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

AUG 30 1994

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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: RfD/Peer Review Report of Bardac 22 (Didecyl Dimethyl Ammonium Chloride)

CASRN. 7173-51-5
EPA Chem. Code: 69149
Caswell No. 331A

PC Code 069149

FROM: George Z. Ghali, Ph.D.
Manager, RfD/Quality Assurance Peer Review
Health Effects Division (H7509C)

TO: John Lee, PM 31
Fungicide-Herbicide Branch
Registration Division (H7505W)

The Health Effects Division RfD/Peer Review Committee met on January 13, 1994 to discuss and evaluate toxicology data submitted in support of Bardac 22 registration and to assess the Reference Dose (RfD) for this chemical.

The data base for this chemical consists of acute toxicity studies for BARDAC2180 (ISOBARDAC, CASRN 7173-51-5, PC 069149) and various subchronic and chronic studies for two other quaternary ammonium salts; ADBAC (N-alkyl dibenzyl ammonium chloride) and BARDAC 2280, 80% and 2250, 50% (didecyl dimethyl ammonium chloride). Rather than requiring separate data for each individual QUAT, the Agency adopted a clustering approach (PR Notice 88-2, dated February 26, 1988), which permitted representative members of each cluster to be used in toxicity studies, instead of requiring separate studies on each QUAT. BARDAC 2180 and BARDAC 2280/2250 are both Group I QUATs. Therefore, the acute studies with BARDAC 2180 and the subchronic, chronic, developmental and reproductive toxicity for BARDAC 2280/2250 can be used to support the registration of BARDAC 2180. However, the studies pertaining to ADBAC, a Group II QUAT, cannot be used to support the registration of BARDAC 2180.

The Committee considered the chronic toxicity study in rats **(83-1a)** and dogs **(83-1b)**, the carcinogenicity studies in rats **(83-2a)** and mice **(83-2b)**, developmental toxicity studies in rats and

rabbits **(83-3a and -3b)** and the reproductive toxicity study in rats **(83-4)** to be acceptable and the data evaluation records for these studies to be adequate.

There was no evidence, based on the available data, to suggest that Bardac 22 was associated with significant reproductive and developmental toxicity.

The Committee considered the high dose tested in the rat study to be appropriate for carcinogenicity testing based on slight but statistically significant decrease in mean body weight (< 10%) and some histopathological changes. The incidence of neoplastic lesions in treated animals was comparable to controls except for a dose-related increase in the incidence of testicular interstitial cell adenoma. Historical control data were not available for review by the Committee. The respective branch has been charged to resolve this issue. In the mouse carcinogenicity study, the high dose tested was considered to be adequate for carcinogenicity testing based upon decreased mean body weights and body weight gains in both males and females in the main study. In a parallel study, histopathological changes were evident at slightly higher dose level. The treatment did not alter the spontaneous tumor profile in this strain of mice. On the basis of these two studies the chemical was, tentatively, classified as a "Group E" pending the receipt of the additional information requested by the Committee and subsequently by the respective branch (Note: subsequent to the meeting, the respective branch decided to ask for a complete histopathological evaluation of the low- and mid-dose groups since the study report included histopathological evaluation only for animals died during the study).

The Committee recommended that an RfD be established on the basis of a NOEL of 1.0 mg/kg/day for maternal toxicity observed at 3 and 10 mg/kg/day in rabbits and rats respectively. An uncertainty factor (UF) of 100 was used to account for the inter-species extrapolation and intra-species variability. On this basis the **RfD** was calculated to be **0.01 mg/kg/day**. It should be noted that this chemical has not been reviewed by the WHO/FAO joint committee on pesticide residues.

A. Individuals in Attendance

1. Peer Review Committee Members and Associates present in at least one of the two meetings (Signature indicates concurrence with the peer review unless otherwise stated).

