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

MAR 9 1994

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: **Revised** RfD/Peer Review Report of Terbufos [S-[(1,1-dimethylethyl) thiomethyl] O, O-diethylphosphorodithioate].

CASRN: 13071-79-9
EPA Chem. Code: 105001
Caswell No. 131A

FROM: George Z. Ghali, PhD G. Ghali 3.9.94
Manager, RfD/Quality Assurance Peer Review Committee
Health Effects Division (H7509C)

TO: Robert Forrest, PM 14
Insecticide-Rodenticide Branch
Registration Division (H7505C)

Lois Rossi, Chief
Re-registration Branch
Re-registration and Special Review Division (H7508W)

The Health Effects Division RfD/Peer Review Committee met on July 1, 1993 to discuss and evaluate the existing toxicology data in support of Terbufos re-registration and to re-assess the Reference Dose for this chemical.

The RfD/Peer Review Committee recommended that an RfD be established based upon a NOEL of 0.005 mg/kg/day for plasma cholinesterase inhibition observed at 0.015 mg/kg/day in a four-week study in dogs. This study was conducted to establish a NOEL for cholinesterase inhibition after a long-term toxicity study in dogs failed to demonstrate a NOEL for changes in this parameter. The least effect level for plasma cholinesterase inhibition in the long-term toxicity study in dogs was 0.015 mg/kg/day, the lowest dose tested. 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 **0.00005 mg/kg/day**. It should be noted that a regulatory value of 0.0002 mg/kg/day was established for this chemical in 1989 by the World Health Organization (WHO).

The Committee considered the long-term feeding study in rats **(83-1a)** and dogs **(83-1b)**, the carcinogenicity studies in rats and mice **(83-2a and -2b)**, and the developmental toxicity studies in rats and rabbits **(83-3a and -3b)** to be acceptable and the data evaluation records to be adequate. The reproductive toxicity study in rats **(83-4)**, though not conforming to the recent Guideline for reproductive toxicity testing, was considered adequate for regulatory purposes. A new study will not be requested at this time. The Committee recommended to revise the NOEL/LOEL for plasma cholinesterase in the four-week study in dogs from 0.0015 and 0.0025 mg/kg/day to 0.005 and 0.015 mg/kg/day.

The high dose tested in the carcinogenicity study in rats was considered to be adequate for carcinogenicity testing in this strain of rats based upon cholinesterase depression. The high dose tested in mice was considered to be adequate for carcinogenicity testing in this strain of mice based upon body weight gain depression (10.1 and 19.7% in males and females, respectively). The treatment did not alter the spontaneous tumor profile in these strains of rats and mice under the testing conditions. On the basis of these two studies, the chemical was classified as a **"Group E"**.

A. Individuals in Attendance

1. Peer Review Committee Members and Associates (Signature indicates concurrence with the peer review unless otherwise stated).

William Burnam

Marcia Van Gemert

Karl Baetcke

Henry Spencer

William Sette

Roger Gardner

John Tice

George Ghali

Rick Whiting

2. Peer Review Committee Members and Associates in Absentia (Signature indicates concurrence with the peer review unless otherwise stated. However, signature may not ~~be~~ required).

Reto Engler

James Rowe

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

Jess Rowland 1-10-94

Alan Levy 1-10-94

CC: Penny Fenner-Crisp
Richard Schmitt
Kerry Dearfield
Marcia Van Gemert
Jess Rowland
Alan Levy
James Kariya
RfD Files
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 long-term toxicity study in dogs (83-1b), a carcinogenicity study in mice (83-2b), developmental toxicity studies in rats and rabbits (83-3a and -3b), a reproductive toxicity study in rats (83-4), subchronic toxicity studies in rats, dogs and mice and the tox. one-liner. The Committee focused on the following studies:

1. American Cyanamid Co. (1977). A three and twenty-four month feeding study of Counter, terbufos insecticide in rats. MRID No. 00121741, HED Doc. No 003847, 004893.

Core Classification: Core-minimum data

Committee's Conclusions and Recommendations:

The chemical was tested in rats at 0.25, 1.00 and 2.0/4.0/ 8.0 ppm (equivalent to 0.0125, 0.05 and 0.1/0.2/0.4 mg/kg/day in males and 0.0125, 0.05 and 0.1/0.2/0.4 mg/kg/day in females). A NOEL for cholinesterase inhibition was not established. The LOEL was considered to be 0.0125 mg/kg/day, the lowest dose tested. The high dose employed in the carcinogenicity phase of this study was considered adequate for carcinogenicity testing. The Committee agreed with the reviewer's evaluation and interpretation of data. The study was considered to be acceptable and the data evaluation record was considered to be adequate. This study, when considered in light of the results of the one year feeding study in rats (No. 2, below), satisfies data requirement 83-1a and -2a of Subpart F of the Pesticide Assessment Guideline for chronic toxicity/ carcinogenicity testing in rats.

