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

NOV 10 1993

MEMORANDUM

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

SUBJECT: Fonofos : RfD/Peer Review Report

CASRN: 944-22-9
EPA Chem. Code: 041701
Caswell No. 454B

FROM: George Z. Ghali, PhD
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)

Jack Housenger, Chief
Special Review Branch
Re-registration and Special Review Division (H7508W)

The Health Effects Division RfD/Peer Review Committee met on August 12, 1993 to discuss and evaluate the existing toxicology data in support of Fonofos (Dyfonate) 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 0.75 mg/kg/day for neurotoxicity signs and brain cholinesterase inhibition observed at 2.5 and 2.6 mg/kg/day in a subchronic neurotoxicity and chronic toxicity studies in rats. An uncertainty factor (UF) of 100 was recommended to account for the inter-species extrapolation and intra-species variability. **On this basis the RfD was calculated to be 0.0075 mg/kg/day.**

The Committee considered the chronic toxicity/ carcinogenicity study in rats **(83-1a and -2a)**, the carcinogenicity study in mice **(83-2b)**, the developmental toxicity studies in rabbits **(83-3a)** and mice **(83-3b)** to be acceptable and the data evaluation records to be, generally, adequate. The chronic toxicity study in dogs **(83-1b)** and the reproductive toxicity study

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in rats (83-4) were considered inadequate. The neurotoxicity studies were considered inadequate as presented. The Committee was informed that an acute delayed neurotoxicity study has already been requested.

The high dose tested in the carcinogenicity study in rats was considered adequate for carcinogenicity testing based upon cholinesterase depression. The high dose tested in mice was considered adequate based upon cholinesterase depression and some histopathological findings. The treatment did not alter the spontaneous tumor profile in these strains of rats and mice under the test conditions. On the basis of these two studies, the chemical was classified as a **"Group E"**.

CC. James Kariya

A. Individual in Attendance

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

William Burnam*

Reto Engler

Marcia Van Gemert*

Karl Baetcke

Henry Spencer*

William Sette*

Esther Rinde*

Roger Gardner*

James Rowe

John Tice

George Ghali

Rick Whiting

Wang Phang*

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

Pam Hurley

Roger Gardner

3. Others:

Myron Ottley and Stephanie Willett Division as observers

CC: Penny Fenner-Crisp
Richard Schmitt
Kerry Dearfield
Karl Baetcke
Roger Gardner/Pam Hurley
Rick Whiting/RfD Files
James Kariya

* Permanent or rotational members unable to attend.

B. Material Reviewed

Material available for review included 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), acute and subchronic delayed neurotoxicity studies in rats (81-8 and 82-7), a subchronic neurotoxicity study in hens (82-5) and the tox. one-liner. The following are the Committee's conclusions and recommendations:

1. Pavkov, K. L. and Taylor, D. O. N. (1988). Rat chronic toxicity study and oncogenicity study with Dyfonate T11997.

Core Classification: Core-minimum data

Committee's Conclusions and Recommendations:

The chemical was tested in the main study at 4, 15 and 60 ppm (equivalent to 0.17, 0.65 and 2.6 mg/kg/day). Another group was given 120 ppm (equivalent to 6.6 mg/kg/day). The NOEL was considered to be 15 ppm and the LOEL was considered to be 60 ppm based on brain cholinesterase inhibition. The high dose tested was considered adequate for carcinogenicity testing based on cholinesterase inhibition. The Committee agreed with the reviewer's evaluation and interpretation of the data. The study was considered acceptable and the DER was considered adequate. This study satisfies data requirement 83-1a and -2a (or 85-1) of Subpart F of the Pesticide Assessment Guideline for chronic toxicity/carcinogenicity testing in rats. Comments received from some of the developmental/reproductive toxicologists of the Health Effects Division indicated that a developmental/reproductive/neurotoxicity study should be requested.

2. Woodard, M. W. et al. (1969). Dyfonate (N-2790)- Safety evaluation by dietary administration to dogs for 106 weeks. MRID No. 0082233, HED Doc. No. 000631, 008806.

Core Classification: Core-supplementary data

Committee's Conclusions and Recommendations:

The chemical was tested at 16 (8.0), 60 and 240 ppm equivalent to 0.4 (0.2), 1.5 and 6 mg/kg/day). The low dose level of 16 ppm was reduced to 8 ppm after 14 weeks. The NOEL for cholinesterase inhibition considered to be 8 ppm and the LOEL was considered to be 16 ppm. The NOEL for systemic toxicity was considered 16 (8.0) ppm and the LOEL was considered to be 60 ppm. The Committee agreed with the reviewer's evaluation and interpretation of the data. Because of major deficiencies, the study was considered inadequate. This study does not satisfy data requirement 83-1b of Subpart F of

the Pesticide Assessment Guideline for chronic toxicity testing in dogs. A new study will be required.

3. Sprague, G. L. and Zwicker, G. M. (1987). 18-Month dietary oncogenicity study with Dyfonate technical in mice. MRID No. 40150121, HED Doc No. 008784.

Core Classification: Core-Guideline

Committee's Conclusions and Recommendations:

The chemical was tested at 5, 25 and 100 ppm (equivalent to 1, 3 and 12 mg/kg/day in males and 1, 4 and 15 in females). The NOEL was considered to be 5 ppm and the LOEL was considered to be 25 ppm based on cholinesterase inhibition. The high dose tested was considered adequate for carcinogenicity testing based on cholinesterase inhibition and histopathological changes. The Committee agreed with the reviewer's evaluation and interpretation of the data. The study was considered acceptable and the DER was considered adequate. This study satisfies data requirement 83-2b of Subpart F of the Pesticide Assessment Guideline for carcinogenicity testing in mice.

