11441

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

MAR 9 1995

MEMORANDUM

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

SUBJECT: RfD/Peer Review Report of Fortress [O,O-diethyl O-(1,2,2,2-tetrachloroethyl) phosphorothioate]

CASRN. 54593-83-8
EPA Chem. Code: 129006
Caswell No. 663P

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

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

Reto Engler, Ph.D.
Co-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 November 3, 1994 to discuss and evaluate toxicology data submitted in support of Fortress (Chloroethoxyfos) registration and to assess the Reference Dose (RfD) for this chemical.

Material available for review consisted of data evaluation records (DERs) 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), multi-generation and one-generation reproductive toxicity studies in rats (83-4), two subchronic toxicity studies (3-month) and a subacute toxicity study (6-week) in rats (82-1a), two subchronic toxicity studies (82-1b, 3-month, and 6-month) in dogs, a subchronic (3-month) toxicity study and two subacute toxicity studies (6-week) in mice (82-1a) and acute (81-8ss) and subchronic (82-7ss) neurotoxicity studies in rats.

A. Chronic and Subchronic Toxicity:

The Committee considered the chronic toxicity study in rats (83-1a, MRID No. 41736837, HED Doc. No. 011373 supported by MRIDs 41290627 and 42559215, HED Doc. Nos. 008330 and 011373) to be acceptable and the data evaluation records to be adequate. The Committee considered the subchronic (3-month) study in rats (MRID 425592-15) (82-1a) (HED Doc. No. 011373) to be acceptable for the purposes for which it was intended when used together with another 3-month rat study (MRID No. 41290627, HED Doc. No. 008330) and a six-week rat study (MRID No. 41290632, HED Doc. No. 008330). These three studies in combination fulfill the requirement for a subchronic oral toxicity study in rodents and the data taken together meet the criteria for classification as Core-Minimum. The data evaluation records (HED Doc. No. 000000; 008330) were considered to be adequate as presented. When all the rat feeding studies were considered together, an overall no-observable effect level (NOEL) based on cholinesterase inhibition in females was estimated to be 1 ppm (0.132 mg/kg/day, see MRID No. 41290632 for dose conversion).

The Committee considered the chronic toxicity study in dogs (83-1b, MRID No. 41736833) to be acceptable and the data evaluation record (HED Doc. No. 011373) to be adequate. The Committee considered the subchronic toxicity study (3-month) in dogs (82-1b, MRID No. 40898703, 40898704) to be acceptable and the data evaluation record (HED Doc. No. 007112) to be adequate. The other subchronic toxicity study (6-month) in dogs (MRID, No. 42559221) was conducted to address the visual system toxicity potential of this chemical and to define the no-observable effect level for plasma and erythrocyte cholinesterase inhibition following acute administration of the test material. The study was considered to be acceptable for the purposes for which it was intended and the data evaluation record (HED Doc. No. 011373) was considered to be adequate. When all the dog feeding studies were considered together, an overall NOEL based on cholinesterase inhibition was estimated to be 2 ppm (0.061 mg/kg/day for males and 0.062 mg/kg/day for females) established in the 6-month and one-year feeding studies and supported by the 90-day study feeding study in dogs. At this level (2 ppm), plasma cholinesterase was inhibited 12 to 21% in both males and females (statistically significant inhibition of 21% at week 6 in females) in the six month study. The inhibition at 2 ppm was consistent at measurement timepoints from day 6 on and was part of a dose-related decreasing trend at these timepoints in both sexes. The 2 ppm level was, therefore, considered to be a threshold NOEL for this species and the decreases in plasma cholinesterase activity observed at or around this level were not attributed solely to normal data variability. In the 90 day feeding study, plasma and brain cholinesterase inhibition in females and plasma cholinesterase inhibition in males were observed at 5 ppm. The Committee generally agreed with the reviewer's evaluation and interpretation of the data and

2

recommended no revisions to the data evaluation records.

The Committee considered the subchronic (3-month) and two subacute (6-week) toxicity studies in mice (83-2a, MRID No. 41290629; 41290632; 41290630) to be Supplemental but acceptable in providing support for dose selection in the mouse 18-month carcinogenicity study. The data evaluation records (HED Doc. No. 008330;) were considered to be adequate as presented.