2. Daly, I. W. (1987) A One-year dietary toxicity study with AC 92,100 in rats. MRID No. 40089602, HED Doc. No. 006352.

Core Classification: Core-minimum data

Committee's Conclusions and Recommendations:

The chemical was tested at 0.125, 0.50 and 1.0 ppm (equivalent to 0.007, 0.028 and 0.055 mg/kg/day in males and 0.009, 0.036 and 0.071 mg/kg/day in females). The NOEL/LOEL for plasma and brain cholinesterase inhibition were considered to be 0.028 and 0.055 mg/kg/day in males and 0.036 and 0.071 mg/kg/day in females. The data evaluation record was considered adequate. The study was considered a supplement to the long-term feeding in rats discussed above, conducted mainly to determine a NOEL for cholinesterase inhibition. The Committee agreed with the reviewer's evaluation and interpretation of data. The study was considered to be acceptable and the data evaluation record was considered to be adequate. This

study, when considered together with the two-year feeding study in rats (No. 1, above), satisfies data requirement 83-1a of Subpart F of the Pesticide Assessment Guideline for chronic toxicity testing in rats.

3. Shellenberger, T. (1986). One-year oral toxicity study in purebred beagle dogs with AC 92,100. MRID No. 00161572, HED Doc. No. 005910.

Classification: Core-minimum data

Committee's Conclusions and Recommendations:

The chemical was tested in purebred beagle dogs at 0.015, 0.06, 0.09 and 0.12 mg/kg/day. No NOEL was established for plasma cholinesterase inhibition. The NOEL/LOEL for brain and RBC cholinesterase inhibition were considered to be 0.06 and 0.09 mg/kg/day. The Committee agreed with the reviewer's evaluation and interpretation of data. The study was considered to be acceptable and the data evaluation record was considered to be adequate. This study, when considered together with the 6- month and 4-week feeding study in dogs (No. 4 and 5 below), satisfies data requirement 83-1b of Subpart F of the Pesticide Assessment Guideline for chronic toxicity testing in dogs.

4. Morgareidge, K. and Bistner, K. (1973). Six-month feeding study in dogs on AC-92,100. MRID No. 00041139, HED Doc. No. 003144.

Classification: Core-supplementary data

Committee's Conclusions and Recommendations:

The chemical was tested in beagle dogs at 0.0025, 0.01, 0.04 mg/kg/day. The NOEL/LOEL for plasma and RBC cholinesterase inhibition were considered to be 0.0025 and 0.01 mg/kg/day. The study was considered to be of supplementary nature and the data evaluation record was considered to be adequate. This study, by itself, does not satisfy data requirement 83-1b of Subpart F of the Pesticide Assessment Guideline for chronic toxicity testing in dogs.

5. Shellenberger, T. (1984). 28-Day oral toxicity in the dog with AC 92,100. MRID No. 40374701, HED Doc. No. 006525.

Classification: Core-supplementary data

Committee's Conclusions and Recommendations:

This study is a supplement to the chronic feeding study in dogs. The purpose of this special study was to define the plasma cholinesterase NOEL which was not achieved in a previously

submitted one-year study in dogs. The chemical was tested in Beagle dogs at 0.00125, 0.0025, 0.005 and 0.015 mg/kg/day. The NOEL/LOEL for plasma cholinesterase inhibition were considered to be 0.00125 and 0.0025 mg/kg/day. The NOEL for RBC and brain cholinesterase inhibition was considered to be 0.015 mg/kg/day, the highest dose tested. The committee recommended to raise the NOEL for plasma cholinesterase inhibition from 0.00125 to 0.005 mg/kg/day. It should be noted that the least effect level for plasma cholinesterase inhibition in the long-term toxicity study in dogs was 0.015 mg/kg/day, the lowest dose tested. This study was considered to be acceptable for the purpose of establishing a NOEL for plasma cholinesterase inhibition, and the data evaluation record was considered to be adequate.

6. Shellenberger, T. E. (1986). Chronic dietary toxicity and oncogenicity study with AC 92,100 (Terbufos) in mice. MRID No. 40089603, HED Doc. No. 006352.

Classification: Core-minimum data

Committee's Conclusions and Recommendations:

The chemical was tested in CD-1 mice at 3, 6 and 12 ppm (equivalent to 0.45, 0.9 and 1.8 mg/kg/day). The high dose tested in mice was considered adequate based upon body weight gain depression (10.1 and 19.7% in males and females, respectively). The treatment did not alter the spontaneous tumor profile in this strain of mice under the testing conditions. The Committee agreed with the reviewer's evaluation and interpretation of data. The study was considered to be acceptable and the data evaluation record was considered to be adequate. This study satisfies data requirement 83-2b of Subpart F of the Pesticide Assessment Guideline for chronic carcinogenicity testing in mice.

