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

JAN 26 1994

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: RfD/Peer Review Report of Ethion

CASRN. 563-12-2
EPA Chem. Code: 058401
Caswell No. 427

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

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

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

The Health Effects Division RfD/Peer Review Committee met on October 14, 1993 to evaluate the existing toxicology data in support of Ethion re-registration and to re-reassess the Reference Dose (RfD) for this chemical.

The RfD for this chemical was first assessed by the Health Effects Division RfD Committee on August 15, 1986 and again reassessed on April 19, 1989. The RfD was verified by the Agency RfD Work Group on September 16, 1986 and again on May 17, 1989. The RfD was based on a no-observable effect level (NOEL) of 0.05 mg/kg/day for depression of plasma cholinesterase activity observed at 0.075 mg/kg/day in a 21-day study in human volunteers. An Uncertainty Factor (UF) of 100 was used to account for the intra-species variability. On this basis, the RfD was calculated to be 0.0005 mg/kg/day.

In the meeting of October 14, 1993 the RfD Peer Review Committee was informed that a new two-year feeding study in dogs was under review. The Committee determined that the RfD should remain unchanged unless the new dog study provides a significantly lower NOEL than the NOEL established in the human study. The Committee, however, recommended that if the human study is used to establish the RfD, the UF should be reduced from 100 to 10. On this

basis, the RfD would be 0.005 mg/kg/day. It should be noted that a regulatory value of 0.002 mg/kg/day had been established for this chemical by the World Health Organization (WHO) in 1990.

The Committee considered the chronic toxicity/carcinogenicity study (83-1a and 83-2a) in rats to be acceptable. The NOEL/LOEL in the chronic toxicity phase of the study were supported by the findings of a subchronic toxicity study in rats. The high dose tested was considered adequate for carcinogenicity testing. The dose levels selected for the carcinogenicity testing in the rat were based upon the findings of the subchronic testing. The treatment did not alter the spontaneous tumor profile in this strain of rats under the testing conditions. The Committee questioned the adequacy of the dose levels tested in the mouse carcinogenicity study (83-2b). Unlike the rat study, there was no range finding study to support the dose selection for the mouse carcinogenicity study. It was the Committee's opinion that the high dose level tested, although not high enough to cause systemic effects, approached an appropriate level for carcinogenicity testing when all the evidence was considered. It was the judgement of members of the Committee present that further testing was not necessary and would add little to the toxicological profile of this chemical. This conclusion was based on the following: 1) Plasma cholinesterase activity was significantly inhibited in both males and females of the high dose in this study, the pattern of cholinesterase inhibition for this chemical indicates that RBC and brain cholinesterases are inhibited at levels slightly higher than those affect plasma cholinesterase, 2) Plasma cholinesterase is the same end-point used to set the RfD for this chemical, 3) Ethion is not structurally related to any known carcinogen, 4) Ethion is not mutagenic, and 5) retesting of such a highly acutely toxic organophosphate is difficult since early death often precludes testing at doses which result in body weight gain or organ weight decreases. The study was considered to be acceptable and the data evaluation record was considered to be adequate. The treatment did not alter the spontaneous tumor profile in this strain of mice under the testing conditions. The Committee, therefore, agreed to classify the chemical as a "Group E" carcinogen on the basis of these two studies.

The Committee considered the chronic toxicity study in dogs (83-1b) to be inadequate, however, the Committee was informed that another study was recently submitted to the Agency.

Although the Committee down-graded the reproductive toxicity study (83-4) from Core-minimum to Core-supplementary data, the study was considered to be adequate for regulatory purposes, and a new study would not be needed at this time. The developmental toxicity study in rats (83-3a) and rabbits (83-3b) were considered acceptable as Core-minimum. The Committee recommended revision of the maternal and developmental toxicity NOEL and questioned the significance of the developmental toxicity reported in the data

evaluation record of the rabbit study. There was no evidence, based on the available data, to suggest that the chemical was associated with significant reproductive or developmental toxicity under the testing conditions.

A. Individual in Attendance

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

Marcia Van Gemert

Karl Baetcke

Henry Spencer

William Sette

James Rowe

John Tice

David Anderson

Steven Dapson

George Ghali

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

Reto Engler

William Burnam

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

Whang Phang

3. Others

S. Makris, F. Chow and N. B. Thoa D. McCall as observers

CC: Penny Fenner-Crisp
Richard Schmitt
Kerry Dearfield
Marcia Van Gemert
Whang Phang
Rick Whiting
James Kariya

B. Material Reviewed:

Material available for review by the Committee included data evaluation records for a chronic toxicity/carcinogenicity study in rats (83-1a), 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) and a reproductive toxicity study in rats (83-4) and the tox-one liner. The Committee focused the discussion on the following studies:

1. Morrow, L. and Mayhew, D. (1985). Twenty-four month combined oral toxicity and oncogenicity study in rats utilizing ethion (FMC 1240) technical. MRID No. 00148991, HED Doc. 005215, 007033.

