6-18-96

DATE STAMPED: 06/18/96

MEMORANDUM

SUBJECT: RfD/Peer Review Report of Thiodicarb (Larvin) [Dimethyl N,N-(thiobis(methylimino)carbonyloxy)bis (ethanimidothioate]

CASRN: 59669-26-0
EPA Chem. Code: 114501
Caswell No.: 900AA

FROM: George Z. Ghali, Ph.D.
Manager, RfD/QA Peer Review Committee
Health Effects Division (7509C)

THRU: William Burnam
Chairman, RfD/QA Peer Review Committee
Health Effects Division (7509C)

TO: Dennis Edwards, PM 19
Insecticide-Rodenticide Branch
Registration Division (7505C)

The Health Effects Division-RfD/Peer Review Committee met on January 18, 1996 to discuss and evaluate the toxicology data submitted in support of Thiodicarb (Larvin) registration and to reassess the Reference Dose (RfD) for this chemical.

Material available for review consisted of data evaluation records (DERs) for two chronic toxicity/carcinogenicity studies in rats **(83-5 or 83-1a and -2a)**, three carcinogenicity studies in mice **(83-2b)**, a chronic toxicity study (1-year) in dogs **(83-1b)**, a multi-generation reproductive toxicity study in rats **(83-4)**, developmental toxicity studies in rats and rabbits **(83-3a and -3b)** subchronic toxicity studies in rats, mice **(82-1a)** and dogs **(82-1b)**, and two delayed neurotoxicity studies in hens.

A. Chronic and Subchronic Toxicity:

The Committee considered the chronic toxicity phase of the rat study (83-1a, 1994, MRID No. 43308201, 43405001, 43596401) to be acceptable as Core-minimum data, and the data evaluation record for this study (HED Doc. No. 011359, 011378) to be adequate.

The no-observable effect level (NOEL) was reported to be 60 ppm (3.3 mg/kg/day in males and 4.5 mg/kg/day for females), and the lowest-observable effect level (LOEL) was reported to be 200 ppm (12 mg/kg/day for males and 15 mg/kg/day for females) based on the increased incidence of extramedullary hemopoiesis in males and decreased red blood cell cholinesterase activity in females. The Committee agreed with the reviewer's evaluation and interpretation of data and classification of the study.

A second chronic toxicity study in rats (83-1a, 1980, MRID No. not available/Accession No. 070764) was available for review by the Committee. The study was originally classified as supplementary data and was then upgraded to Core-minimum data. The NOEL/LOEL were reported to be 3 and 10 mg/kg/day. The results of this study were considered to be consistent and supportive to the findings of the more recent study described above. This study was not discussed by the Committee since it is superseded by the new study (MRID No. 43308201, 43405001, 43596401) described above.

The Committee examined the chronic toxicity phase of the carcinogenicity study in mouse (83-2b, 1993, MRID No. 43000501, 43619301) and agreed with the reviewer's evaluation and interpretation of the data. The NOEL/LOEL were considered to be 70 and 1000 mg/kg/day based on increased mortality in both sexes which was more pronounced in females, decreased body weight gain in males, decreased hemoglobin, erythrocytes, and hematocrit, alterations in blood chemistry, increased liver and spleen weights accompanied by histopathological changes. The effects seen in this study on the hemopoietic system are similar to those seen in the rat study. The Committee noted that there was some increase in extramedullary hemopoiesis in females at 70 mg/kg/day, but this effect was considered to be marginal; no other effects were observed at this level in either males or females.

The Committee did not examine the chronic toxicity phases of the other two carcinogenicity studies in mouse (83-2b, 1980, MRID No. 000541407, HED Doc. No. 001820, 003706; 1984, MRID No. 00160368, HED Doc. No. 005702). These two studies were superseded by the more recent study described above.

The Committee considered the one-year chronic toxicity study in dogs (83-1b, MRID No. 00159813) to be acceptable as Core-minimum data and the data evaluation record (HED Doc. No. 005934) to be adequate. The systemic NOEL was considered to be 487 ppm (12.8 mg/kg/day in males and 13.8 mg/kg/day in females), and the systemic

LOEL was considered to be 1506 ppm (38.3 mg/kg/day in males and 39.5 mg/kg/day in females) based on reduced hematology parameters including erythrocytes, hemoglobin, and hematocrit. The NOEL for cholinesterase inhibition was considered to be 164 ppm (4.4 mg/kg/day in males and 4.5 mg/kg/day in females) and the LOEL was considered to be 487 ppm (12.8 mg/kg/day for males and 13.8 mg/kg/day for females). The Committee agreed with the reviewer's evaluation and interpretation of data and classification of the study.

The Committee did not examine several subchronic toxicity studies of different durations in rats, mice (82-1a, MRID No. 00135782; 43611701) and dogs (82-1b, MRID No. 00044966; 00079474).