7. Smith, J. M. et al. (1972). A three-generation reproduction study of pesticide AC 92,100 in rats. MRID No. 00085172, HED Doc. No. 010186.

Classification: Core-supplementary data

Committee's Conclusions and Recommendations:

The chemical was tested in Long Evans rats at 0.25 and 1.0 ppm (equivalent to 0.0125, 0.05 mg/kg/day). The high dose tested was considered to be inadequate for reproductive toxicity testing. No toxic effects on adults or offspring were seen at the high dose level. The Committee agreed with the reviewer's evaluation and interpretation of data. The study was considered to be deficient, but the committee felt that a repeat of the study will not be required at this time. The data evaluation record was considered to be adequate. This study is deficient and does not satisfy data requirement 83-4 of Subpart F of the Pesticide Assessment Guideline

for reproductive toxicity testing in rats. However, a new study will not be required at this time.

8. Rodwell, D. E. (1985). A teratology study with AC 92,100 in rats. MRID No. 000147533, HED Doc. No. 006352.

Core Classification: Core-minimum data.

Committee's Conclusions and Recommendations:

The chemical was tested in COBS CD rats at 0.05, 0.10, and 0.2 mg/kg/day. Maternal toxicity NOEL was considered to be 0.2 mg/kg/day, the highest dose tested. Developmental toxicity NOEL/LOEL were considered to be 0.1 and 0.2 mg/kg/day based upon a modest increase in the number of early resorptions (mean number/litter as well as the number of litters with 2 or more fetal resorptions) seen in the high dose groups as compared to the control. Further support for this observation being compound-related is the observation of 100% early resorption rates obtained in the range-finding study in dams administered 0.4 mg/kg/day and the fact that the mean implantation loss in the high dose group is outside the historical control range. The Committee generally agreed with the reviewer's evaluation and interpretation of data. The study was considered to be acceptable and the data evaluation record was considered to be adequate. This study satisfies data requirement 83-3a of Subpart F of the Pesticide Assessment Guideline for developmental toxicity testing in rats.

9. Hoberman, A. M. (1988). A developmental toxicity (embryo-fetal toxicity/teratogenicity) study with AC 92,100 [Terbufos] in rabbits. MRID No. 40886301, HED Doc No. 007039.

Core Classification: Core-minimum data.

Committee's Conclusions and Recommendations:

The chemical was tested in New Zealand white rabbits at 0.05, 0.10, 0.25 and 0.50 mg/kg/day. Maternal toxicity NOEL/LOEL were considered to be 0.1 and 0.25 mg/kg/day based upon apparent decreases, though not statistically significant, in mean body weight gain during the dosing period. Developmental toxicity NOEL/LOEL were considered to be 0.25 and 0.50 mg/kg/day based upon a modest decrease (not statistically significant) in fetal body weight and a larger number of animals with resorptions. The Committee generally agreed with the reviewer's evaluation and interpretation of data. The study was considered to be acceptable and the data evaluation record was considered to be adequate. This study satisfies data requirement 83-3b of Subpart F of the Pesticide Assessment Guideline for developmental toxicity testing in rabbits.

C. Committee's Conclusions and Recommendations

1. Reference Dose

The RfD/Peer Review Committee recommended that an RfD be established based upon a NOEL of 0.005 mg/kg/day for plasma cholinesterase inhibition observed at 0.015 mg/kg/day in a four-week study in dogs. This study was conducted to establish a NOEL for cholinesterase inhibition after a long-term toxicity study in dogs failed to demonstrate a NOEL for changes in this parameter. 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 0.00005 mg/kg/day.** It should be noted that a regulatory value of 0.0002 mg/kg/day was established for this chemical in 1989 by the World Health Organization (WHO).

2. Data Base

The Committee considered the long-term feeding study in rats **(83-1a)** and dogs **(83-1b)**, the carcinogenicity studies in rats and mice **(83-2a and -2b)**, the developmental toxicity studies in rats and rabbits **(83-3a and -3b)** to be acceptable and the data evaluation records to be adequate. Although the reproductive toxicity study in rats **(83-4)** did not conform to the current Guideline for reproductive toxicity testing, was considered adequate for regulatory purposes. A new study will not be requested at this time. The Committee recommended to revise the NOEL/LOEL for plasma cholinesterase in the four-week study in dogs from 0.0015 and 0.0025 mg/kg/day to 0.005 and 0.015 mg/kg/day. It should be noted that the least effect level for plasma cholinesterase inhibition in the long-term toxicity study in dogs was 0.015 mg/kg/day, the lowest dose tested.