Core Classification: Core-minimum data.

Committee's Conclusions and recommendations:

The chemical was tested in Sprague-Dawley rats at 2, 4 and 40 ppm. The NOEL/LOEL were considered to be 4 and 40 ppm for depression of serum cholinesterase activity in both sexes. The Committee agreed with the reviewer's evaluation and interpretation of data. The treatment did not alter the spontaneous tumor profile in this strain of rats under the testing conditions. The study was considered acceptable and the data evaluation record was considered adequate. This study satisfies data requirement 83-1a and 83-1b of Subpart F of the Pesticide Assessment Guideline for chronic toxicity/carcinogenicity testing in rats.

2. Morrow, L. D. (1985). Lifespan oncogenicity study in mice utilizing ethion technical. MRID No. 00148989, HED Doc. No. 007033.

Core Classification: Core-minimum data

Committee's Conclusions and Recommendations:

The chemical was tested in Charles River CF1 Albino mice at 0.75, 1.5 and 8 ppm. Plasma cholinesterase inhibition was observed in males and females at 8 ppm. No other signs of toxicity were observed. The Committee questioned the adequacy of the dose levels tested in the mouse carcinogenicity study (83-2b). Unlike the rat study, there was no range finding study to support the dose selection for the mouse carcinogenicity study. It was the Committee's opinion that the high dose level tested, although not high enough to cause systemic effects, approached an appropriate level for carcinogenicity testing when all the evidence was considered . It was the judgement of members of the Committee present that further testing was not necessary and would add little to the toxicological profile of this chemical. This conclusion was based on the following: 1) Plasma cholinesterase activity was significantly inhibited in both males and females of the high dose in this study, the pattern of cholinesterase inhibition for this

chemical indicates that RBC and brain cholinesterases are inhibited at levels slightly higher than those affect plasma cholinesterase, 2) Plasma cholinesterase is the same end-point used to set the RfD for this chemical, 3) Ethion is not structurally related to any known carcinogen, 4) Ethion is not mutagenic, and 5) retesting of such a highly acutely toxic organophosphate is difficult since early death often precludes testing at doses which result in body weight gain or organ weight decreases. The treatment did not appear alter the spontaneous tumor profile in this strain of mice under the testing conditions. 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 carcinogenicity testing in mice, provide that a plausible explanation for the dose selection is made available.

3. Hartke, K. (1972). Two-year chronic oral toxicity with ethion technical in Beagle dogs. MRID No. 00141845, HED Doc. No. 007033.

Core Classification: Core-supplementary data

Committee's Conclusions and Recommendations:

The study was considered inadequate to satisfy data requirement 83-1b of Subpart F of the Pesticide Assessment Guideline for chronic toxicity testing in dogs. The Committee was informed that a new dog study was recently submitted to the Agency.

4. Hoberman, A. et al. (1983). Teratogenic potential of ethion in pregnant Crl:COBS CD BR Charles River rats. MRID No. 00131852, HED Doc. No. 003369, 007033.

Core Classification: Core minimum data.

Committee's Conclusions and Recommendations:

The chemical was tested in rats at 0.2, 0.6 and 2.5 mg/kg/day. The NOEl/LOEL for maternal toxicity were considered to be 0.6 and 2.5 mg/kg/day based upon increased incidence of hyperactivity. The NOEL/LOEL for developmental toxicity were considered to be 0.6 and 2.5 mg/kg/day based upon increased incidence of delayed ossification of pubes. The Committee generally agreed with the reviewer's evaluation and interpretation of data. However, the Committee considered the delayed ossification of pubes to be a highly variable parameter and should not be used for acute risk assessment. This study satisfies data requirement 83-3a of Subpart F of the Pesticide Assessment Guideline for developmental toxicity testing in rats.

5. Hoberman, A. et al. (1983). Teratogenic potential of ethion technical administered orally via stomach tube to New Zealand white rabbits. MRID No. 00131853, HED Doc. No. 003369, 007033.

Core Classification: Core minimum data.