B. Carcinogenicity:

The carcinogenicity issue has been addressed by the Health Effects Division-Carcinogenicity Peer Review Committee [HED-CPRC; meeting of 11/29/95]. Thiodicarb has been classified by the HED-CPRC as a Group B2, probable human carcinogen, based on increases in liver tumors in both sexes of the CD-1 mouse, statistically significant by both pair-wise and trend analysis and statistically-significant increases in testicular interstitial cell tumors in the male Sprague-Dawley rat. While there was low concern for mutagenicity, data from related structural analogs provided additional support.

The CPRC noted that while the highest dose in mice may have been excessive, the overall dose selection was improper with the highest dose (1000 mg/kg/day) more than 10-fold that of the mid-dose (70 mg/kg/day). The CPRC also noticed that there was a suggestive tumor response in the male mouse liver even at the mid-dose, and the incidence exceeded that of historical controls. Additionally, the tumor incidences were unusually high (hepatocellular combined adenoma/carcinoma at the highest dose was 76% vs 18% in the controls for males and 62% vs 2% in the controls for females).

The CPRC felt it was inappropriate to apply a linear low-dose extrapolation to the animal data because the increased incidences of tumors were statistically significant only at the highest dose in both species; in the case of the mice, the highest dose may even have been excessive. In addition, there was no evidence of genotoxicity. Therefore, for the purposes of risk characterization, the CPRC recommended that a non-linear methodology [MOE] be applied for the estimation of human risk, based on the hepatocellular combined adenoma/carcinoma in male mice, with the point of departure set at the 5 mg/kg/day dose (NOEL).

C. Reproductive and Developmental Toxicity:

The Committee considered the 2-generation reproductive toxicity study in rats (83-4, 1992, MRID No. 42381301, 42735101) to be acceptable and the data evaluation record (HED Doc. No. 009832, 011134) to be adequate.

According to the data evaluation record, the systemic toxicity NOEL was considered to be 100 ppm (5 mg/kg/day) and the LOEL was considered to be 300 ppm (15 mg/kg/day) based on decreased body weight and body weight gain and food consumption in males and females.

According to the data evaluation record, reproductive effects manifested as decreased F2b pup body weight occurred at all dose levels, and decreased viability index for F1, F2a, and F2b litters occurred at the mid- (300 ppm) and high-dose (900 ppm) levels. Offspring viability and growth were adversely affected at dose levels of 300 and 900 ppm and 100, 300, and 900 ppm, respectively. On this basis, the NOEL for effects on offspring could not be established.

Subsequently, a benchmark dose (BMD) approach was performed on male and female pup weights at 0 ppm and 100 ppm using a commercially available software, THC; a computer program for computation of reference dose from continuous animal toxicity data using the BMD approach (H. Pettigrew, HED, memo dated July 18, 1994). A BMD approach is usually applied on a set of data with continuous response called a benchmark response. For continuous data , responses of 5% or 10% have been suggested. Accordingly, benchmark responses of 5% reduction and 10.0% reduction relative to control pup weight, as well as responses corresponding to the smallest acceptable reductions at 67% and 80% power as reported by the registrant were selected.

The no-effect estimated levels (NOELs) computed by the registrant's suggested methodology correspond to the Maximum Likelihood Estimates (MLEs) obtained by the Benchmark method, but no allowance for experimental variability was made by calculating a lower confidence limit on dose. The use of a 95% lower confidence limit on the dose, corresponding to a 5% decrease in mean pup weight was recommended (as agreed upon by SAB and TB II), resulting in BMDs of approximately 34.7 ppm for males, and 35.2 ppm for females.

The traditional method of deriving a NOEL (when the data fail to establish the NOEL) divides the LOEL of 100 ppm by a factor which varied from 3 to 10, depending on the severity of the effect observed at the lowest dose level. Using this method,i.e. dividing the lowest dose level of 100 ppm by 3 gives essentially the same result as the Benchmark approach (memo by H. Pettigrew, 7/18/94).

However, evaluation of the study by the Committee and considering the 10% reduction in body weight value determined that the lowest dose level of 100 ppm is at or near the NOEL for reproductive/developmental toxicity. Furthermore, the Committee redefined the reproductive effects at this level as developmental type effects rather than reproductive effects.

There were two developmental toxicity studies in rats (83-3a, MRID No. 00043740, 00053254; 0043741, 00053256) available for review by the Committee. The Committee considered both studies, taken together, to be adequate and the data evaluation records (HED Doc. No. 001996, 001997, 003694) to be adequate when the additional data tables generated for the Committee's consideration are appended to the original DERs. The NOEL/LOEL for maternal toxicity was considered to be 10 and 20 mg/kg/day, respectively, based on clinical signs (tremors, inactivity). The developmental toxicity NOEL/LOEL were considered to be 3 and 10 mg/kg/day, based on decreased fetal body weights and increased incidence of litters and fetuses with developmental variations (unossification of sternebrae 5 and/or 6 and other sternebrae).

