011229

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

SEP 7 1994

MEMORANDUM

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

SUBJECT: RfD/Peer Review Report of Naptalam [2-[(1-naphthaleneylamino) carbonyl-benzoic acid] and Naptalam Sodium

CASRN. 132-66-1
EPA Chem. Code: 030702
Caswell No. 592

FROM: George Z. Ghali, Ph.D. G. Ghali 7.1.94
Manager, RfD/Quality Assurance Peer Review
Health Effects Division (7509C)

THRU: William Burnam
Co-Chair, RfD/Peer Review Committee
Health Effects Division (7509C)

Reto Engler, PhD
Co-Chair, RfD/Peer Review Committee
Health Effects Division (7509C)

TO: Cynthia Giles-Parker, PM 22
Fungicides-Herbicide Branch
Registration Division (7505C)

Esther Saito, Chief
Re-registration Branch
Special Review and Re-registration Division (7508W)

The Health Effects Division RfD/Peer Review Committee met on August 25, 1994 to discuss and evaluate existing and recently submitted toxicology data in support of Naptalam re-registration and to assess the Reference Dose (RfD) for this chemical.

Material available for review consisted of data evaluation records (DER's) for a chronic toxicity/carcinogenicity study in rats **(83-5 or 83-1a and -2a)**, a carcinogenicity study in mice **(83-2b)**, a long-term feeding toxicity study in dogs **(83-1b)**, developmental toxicity studies in rats and rabbits **(83-3a and -3b)**, a two-generation reproductive toxicity study in rats **(83-4)**, a subchronic toxicity study in rats **(82-1a)** and a subchronic toxicity study in dogs **(82-1b)**.

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. In the dog study, the Committee recommended that the no-observable effect level (NOEL) be based on body weight changes and not the changes in alkaline phosphatase activity. No revisions to the data evaluation records were recommended.

The Committee considered the carcinogenicity phase of the chronic toxicity/carcinogenicity study in rats (MRID No. 00077053, 41838801, 42784001) to be marginally acceptable because of dosing selection. 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; one pathologist read the controls and high dose groups only, the other pathologist read only the low and mid-dose groups, 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.

The reproductive toxicity study in rats (MRID No. 00031684, 42739702) and the developmental toxicity studies in rabbits (MRID No. 00157186) were considered to be acceptable, and the data evaluation records (HED Doc. No. 009803, 010741; 005873, 009801) were considered to be adequate. The Committee generally agreed with the reviewer's evaluation and interpretation of data. Although the developmental toxicity study in the rat (MRID No. 00106320) was classified as Core-supplementary due to missing or inadequate information, the scientific validity of the endpoints was not in question, and it was considered adequate for the evaluation of developmental toxicity in this species. The

Committee further noted that the maximal body weight changes at the mid-dose in this study, upon which the LOEL and NOEL were based, were not supported statistically, but were considered biologically relevant because of their magnitude (more than 10% lower than the concurrent controls), and because of the apparent dose related trend observed. The Committee recommended that the classification of the study remain unchanged until all questions raised by the respective branch are addressed. No changes to the data evaluation records were recommended. There was no evidence, based on the data available, to suggest that Naptalam was associated with major developmental or reproductive toxicity.

The Committee recommended that an RfD for this chemical be established based on a one-year feeding study in dogs 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. An uncertainty factor (UF) of 100 was applied to account for the inter-species extrapolation and intra-species variability. On this basis, the RfD was calculated to be 0.053 mg/kg/day. It should be noted that this chemical has not been reviewed by the World Health Organization (WHO) and an acceptable daily intake (ADI) has not been established.

Individuals in Attendance

Peer Review Committee members and associates present were William Burnam (Chief, SAB, Co-chair), Reto Engler (HED, Senior Science Advisor, Co-Chair), Karl Baetcke (Chief, TB I), Marcia Van Gemert (Chief, TB II), George Ghali (Manager, HED-RfD/QA), Rick Whiting, Susan Makris and Myron Ottley.

Scientific reviewer (Committee or non-committee member(s) responsible for data presentation; signature (s) indicate technical accuracy of panel report)

Stephen Dapson

Mike Ioannou

Respective branch chief (Committee member; Signature indicates concurrence with the peer review unless otherwise stated)

Marcia Van Gemert

CC: Richard Schmitt
Stephanie Irene
Marcia Van Gemert
Mike Ioannou
Stephen Dapson
Debra Edwards
Kerry Dearfield
James Kariya
RfD File
Caswell File

Material Reviewed

1. Serota, D. G. et al. (1981). 104-week chronic toxicity study in rats 6Q8, Na salt (Alanap technical). MRID No. 00077053, 41838801, HED Doc. No. 009801, 010741. Classification: Core-minimum data for both chronic toxicity and carcinogenicity. This study satisfies data requirement 83-1a and -2a (or 83-5) of Subpart F of the Pesticide Assessment Guideline for chronic toxicity/ carcinogenicity testing in rats.

2. Jessup, D. et al.(1982). Lifetime carcinogenicity study in mice. MRID No. 00119003, HED Doc. No. 002777. Classification: Core-Supplementary data. This study does not satisfy data requirement 83-2b of Subpart F of the Pesticide Assessment Guideline for carcinogenicity testing in mice.

3. Tegeris, A. S. (1989). 12-Month oral toxicity study in dogs with Alanap. MRID No. 41057501, HED Doc. No. 009801. Classification: Core-minimum data. This study satisfies data requirement 83-1b of Subpart F of the Pesticide Assessment Guideline for chronic toxicity testing in dogs.

4. Nemec, M. D. (1991). A dietary two-generation reproduction study of S-23031 in rats. MRID No. 00031684, 42739702, HED Doc. No. 009803, 010741. Classification: Core-minimum data. This study satisfies data requirement 83-4 of Subpart F of the Pesticide Assessment Guideline for reproductive toxicity testing in rats.

5. Knickerbrocker, M. and Re, T. A. (1978) Teratologic evaluation of Alanap S technical in Sprague-Dawley rats. MRID No. 00106320, HED Doc. No. 000000. Classification: Core-supplementary data. This study does not satisfy data requirement 83-3a of Subpart F of the Pesticide Assessment Guideline for developmental toxicity testing in rats.

6. Arnold, K. S. et al (1985). Teratology study in rabbits with technical Alanap (Na salt). MRID No. 00157186, HED Doc. No. 005873, 009801. Classification: Core-minimum data. This study satisfies data requirement 83-3b of Subpart F of the Pesticide Assessment Guideline for developmental toxicity testing in rabbits.

7. Holsing, G. C. (1968). Subchronic dietary administration-rats, Alanap S. MRID No. 000106276, HED Doc. No. 000000. Classification: Core-supplementary data. This study does not satisfy data requirement 82-1a of Subpart F of the Pesticide Assessment Guideline for subchronic toxicity testing in rats.

8. Holsing, G. C. (1968). 13-Week dietary feeding-dog. MRID No. 00106277, HED Doc. No. 000000. Classification: Core-

supplementary. This study does not satisfy data requirement 82-1b of Subpart F of the Pesticide Assessment Guideline for subchronic toxicity testing in dogs.

13544

031724

Chemical:	**Benzoic acid, 2-((1-naphthalenylamino)ca**
PC Code:	**030702**
HED File Code	**21200 PEER REVIEW**
Memo Date:	**09/07/94**
File ID:	**TX011229**
Accession Number:	**412-02-0012**

HED Records Reference Center
03/21/2002