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

AUG 31 1994

#586

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: RfD/Peer Review Report of Naled [1,2-dibromo-2,2-dichloroethyl dimethyl phosphate]

CASRN. 300-76-5
EPA Chem. Code: 034401
Caswell No. 586

PCCODE

FROM: George Z. Ghali, Ph.D. *G. Ghali*
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Health Effects Division (7509C)

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

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

TO: Robert Forrest, PM 14
Insecticide-Rodenticide 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 18, 1994 to discuss and evaluate the existing and recently submitted toxicology data in support of Naled (Dibrom) re-registration and to re-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) and a 28-day dermal toxicity study in rats (82-2).

The Committee considered the chronic toxicity studies in rats (MRID No. 00128701, 00141784, 40418901) and dogs (MRID No. 1)



00160751) to be acceptable and the data evaluation records (HED Doc. 002997, 004128, 004521, 006711; 005774) to be adequate. In the rat study, the Committee recommended revising the no-observable effect level (NOEL) for plasma and red blood cell cholinesterase inhibition from 2.0 to 0.2 mg/kg/day. In the dog study, the Committee recommended revising the systemic toxicity NOEL from 2.0 to 0.2 mg/kg/day based on spinal cord lesions observed in this study. The Committee considered the NOEL for cholinesterase inhibition in the dog study to be 0.2 mg/kg/day in females (for brain, plasma and red blood cells), 0.2 mg/kg/day in males (for plasma and red blood cells), and 2.0 mg/kg/day in males for brain cholinesterase inhibition.

The Committee considered the carcinogenicity phase of the chronic toxicity/carcinogenicity study in rats (MRID No. 00128701, 00141784, 40418901) and the carcinogenicity study in mice (MRID No. 00128701, 00141784, 40418901) to be acceptable and the data evaluation records (HED Doc. No. 002997, 004128, 004521, 006711; 004128, 004521) to be adequate. The dose levels tested in the rat study were considered to be adequate for carcinogenicity testing based on cholinesterase inhibition in brain, plasma and red blood cells. The dose selection for the carcinogenicity study in rats was based on the results of a subchronic (range finding) study. The dose levels tested in the mouse carcinogenicity study were considered to be adequate for carcinogenicity testing based on increased mortality noted in the range finding and the main study. The Committee concluded that the treatment did not alter the spontaneous tumor profile in these strains of rat and mouse under the testing conditions. The chemical was classified as a "Group E".

The reproductive toxicity study in rats (83-4, MRID No. 00146498) and the developmental toxicity studies in rats (83-3a, MRID No. 00138682, 00144026) and rabbits (83-3b, MRID No. 00146496) were considered to be acceptable and the data evaluation records (HED Doc. No. 005000; 003815, 004170; 0050000, 005332) were considered to be adequate. The Committee generally agreed with the reviewer's evaluation and interpretation of data. However, the Committee noted marginal increase in incidence of resorptions in the high dose group in the rat developmental study. On the other hand, these effects were questionable as developmental toxicity effects since they were observed at a maternally toxic level. No changes to the data evaluation records were recommended.

The requirement for a developmental neurotoxicity study was discussed, but was not recommended. Furthermore, the scientific reviewer indicated that acute and subchronic mammalian neurotoxicity studies were under review at that time. The scientific reviewer indicated also that a non-mammalian delayed neurotoxicity study has already been reviewed by the Agency. Based on the results of the acute non-mammalian delayed neurotoxicity study, the respective branch recommended that a 28-day (or a 90-

day) repeated dose delayed neurotoxicity study in the hen be submitted (Note: the 28-day repeated dose delayed neurotoxicity study has already been submitted to the Agency).

The Committee recommended that the existing RfD for this chemical remain unchanged. The current RfD was generated by the Health Effects Division - RfD Committee in March 17, 1987 and verified by the Agency RfD Work Group on April 15, 1987. The RfD was based on a two-year feeding study in rats with a NOEL of 0.2 mg/kg/day. Cholinesterase inhibition was observed for plasma, red blood cells and brain at 2.0 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 0.002 mg/kg/day. The Committee recommended including the chronic toxicity study in dogs with a NOEL of 0.2 mg/kg/day for plasma, red blood cell and brain cholinesterase inhibition and spinal cord lesions. 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 developed.

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, Henry Spencer, William Sette, James Rowe and Myron Ottley.

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

Pamela Hurley

Pamela M. Hurley 8/24/94

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

Karl Baetcke

Karl Baetcke

CC: Richard Schmitt
Stephanie Irene
Karl Baetcke
Pamela Hurley
Debra Edwards
Kerry Dearfield
James Kariya
RfD File
Caswell File

Material Reviewed

1. Batham, P. et al. (1984). Dibrom chronic oral toxicity/carcinogenicity study in rats. MRID No. 00128701, 40418901, HED Doc. No. 002997, 004128, 004521, 006711. Classification: Core-minimum data. 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. Brewer, L. (1984). Dibrom: Lifetime oral carcinogenicity study in mice. MRID No. 00141785, 00148569, HED Doc. No. 004128, 004521. Classification: Core-minimum data. This study satisfies data requirement 83-2b of Subpart F of the Pesticide Assessment Guideline for carcinogenicity testing in mice.

3. Johnson, D. E. et al. (1986). One-year chronic oral toxicity study in dogs with naled. MRID No. 00160750, HED Doc. No. 005774. 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. Schroeder, R. E. and Daly, I. W. (1985). Two-generation reproduction study in rats. MRID No. 00146498, HED Doc. No. 005000. 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. Holson, J. and Gallagher, E. (1984). Teratology study in rats with Naled technical. MRID No. 00138682, 00144026, HED Doc. No. 003815, 004170. Classification: Core-minimum data. This study satisfies data requirement 83-3a of Subpart F of the Pesticide Assessment Guideline for developmental toxicity testing in rats.

6. Fitzgerald, L. et al. (1985). Teratology study in rabbits with Chevron Naled technical (SX-1397). MRID No. 00146496, HED Doc. No. 005000, 005332. 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. Rausina, G. A. and Zimmerman, R. A. (1986). A twenty-eight day dermal study with Naled technical in rats. MRID No. 00160750, HED Doc. No. 005774. Classification: Core-minimum data. This study satisfies data requirement 82-2 of Subpart F of the Pesticide Assessment Guideline for 28-day dermal toxicity testing in rats.

5