There was one developmental toxicity study in rabbits (83-3b, MRID No. 00159814; 00053257, 00053258) available for review by the Committee. The Committee considered the study to be adequate and the data evaluation records (HED Doc. No. 005934; 004681) to be adequate. The NOEL/LOEL for maternal toxicity were considered to be 20 and 40 mg/kg/day, respectively, based on reduced body-weight gain and food consumption. The developmental toxicity NOEL was considered to be 40 mg/kg/day, the highest dose level tested.

There was one developmental toxicity study in mice (83-3a, MRID No. 00053257, 00053258) available for review by the Committee. The Committee considered the study to be acceptable and the data evaluation record (HED Doc. No. 001996, 001997) to be adequate when additional data tables generated for the Committee's review are added to the original DER. The NOEL/LOEL for maternal toxicity were considered to be 100 and 200 mg/kg/day, respectively, based on increased mortality.

D. Acute and Subchronic Neurotoxicity:

There were no acute or subchronic neurotoxicity studies in rats (81-8 and 82-7) available for review by the Committee. The Committee recommended that an acute neurotoxicity study be conducted.

Based on open literature studies, the Committee determined that Thiodicarb was not a delayed neurotoxin under the testing conditions in the hen.

E. Mutagenicity:

There were no mutagenicity data (84-2) available for review by the Committee. The mutagenicity issue has already been addressed by the Health Effects Division-Carcinogenicity Peer Review Committee.

F. Reference Dose (RfD):

The Committee recommended that a RfD for this chemical remain unchanged. The RfD for this chemical was established based on the older chronic toxicity study in rats (1980, MRID No. N/A, Accession No. 070764; HED Doc. No. 001820, 003706) with a NOEL of 3 mg/kg/day. However, since a more recent chronic toxicity study in rats (1994, MRID No. 43308201, 43405001, 43596401; HED Doc. No. 011359, 011378) was available, the Committee recommended setting the RfD on the more recent rat study which demonstrated a similar NOEL (60 ppm, equivalent to 3.3 and 4.5 mg/kg/day in males and females, respectively). At the next higher dose level of 200 ppm (12 mg/kg/day for males and 15 mg/kg/day for females), increased incidence of extramedullary hemopoiesis in males and decreased red blood cell cholinesterase activity in females were observed.

An Uncertainty Factor (UF) of 100 was applied to account for both the interspecies extrapolation and intraspecies variability. On this basis, the RfD was calculated to be 0.03 mg/kg/day.

This chemical has been reviewed by the WHO/FAO Joint Meeting on Pesticide Residues (JMPR) in 1986 and an Acceptable Daily Intake (ADI) of 0.03 has been established.

G. Individuals in Attendance:

Peer Review Committee members and associates present were William Burnam (Chairman, RfD/QA Peer Review Committee), George Ghali (Manager, RfD/QA Peer Review Committee), Karl Baetcke, Mike Ioannou, Marion Copley, Stephen Dapson, Roger Gardner, Guruva Reddy, William Sette, Henry Spencer and Rick Whiting. In attendance also was Kit Farwell of HED as an observer.

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

Linda Taylor _____

Clark Swentzel _____

Respective Branch Chief or Senior Scientist (Committee member; signature indicates concurrence with the peer review unless otherwise stated)

Mike Ioannou _____

CC: Stephanie Irene
Debra Edwards
Mike Ioannou
Linda Taylor
Clark Swentzel
Albin Kocialski
Karen Whitby
Paula Deschamp
Beth Doyle
Amal Mahfouz (OW)
RfD File
Caswell File

H. Material Reviewed:

1. Atkinson, C. et al. (1994). 104-Week dietary carcinogenicity study in rats. MRID No. 43308201, 43405001, 43596401, HED Doc. No. 011359, 011378. Classification: Core-minimum data. This study satisfies data requirement 83-1a of Subpart F of the Pesticide Assessment Guideline for chronic toxicity testing in rats. It should be noted that the acceptability of the carcinogenicity phase has been determined by the HED-Carcinogenicity Peer Review Committee.

2. Carneigie-Mellon Bushy Run Research Center. (1980). Chronic toxicity and oncogenicity feeding study in Fischer 344 rats. Accession No. 070764, HED Doc. No. 001820, 003706. This study was not discussed by the Committee; the study has been superseded by a more recent study in the rat (MRID No. 43308201, 43405001, 43596401.

3. Perry, C. J. et al. (1993). Thiodicarb: 97 Week dietary carcinogenicity study in mice with 52 week interim kill (results after 97 weeks). MRID No. 43000501, HED Doc. No. 011030. Classification: Guideline data. The Committee examined the chronic toxicity phase. The carcinogenicity phase of the study has been evaluated by the HED-Carcinogenicity Peer Review Committee.