4. Sauerhoff, M. W. (1987). A teratology study in rabbits with Dyfonate technical. MRID No. 40150122, HED Doc No. 008801.

Core Classification: Core minimum data

Committee's Conclusions and Recommendations:

The chemical was tested at 0.2, 0.5 and 1.5 mg/kg/day. The NOEL for maternal and developmental toxicity was considered to be 1.5 mg/kg/day, the highest dose tested. The Committee agreed with the reviewer's evaluation and interpretation of the data. The study was considered acceptable and the DER was considered adequate. This study satisfies data requirement 83-3a of Subpart F of the Pesticide Assessment Guideline for developmental toxicity testing in rabbits.

5. Minor, J. L. and Downs, J. R. (1982). A teratology study in CD-1 mice with Dyfonate technical. MRID No. 00118423, HED Doc No. 002998, 004302.

Core Classification: Core minimum data

Committee's Conclusions and Recommendations:

The chemical was tested at 2, 4, 6 and 8 mg/kg/day. The NOEL for fetotoxicity was set at 4 mg/kg/day, the NOEL for maternal toxicity was set at 6 mg/kg/day and the NOEL for developmental toxicity was considered to be > 8 mg/kg/day, the highest dose tested. The Committee generally agreed with the reviewer's evaluation and

interpretation of the data. However, the Committee recommended to revise the NOEL/LOEL for developmental toxicity to 2/4 mg/kg/day based upon 1) the increased litter and fetal incidence of slight 4th ventricle dilation (4 litters, 7 fetuses in the high dose group vs 0 litters and fetuses in the control), 2) the closeness of dose spacing. The biological significance of this findings is uncertain and may be due to the test substance or to the method of examination of the fetuses. However, it can not be ruled out as a possible real effect because the test substance is a potent cholinesterase inhibitor with the brain as a potential target organ. The Committee emphasized that this study should not be used for an acute dietary risk assessment. The study was considered acceptable and the DER was considered adequate. This study satisfies data requirement 83-3b of Subpart F of the Pesticide Assessment Guideline for developmental toxicity testing in rodents.

6. Woodard, G. et al. (1969). Dyfonate (N-2790) three-generation study in rats. MRID No. 00082234, HED Doc No. 0000000.

Core Classification: Core supplementary data

Committee's Conclusions and Recommendations:

The chemical was tested at 10.0 and 31.6 mg/kg/day. Deficiencies in the study prevent adequate assessment of parental toxicity or reproductive effects. Therefore, an accurate NOEL cannot be established. The tox-one liner should reflect this recommendation by indicating that the data are insufficient to estimate a NOEL for this study. The Committee agreed with the reviewer's evaluation and interpretation of the data. The study was considered inadequate. This study does not satisfy data requirement 83-4 of Subpart F of the Pesticide Assessment Guideline for reproductive toxicity testing in rats.

7. Horner, J. M. (1993). Fonofos: acute neurotoxicity study in rats. MRID No. 42777801, HED Doc. No. 000000.

Core Classification: Core supplementary data

8. Horner, J. M. (1993). Fonofos: subchronic neurotoxicity study in rats. MRID No. 42792601, HED Doc. No. 000000.

Core Classification: Core supplementary data

9. Miller, J. L. (1978). Neurotoxicity of 90-day oral administration of technical Dyfonate to adult hens. MRID No. 40150120, HED Doc. No. 009430.

Core classification: Core supplementary data.

Committee's Conclusions and Recommendations:

The Committee addressed the above three neurotoxicity studies together and agreed with the reviewer's evaluation and interpretation of the data. The Committee considered the NOEL for brain cholinesterase inhibition in the rat subchronic neurotoxicity to be 0.75 mg/kg/day and the LOEL to be 2.5 mg/kg/day. Because of some deficiencies in these studies, a final conclusions could not be made. The three studies, as presented, were considered inconclusive assessment of the neurotoxicity potential of this chemical. However, it was pointed out that once the additional information are submitted, the classification of these studies might be elevated or, at least, the studies might be adequate for risk assessment purposes. The Committee was informed that an acute delayed neurotoxicity study has already been requested. <u>These studies, as presented, do not satisfy data requirements 81-8 for acute delayed neurotoxicity or 82-5 and -7 for subchronic neurotoxicity testing, required under Subpart F of the Pesticide Assessment Guideline</u>.

C. Conclusions and Recommendations

1. Reference Dose

The RfD/Peer Review Committee recommended that an RfD be established based upon a NOEL of 0.75 mg/kg/day for neurotoxicity signs and brain cholinesterase inhibition observed at 2.5 and 2.8 mg/kg/day in a subchronic neurotoxicity and chronic toxicity studies in rats. An uncertainty factor (UF) of 100 was recommended to account for the inter-species extrapolation and intra-species variability. **On this basis the RfD was calculated to be 0.0075 mg/kg/day.**

2. Data Base

The Committee considered the chronic toxicity/carcinogenicity study in rats **(83-1a and -2a)**, the carcinogenicity study in mice (83-2b), the developmental toxicity studies in rabbits (83-3a) and mice (83-3b) to be acceptable and the data evaluation records to be, generally, adequate. The chronic toxicity study in dogs (83-1b) and the reproductive toxicity study in rats (83-4) were considered inadequate. The neurotoxicity studies were considered inadequate as presented. The Committee was informed that an acute delayed neurotoxicity study has been requested.

3. Carcinogenicity

The high dose tested in the carcinogenicity study in rats was considered adequate for carcinogenicity testing based upon cholinesterase depression. The high dose tested in mice was considered adequate based upon cholinesterase depression and some histopathological findings. The treatment did not alter the spontaneous tumor profile in these strains of rats and mice under the test conditions. On the basis of these two studies, the chemical was classified as a **"Group E"**.