# 00106320, 43767101, 43774401), sexually mature Sprague-Dawley rats of the BLU: (SD) BR strain from Blue Spruce Farms, Inc., Altamont, NY received either 0, 15, 115, or 500 mg/kg/day Alanap S Technical (Na Salt; 91.6% a.i.; Batch No. B19062, CC4035) by oral gavage in corn oil. The study originally had a high dose of 900 mg/kg/day of which all animals died after the first few doses; a new group was substituted using 500 mg/kg/day.

Maternal systemic toxicity was noted at 115 mg/kg/day and above in the form of reduced body weight gain during the dosing period (gestation days 6-15), the post dosing period (gestation days 15-20), for the combined dosing plus post dosing period (gestation days 6-20) and for the entire gestation period (except 115 mg/kg/day). All animals in the 900 mg/kg/day dose group died and there was increased maternal wastage at 500 mg/kg/day. **The Maternal Systemic Toxicity NOEL is 15 mg/kg/day and the Maternal Systemic Toxicity LOEL is 115 mg/kg/day based on reduced maternal body weight gain.**

Developmental toxicity was noted in the 500 mg/kg/day dose group as lower mean fetal weight compared to the control group and there was an increased incidence of unspecified missing sternebrae, incomplete ossification of unspecified vertebrae, unspecified

skull bones, unspecified extremities and increased missing or reduced hyoid bone in the 500 mg/kg/day dose group. **The Developmental Toxicity NOEL is 115 mg/kg/day and the Developmental Toxicity LOEL is 500 mg/kg/day based on reduced mean fetal weight and increased incidence of skeletal anomalies.**

This study is classified as Acceptable and satisfies the guideline requirement for a developmental toxicity (teratology) study (§83-3a) in the rat.

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	Yes[3]
§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] = a new study may be required if use patterns for this chemical change in the future.
[3] = see discussion in this document.

IV. Data Gaps

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

§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
§83-2(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

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

The company response has been discussed above.

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.

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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Chemical:	**Benzoic acid, 2-((1-naphthalenylamino)ca; Benzoic acid, 2-((1-naphthalenylamino)ca**
PC Code:	**030703; 030702**
HED File Code	**13000 Tox Reviews**
Memo Date:	**05/23/96**
File ID:	**TX011936**
Accession Number:	**412-02-0280**

HED Records Reference Center
04/10/2002