4. DePass, L. R. et al. (1980). UC 51 762 - Chronic oncogenicity feeding study in mice. MRID No. 00041407, HED 001820, 003706. The chronic toxicity phase of this study was not discussed by the Committee; the study has been superseded by a more recent study in the mouse (MRID No. 4300501.

5. Yoshida, A. (1984). Thiodicarb: Oral chronic toxicity and oncogenicity study in mice. MRID No. 00160368, HED 005702. The chronic toxicity phase of this study was not discussed by the Committee; the study has been superseded by a more recent study in the mouse (MRID No. 4300501.

6. Hamada, N. N. (1986). One-year feeding study in dogs. MRID No. 00159813, HED Doc. No. 005934. Classification: Core-minimum data. This study satisfies data requirement 83-1b of Subpart F of the Pesticide Assessment Guideline for chronic toxicity testing in rats.

7. Henwood, S. M. (1992). Two-generation reproduction toxicity study with Thiodicarb technical in rats. MRID No. 42381301, HED Doc. No. 009832, 011134. Classification: Core-minimum data (as upgraded by the Committee). This study satisfies data requirement 83-4 of Subpart F of the Pesticide Assessment Guideline for reproductive toxicity testing in rats.

8. Henwood, S. M. (1991). Range -finding reproduction study with

thiodicarb technical in rats. MRID No. 42381302, HED Doc. No. 009832. Classification: Acceptable. This study is a range-finding study and as such, does not does not satisfy data requirement 83-4 of Subpart F of the Pesticide Assessment Guideline for reproductive toxicity testing in rats.

9. Rodwell, D. E. (1979). Teratology study in rats. MRID No. 00043740, 00053254, HED Doc. No. 001996. Classification: Core-supplementary data. This study, when considered together with the other rat teratology study (MRID No. 00043741, 00053251) satisfies data requirement 83-3a of Subpart F of the Pesticide Assessment Guideline for developmental toxicity testing in rats.

10. Woodside, M. D. et al. (1979). UC 51762: Rat teratology studies. MRID No. 00043741, 00053251, HED Doc. No. 003694. Classification: Core-supplementary data. This study, when considered together with the other rat teratology study (MRID No. 00043740, 00053254) satisfies data requirement 83-3a of Subpart F of the Pesticide Assessment Guideline for developmental toxicity testing in rats.

11. Rodwell, D. E. and Ziemke, K. A. (1979). Pilot teratology study in rats. MRID No. 00053255, HED Doc. No. 001996. Classification: Core-supplementary data. This study is a pilot study; therefore it does not satisfies data requirement 83-1a of Subpart F of the Pesticide Assessment Guideline for subchronic toxicity testing in rats.

12. Rodwell, D. E. (1986). A teratology study in rabbits with thiodicarb. MRID No. 00159814, HED Doc. No. 005934. Classification: Core-supplementary data. This study, when viewed with the range-finding studies (MRID No. 4028001), satisfies data requirement 83-3b of Subpart F of the Pesticide Assessment Guideline for developmental toxicity testing in rabbits.

13. Rodwell, D. E. and Dangler, T. L. (1979). Pilot teratology study in mice. MRID No. 00053257, HED Doc. No. 001996, 001997. Classification: Supplementary. This study is a pilot study; therefore it does not satisfies data requirement 83-1a of Subpart F of the Pesticide Assessment Guideline for subchronic toxicity testing in mice.

14. Rodwell, D. E. and Janes, J. M. (1980). Teratology study in mice. MRID No. 00053258, HED Doc. No. 001996, 001997. Classification: Core-supplementary data. This study does not satisfies data requirement 83-1a of Subpart F of the Pesticide Assessment Guideline for developmental toxicity testing in mice.

15. Wolfe, G. W. et al. (1981). Subchronic toxicity study in dogs: Larvin™ Thiodicarb. MRID No. 00079474, HED Doc. No. 003062. Classification: Acceptable (according to the DER). This study was not discussed by the Committee.

16. Homan, E. R. et al. (1978). UC 52702: Inclusion in the diet of dogs for thirteen weeks. MRID No. 00044966, HED Doc. No. 003697. Classification: Core-guideline data (according to the DER). This study was not discussed by the Committee.

17. Homan, E. R. et al. (1978). UC 52702: Inclusion in the diet of rats for thirteen weeks. MRID No. 00135782, HED Doc. No. 003697. Classification: Core-supplementary data (according to the DER). This study was not discussed by the Committee.

18. Atkinson, C. et al. (1991). Thiodicarb: 4 Week dietary dose range finding study in mice. MRID No. 43611701, HED Doc. No. 000000. Classification: Acceptable (according to the DER). This study was not discussed by the Committee.