William Burnam _____

Marcia Van Gemert _____

Karl Baetcke _____

Henry Spencer _____

Roger Gardner _____

James Rowe _____

Esther Rinde _____

George Ghali _____

Rick Whiting _____

2. Scientific Reviewer (Committee or non-committee members responsible for data presentation; signatures indicate technical accuracy of panel report).

Robert Fricke _____

Jess Rowland _____

3. Others:

J. Smith, S. Reilly and B. Backus of HED as observers.

CC: Penny Fenner-Crisp
Richard Schmitt
Kerry Dearfield
Marcia Van Gemert
Jess Rowland
Robert Fricke
James Kariya
Flora Chow
RfD File
Caswell File

B. Material Reviewed

Material available for review included data evaluation records for a chronic toxicity/carcinogenicity study in rats **(83-5 or 83-1a and -2a)**, a carcinogenicity study in mice **(83-2b)**, a chronic toxicity study in dogs (83-1b), developmental toxicity studies in rats and rabbits **(83-3a and -3b)** and a reproductive toxicity study in rats **(83-4)**.

1. Gill, M. W. (1991). Chronic dietary toxicity/oncogenicity study with didecyl dimethyl ammonium chloride [in rats]. MRID No. 41965101, HED Doc No. 010689.

Core Classification: Core minimum data.

Committee's Conclusion and Recommendations:

The chemical was tested in Sprague-Dawley rats at 300, 750 and 1500 ppm (13, 32 and 64 mg/kg/day in males and 16, 41 and 83 mg/kg/day in females). The NOEL/LOEL were considered to be 750 and 1500 ppm based on increased incidence of nonneoplastic lesions in the mesenteric lymph nodes (sinusoidal blood, hemosiderosis and histiocytosis). The Committee considered the high dose tested in the rat study to be appropriate for carcinogenicity testing based on slight but statistically significant decrease in mean body weight (< 10%) and some histopathological changes. The incidence of neoplastic lesions in treated animals was comparable to controls, except for a dose-related increase in the incidence of testicular interstitial cell adenoma. (Note: Subsequent to the meeting, the respective branch decided to ask for a complete histopathological evaluation of the low- and mid-dose since the study report included histopathological evaluation only for animals died during the study). The Committee generally agreed with the reviewer's evaluation and interpretation of data and the classification of the study. The study was considered to be acceptable and the data evaluation record was considered to be adequate. This study satisfies data requirements 83-1a and 83-2a of subpart F of the Pesticide Assessment Guideline for chronic toxicity/carcinogenicity testing in rats.

2. Gill, M. W. et al. (1991). Chronic dietary toxicity/ oncogenicity study with didecyl dimethyl ammonium chloride in mice. MRID No. 41802301, HED Doc No. 010689.

Core Classification: Core minimum data.

Committee's Conclusion and Recommendations:

The chemical was tested in CD-1 mice at 100, 500 and 1000 ppm (15, 76.3 and 155.5 mg/kg/day in males and 18.6, 93.1 and 193.1 mg/kg/day in females). The NOEL/LOEL were considered to be 500 and 1000 ppm based on decreased mean body weight and body weight gain

in both males and females. The Committee considered the high dose tested in this study to be appropriate for carcinogenicity testing based on slight but statistically significant decrease in mean body weight (< 10%) and body weight gain. The incidence of neoplastic lesions in treated animals was comparable to controls. The Committee generally agreed with the reviewer's evaluation and interpretation of data and the classification of the study. The study was considered to be acceptable and the data evaluation record was considered to be adequate. This study satisfies data requirements 83-2b of subpart F of the Pesticide Assessment Guideline for carcinogenicity testing in mice.

3. **Schulze, G. E. (1991). Chronic oral toxicity study of didecyl dimethyl ammonium chloride in dogs. MRID No. 41970401, HED Doc No. 010689.**

Core Classification: Guideline data.