B. Carcinogenicity:

The Committee considered the carcinogenicity phase of the chronic toxicity/carcinogenicity study in rats (83-2a, MRID No. 41736837, 41290627, 42559215) and the carcinogenicity study in mice (83-2b, MRID No. 41736834, 41736835) to be acceptable and the data evaluation records (HED Doc. No. 011373), except for the need to include additional tumor tables, to be adequate.

The Committee considered the dose levels tested in the mouse study to be adequate. Dietary levels of Fortress technical for this study were selected based on the results of a 90-day range-finding study and two six week studies. In the mouse carcinogenicity study, increased mortality and clinical signs were observed in both sexes and decreased body weight gain was observed in males only. On this basis, the committee concluded that the high dose level tested was adequate for carcinogenicity testing in this strain of mouse. The Committee, generally, agreed with the reviewer's evaluation and interpretation of the data and recommended no revisions to the data evaluation records. The Committee concluded that the treatment did not alter the spontaneous tumor profile in this strain of mouse under the testing conditions.

The Committee considered the dose levels tested in the rat carcinogenicity study to be adequate for carcinogenicity testing. Dietary levels of Fortress technical used in this study were selected based on the results of two 90-day subchronic toxicity studies (MRID 412906-27, MRID 425592-15) in which decreased plasma and/or erythrocyte cholinesterase activity, clinical signs of toxicity (including tremors, weakness, colored discharge from the eyes and nose) and transiently decreased body weights were observed in males and females. Increased mortality was also observed in one or both [redacted] at doses of 10 ppm and above.

A question was raised regarding the incidence of lymphocytic leukemia in the high dose (8 ppm) females in the combined chronic toxicity/carcinogenicity study in rats. Specifically the Committee wanted to know whether this neoplasm, which was found in numerous organs, occurred in multiple sites in a single animal or in a single or multiple site(s) in multiple animals. The Committee recommended that summary tables for the most frequently observed tumors in males be submitted to the Committee and also appended to

3

the data evaluation record of the study. In this meeting, the Committee concluded that a final decision regarding the carcinogenic potential of this chemical in rats could not be made until the requested information was made available to the Committee.

Subsequently, reevaluation of the individual animal pathology data showed one high dose female (animal No. 423577) with lymphocytic leukemia in numerous organs, which matched up with the incidences at different organ sites noted in the histopathology summary table. This type of neoplasm (lymphocytic leukemia), under this circumstances, was considered to be of no biological significance since it was found (in multiple sites) in a single animal. It should be noted also that lymphocytic leukemia was not found in any group of females at interim sacrifice.

However, in the course of reevaluation of the rat study, it was noted by the respective toxicology branch that kidney tumors appeared to be slightly increased in males of the high dose level group. This increase in kidney tumors was not statistically significant at $p = 0.05$ by the statistical methods used by the study authors. Consequently, the respective branch determined that a weight of the evidence evaluation by the Health Effects Division-Carcinogenicity Peer Review Committee (CPRC) might be required. The registrant was informed and provided additional information and a formal response to the issue.

On February 2, 1995, a group consisting of Mr. William Burnam and Drs. Esther Rinde and Kerry Dearfield (SAB) and Drs. Karl Baetcke and Karen Hamernik (Toxicology Branch I), met to discuss the advisability of taking the issue to the CPRC. The conclusion of the group was that further testing would not be useful and that the available 2 year study in the rat was adequate for carcinogenicity testing. In addition, the group determined that the data did not warrant further consideration by the CPRC. The group recommended that the test material be classified as a "Group D", not classifiable as to human carcinogenicity, because of the inadequacy of evidence. The nature of the effect in the male rat kidney, made it difficult to clearly interprete the data as showing either the presence or absence of a carcinogenic effect.