3. Carcinogenicity

The high dose tested in the carcinogenicity study in rats was considered to be adequate for carcinogenicity testing in this strain of rats based upon cholinesterase depression. The high dose tested in mice was considered to be adequate for carcinogenicity testing in this strain of mice based upon body weight gain depression (10.1 and 19.7% in males and females, respectively). The treatment did not alter the spontaneous tumor profile in these strains of rats and mice under the testing conditions. On the basis of these two studies, the chemical was classified as a **"Group E"**.

for reproductive toxicity testing in rats. However, a new study will not be required at this time.

8. Rodwell, D. E. (1985). A teratology study with AC 92,100 in rats. MRID No. 000147533, HED Doc. No. 006352.

Core Classification: Core-minimum data.

Committee's Conclusions and Recommendations:

The chemical was tested in COBS CD rats at 0.05, 0.10, and 0.2 mg/kg/day. Maternal toxicity NOEL was considered to be 0.2 mg/kg/day, the highest dose tested. Developmental toxicity NOEL/LOEL were considered to be 0.1 and 0.2 mg/kg/day based upon a modest increase in the number of early resorptions (mean number/litter as well as the number of litters with 2 or more fetal resorptions) seen in the high dose groups as compared to the control. Further support for this observation being compound-related is the observation of 100% early resorption rates obtained in the range-finding study in dams administered 0.4 mg/kg/day and the fact that the mean implantation loss in the high dose group is outside the historical control range. The Committee generally agreed with the reviewer's evaluation and interpretation of data. The study was considered to be acceptable and the data evaluation record was considered to be adequate. This study satisfies data requirement 83-3a of Subpart F of the Pesticide Assessment Guideline for developmental toxicity testing in rats.

9. Hoberman, A. M. (1988). A developmental toxicity (embryo-fetal toxicity/teratogenicity) study with AC 92,100 [Terbufos] in rabbits. MRID No. 40886301, HED Doc No. 007039.

Core Classification: Core-minimum data.

Committee's Conclusions and Recommendations:

The chemical was tested in New Zealand white rabbits at 0.05, 0.10, 0.25 and 0.50 mg/kg/day. Maternal toxicity NOEL/LOEL were considered to be 0.1 and 0.25 mg/kg/day based upon apparent decreases, though not statistically significant, in mean body weight gain during the dosing period. Developmental toxicity NOEL/LOEL were considered to be 0.25 and 0.50 mg/kg/day based upon a modest decrease (not statistically significant) in fetal body weight and a larger number of animals with resorptions. The Committee generally agreed with the reviewer's evaluation and interpretation of data. The study was considered to be acceptable and the data evaluation record was considered to be adequate. This study satisfies data requirement 83-3b of Subpart F of the Pesticide Assessment Guideline for developmental toxicity testing in rabbits.

c. Committee's Conclusions and Recommendations

1. Reference Dose

The RfD/Peer Review Committee recommended that an RfD be established based upon a NOEL of 0.005 mg/kg/day for plasma cholinesterase inhibition observed at 0.015 mg/kg/day in a four-week study in dogs. This study was conducted to establish a NOEL for cholinesterase inhibition after a long-term toxicity study in dogs failed to demonstrate a NOEL for changes in this parameter. 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 0.00005 mg/kg/day.** It should be noted that a regulatory value of 0.0002 mg/kg/day was established for this chemical in 1989 by the World Health Organization (WHO).

2. Data Base

The Committee considered the long-term feeding study in rats **(83-1a)** and dogs **(83-1b)**, the carcinogenicity studies in rats and mice **(83-2a and -2b)**, the developmental toxicity studies in rats and rabbits **(83-3a and -3b)** to be acceptable and the data evaluation records to be adequate. Although the reproductive toxicity study in rats **(83-4)** did not conform to the current Guideline for reproductive toxicity testing, was considered adequate for regulatory purposes. A new study will not be requested at this time. The Committee recommended to revise the NOEL/LOEL for plasma cholinesterase in the four-week study in dogs from 0.0015 and 0.0025 mg/kg/day to 0.005 and 0.015 mg/kg/day. It should be noted that the least effect level for plasma cholinesterase inhibition in the long-term toxicity study in dogs was 0.015 mg/kg/day, the lowest dose tested.

3. Carcinogenicity

The high dose tested in the carcinogenicity study in rats was considered to be adequate for carcinogenicity testing in this strain of rats based upon cholinesterase depression. The high dose tested in mice was considered to be adequate for carcinogenicity testing in this strain of mice based upon body weight gain depression (10.1 and 19.7% in males and females, respectively). The treatment did not alter the spontaneous tumor profile in these strains of rats and mice under the testing conditions. On the basis of these two studies, the chemical was classified as a **"Group E"**.