Committee's Conclusion and Recommendations:

The chemical was tested in beagle dogs at 3, 10 and 30/20 mg/kg/day. The NOEL/LOEL were considered to be 10 and 20 mg/kg/day based on increased incidence of clinical observations (emesis and soft/mucoid feces) in males and females and decreased total cholesterol levels in females. The Committee generally agreed with the reviewer's evaluation and interpretation of data and the classification of the study. The study was considered to be acceptable and the data evaluation record was considered to be adequate. This study satisfies data requirements 83-1b of subpart F of the Pesticide Assessment Guideline for chronic toxicity testing in dogs.

4. **Neeper-Bradley, T. L. (1991). Two-generation reproduction study in Sprague-Dawley (CD) rats with didecyl dimethyl ammonium chloride administered in the diet. MRID No. 41804501, HED Doc. No. 010689.**

Core Classification: Guideline data.

Committee's Conclusion and Recommendations:

The chemical was tested in Sprague-Dawley rats at 300, 750 and 1500 ppm (20, 50 and 103 mg/kg/day for males and 24, 61 and 122 mg/kg/day for females). Parental toxicity NOEL/LOEL were considered to be 750 and 1500 ppm based on decreased body weight and body weight gain and food consumption. Reproductive NOEL/LOEL were considered to be 750 and 1000 ppm, respectively, based on decreased mean pup body weight and body weight gain during postnatal period. The Committee generally agreed with the reviewer's evaluation and interpretation of data and classification of the study. However, the Committee recommended that the reproductive NOEL/LOEL be called reproductive/systemic toxicity

NOEL/LOEL since these effects were observed late in lactation. The study was considered to be acceptable and the data evaluation record was considered to be adequate. This study satisfies data requirements 83-4 of subpart F of the Pesticide Assessment Guideline for reproductive toxicity testing in rats.

5. Neeper-Bradley, T. L. (1991). Developmental toxicity evaluation of didecyl dimethyl ammonium chloride administered by gavage to CD (Sprague-Dawley) rats. MRID No. 41886701, HED Doc. No. 009707.

Core Classification: Core minimum data.

Committee's Conclusion and Recommendations:

The chemical was tested in Sprague-Dawley (CD) rats at 1, 10 and 20 mg/kg/day. Maternal toxicity NOEL/LOEL were considered to be 1 and 20 mg/kg/day based on increased incidence of clinical signs, decreased body weight gain during dosing period and decreased food efficiency. Developmental toxicity NOEL/LOEL were considered to be 10 and 20 mg/kg/day based on increased incidence of skeletal variations. The Committee generally agreed with the reviewer's evaluation and interpretation of data and classification of the study. Since two data evaluation records were available for this study (HED Doc No. 009707 and 010689), the Committee recommended that the first DER, i. e. HED Doc No. 009707 should supersede the other. The study was considered to be acceptable and the data evaluation record was considered to be adequate. This study satisfies data requirements 83-3a of subpart F of the Pesticide Assessment Guideline for developmental toxicity testing in rats.

6. Tyl, R. W. (1989). Developmental toxicity study of didecyl dimethyl ammonium chloride administered by gavage to New Zealand rabbits. MRID No. 41018701, 93005004, 93006004, HED Doc. No. 009707.

Core Classification: Core minimum data.

Committee's Conclusion and Recommendations:

The chemical was tested in New Zealand rabbits at 1, 3 and 10 mg/kg/day. Maternal toxicity NOEL/LOEL were considered to be 1 and 20 mg/kg/day based on increased incidence of clinical signs (hyperactivity, labored and audible respiration) and decreased body weight gain during dosing period. Developmental toxicity NOEL/LOEL were considered to be 3 and 10 mg/kg/day based on decreased fetal body weight and increased number of dead fetuses. The Committee generally agreed with the reviewer's evaluation and interpretation of data and classification of the study. The Committee considered the developmental effects to be suggestive. The Committee recommended that the NOEL for maternal toxicity for this study to be used for risk characterization of repeated exposure scenarios.

The study was considered to be acceptable and the data evaluation record was considered to be adequate. This study satisfies data requirements 83-3b of subpart F of the Pesticide Assessment Guideline for developmental toxicity testing in rabbits.