C. Reproductive and Developmental Toxicity:

The Committee considered the 2-Generation reproductive toxicity study in rats (83-4, MRID No. 41736836, HED Doc. No. 011373), the developmental toxicity studies in rats (83-3a, MRID No. 40898705, HED Doc. No. 007112) and rabbits (83-3b, MRID No. 41290633 & 425592-19, HED. Doc. No. 008330 & 011373) to be acceptable and the data evaluation records for these studies to be adequate. The Committee, generally, agreed with the reviewer's evaluation and interpretation of the data and recommended no revisions to the data evaluation records.

The one-generation reproductive toxicity study in rats (MRID No. 41290627, HED Doc. No. 008330) should be regarded as a range finding study and, therefore, should not be considered a reliable assessment of the reproductive toxicity potential of this chemical or used for risk assessment purposes.

The Committee concluded that there was no evidence, based on the available data, to suggest that Fortress was associated with major developmental or reproductive toxicity under the testing conditions. The need for a developmental neurotoxicity study should be determined following review of neuropathology data in acute and/or subchronic neurotoxicity studies.

D. Neurotoxicity:

The Committee concurred with the scientific reviewer that the classification of the acute neurotoxicity (81-8ss, MRID No. 42559210) and subchronic neurotoxicity (82-7ss, MRID No.42559217) (HED Doc. No. 011373) studies in rats should remain as Core-supplementary data. The issue of additional neurotoxicity data was subsequently discussed by an Ad Hoc group and was deferred to the respective branch for a decision.

E. Reference Dose (RfD):

The Committee recommended that an RfD for this chemical be established based upon the combined subchronic and chronic toxicity studies in dogs with an overall NOEL of 2 ppm (0.061 mg/kg/day for males and 0.062 mg/kg/day for females) based on cholinesterase inhibition. At this level (2 ppm), plasma cholinesterase was inhibited 12 to 21% in both males and females in the six month study. The 2 ppm level was, therefore, considered to be a threshold NOEL. In the 90 day feeding study, plasma and brain cholinesterase inhibition in females and plasma cholinesterase inhibition in males were observed at 5 ppm. An uncertainty factor (UF) of 100 was applied to account for inter-species extrapolation and intra-species variability. On this basis, the RfD was calculated to be 0.0006 mg/kg/day.

It should be noted that this chemical has not been reviewed by the FAO/WHO joint committee meeting on pesticide residue (JMPR) and an acceptable daily intake (ADI) was not established.

5

F. Individuals in Attendance

Peer Review Committee members and associates present were Reto Engler (Senior Science Advisor, HED, Co-chairman, RfD/Peer Review Committee), George Ghali (Manager, RfD/Peer Review Committee), Karl Baetcke (Chief, TB I), Marcia Van Gemert (Chief, TB II), Rick Whiting, Henry Spencer, Esther Rinde, William Sette, Susan Makris and Myron Ottley.

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

Karen Hamernik

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

Karl Baetcke

CC: Richard Schmitt
Stephanie Irene
Karl Baetcke
Karen Hamernik
Debra Edwards
Beth Doyle
Kerry Dearfield
RfD File
Caswell File

G. Material Reviewed:

1. Malley, L. A. (1990). Combined chronic toxicity/ oncogenicity with IN 43898 - Two-year feeding study in rats. MRID No. 41736837, HED Doc. No. 011373, supported by MRID 41290627, HED Doc. No. 008330 & MRID 42559215, HED Doc. No. 011373). Classification: Guideline data. This study satisfies data requirement 83-5 or 83-1a and 83-2a of Subpart F of the Pesticide Assessment Guideline for chronic toxicity/ carcinogenicity testing in rats.

2. Malley, L. A. (1990). Oncogenicity study with IN 43898 - eighteen-month feeding study in mice. MRID No. 41736834, 41736835, HED Doc. No. 011373. 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. Malley, L. A. (1989). Chronic toxicity study with IN43898 - one-year feeding study in dogs. MRID No. 41736833, HED Doc. No. 011373. Classification: Guideline data. This study satisfies data requirement 83-1b of Subpart F of the Pesticide Assessment Guideline for chronic toxicity testing in dogs.

4. Malley, L. A. (1990). Reproductive and fertility effects with IN 43898 - multigeneration reproduction study in rats. MRID No. 41736836, HED Doc. No. 011373. Classification: Guideline data. This study satisfies data requirement 83-4 of Subpart F of the Pesticide Assessment Guideline for reproductive toxicity testing in rats.

5. Alvarez, L. (1988). Teratogenicity study of IN 43898 (Fortress Technical) in rats. MRID No. 40898705, HED Doc. No. 007112. 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. Alvarez, L. (1992). Teratogenicity Study in rabbits IN 43898-Fortress Technical. MRID No. 41290633 & 425592-19, HED Doc. Nos. 008330, 011373. 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. Malley, L. A. (1988). Subchronic oral toxicity: 90-day study with IN 43898. 90-day feeding and one-generation reproduction study in rats. MRID No. 41290627, HED Doc. Nos. 008330. Classification: Core-supplementary data. This study does not satisfy data requirement 82-1a or 83-4 of Subpart F of the Pesticide Assessment Guideline for subchronic toxicity or reproductive toxicity testing in rats.

8. Malley, L. A. (1992). Subchronic oral toxicity: 90-day study with IN 43898 - determination of effects on plasma, red blood cell and brain cholinesterase. MRID No. 42559215, HED Doc. Nos. 011373. Classification: Acceptable data. (This is a special study). This special study is acceptable for the purposes for which it was intended. When used in combination with another 90-day rat feeding study (MRID No. 41290627) and a 6-week rat feeding study (MRID No. 41290632), together satisfy data requirement 82-1a of Subpart F of the Pesticide Assessment Guideline for subchronic toxicity testing in rats and, taken together, the data are considered to be Core Minimum.

9. Malley, L. A. (1989). Determination of cholinesterase activity in rats and mice fed DPX-43898 for six weeks. MRID No. 41290632, HED Doc. No. 008330. Classification: Core-supplementary data. This study was performed to aid in dose-setting for a longer term study and not to fulfill specific data requirement under Subpart F of the Pesticide Assessment Guideline.

10. Malley, L. A. (1988). Subchronic oral toxicity: 90-day study with IN 43898 feeding study in dogs. MRID No. 40898703, 40898704, HED Doc. No. 007112. Classification: Core-minimum data. This study satisfies data requirement 82-1b of Subpart F of the Pesticide Assessment Guideline for subchronic toxicity testing in dogs.

11. Atkinson, J. E. et al. (1992). Subchronic oral toxicity: Six-month ocular study with DPX-43898 (Fortress Technical) feeding study in dogs. MRID No. 42559221, HED Doc. No. 011373. Classification: Acceptable data. This study is acceptable for the purposes for which it was intended. The study was performed to evaluate ocular toxicity and determine the NOELs for plasma and erythrocyte cholinesterase inhibition in the dog. There is currently no guideline number for this type of study.

12. Malley, L. A. (1988). Subchronic oral toxicity: 90-day study with IN 43898 feeding study in mice. MRID No.41290629, HED doc. No. 008330. Classification: Core-supplementary data. This study does not satisfy data requirement 82-1a of Subpart F of the Pesticide Assessment Guideline for subchronic toxicity testing in rodents.

13. Malley, L. A. (1989). Subchronic oral toxicity: Six-week study with IN 43898 feeding study in mice. MRID No.41290630, HED doc. No. 008330. Classification: Core-supplementary data. This study was performed to aid in dose-setting for a longer term study and not to fulfill a specific data requirement under Subpart F of the Pesticide Assessment Guideline.

14. Lochry, E. A. (1992). Subchronic neurotoxicity: 90-day study of DPX 43898 feeding study in rats. MRID No. 42559217, HED Doc. No. 011373. Classification: Core-supplementary data. This study does not satisfy data requirement 82-7ss of Subpart F of the Pesticide Assessment Guideline for subchronic neurotoxicity testing in rodents.

15. Lochry, E. A. (1991). Acute neurotoxicity study of DPX 43898 in rats. MRID No. 42559210, HED Doc. No. 011373. Classification: Core-supplementary data. This study does not satisfy data requirement 81-8ss of Subpart F of the Pesticide Assessment Guideline for acute neurotoxicity testing in mammals.