Committee's Conclusions and Recommendations:

The chemical was tested in New Zealand white rabbits at 0.6, 2.4 and 9.6 mg/kg/day. The NOEl/LOEL for maternal toxicity were considered to be 0.6 and 2.4 mg/kg/day based upon reduced maternal body weight gain and changes in urine color (orange color). The NOEL/LOEL for developmental toxicity were considered to be 2.4 and 9.6 mg/kg/day based upon increased incidence of fused sternebrae. The Committee disagreed with the NOEL's as established in the data evaluation record of this study. The Committee considered the NOEL for developmental toxicity to be 9.6 mg/kg/day, the highest dose tested since the incidence of fused sternebrae were not significant on litter basis. The Committee revised the maternal NOEL/LOEL to 2.4 and 9.6 mg/kg/day based upon reduced body weight gain and food consumption. This study satisfies data requirement 83-3a of Subpart F of the Pesticide Assessment Guideline for developmental toxicity testing in rabbits.

6. Salmon, C. M. and Enloe,. P. V. (1985). Three generation reproduction study in albino rats with ethion technical. MRID No. 00148990, HED Doc. NO. 005215, 007033.

Core Classification: Core minimum data.

Committee's Conclusions and Recommendations:

The chemical was tested in New albino rats at 2, 4 and 25 ppm. The reproductive NOEL was considered to be 25 ppm. The systemic NOEL was considered to be 25 ppm in males and 4 ppm in females, based on plasma cholinesterase inhibition. The Committee agreed with the reviewer's evaluation and interpretation of data. The Study should remain as supplementary, but no new study will be required at this time. This study does not conform with the data requirement 83-4 of Subpart F of the Pesticide Assessment Guideline for reproductive toxicity testing in rats. However, despite the study deficiencies, the results may be adequate for regulatory purposes.

C. Conclusions and Recommendations

1. Reference Dose

The RfD for this chemical was first assessed by the Health Effects Division RfD Committee on August 15, 1986 and again reassessed on April 19, 1989. The RfD was verified by the Agency RfD Work Group on September 16, 1986 and again on May 17, 1989. The RfD was based on a no-observable effect level (NOEL) of 0.05 mg/kg/day for depression of plasma cholinesterase activity observed at 0.075 mg/kg/day in a 21-day study in human volunteers. An Uncertainty Factor (UF) of 100 was used to account for the intra-species variability. On this basis, the RfD was calculated to be 0.0005 mg/kg/day.

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2. Data Base

The Committee considered the chronic toxicity study in dogs (83-1b) to be inadequate, however, the Committee was informed that another study was recently submitted to the Agency.

The Committee considered the chronic toxicity/carcinogenicity study (83-1a and 83-2a) in rats to be acceptable. The NOEL/LOEL in the chronic toxicity phase of the study were supported by the findings of a subchronic toxicity study in rats. The high dose tested was considered adequate for carcinogenicity testing. The dose levels selected for the carcinogenicity testing in the rat were based upon the findings of the subchronic testing. The Committee questioned the adequacy of the dose levels tested in the mouse carcinogenicity study (83-2b). Unlike the rat study, there was no range finding study to support the dose selection for the mouse carcinogenicity study. It was the Committee's opinion that the high dose level tested, although not high enough to cause systemic effects, approached an appropriate level for carcinogenicity testing when all the evidence was considered. It was the judgement of members of the Committee present that further testing was not necessary and would add little to the toxicological profile of this chemical. This conclusion was based on the following: 1) Plasma cholinesterase activity was significantly inhibited in both males and females of the high dose in this study, the pattern of cholinesterase inhibition for this chemical

indicates that RBC and brain cholinesterases are inhibited at levels slightly higher than those affect plasma cholinesterase, 2) Plasma cholinesterase is the same end-point used to set the RfD for this chemical, 3) Ethion is not structurally related to any known carcinogen, 4) Ethion is not mutagenic, and 5) retesting of such a highly acutely toxic organophosphate is difficult since early death often precludes testing at doses which result in body weight gain or organ weight decreases. The treatment did not alter the spontaneous tumor profile in this strain of mice under the testing conditions.

3. Carcinogenicity

In view of the above, the Committee agreed to classify the chemical as a "Group E" carcinogen.

4. Developmental and Reproductive toxicity

The developmental toxicity study in rats (83-3a) and rabbits (83-3b) were considered acceptable as Core-minimum. The Committee recommended revision of the maternal and developmental toxicity NOEL and questioned the significance of the developmental toxicity reported in the data evaluation record of the rabbit study.

Although the Committee down-graded the reproductive toxicity study (83-4) from Core-minimum to Core-supplementary data, the study was considered to be adequate for regulatory purposes, and a new study would not be needed at this time.

There was no evidence, based on the available data, to suggest that the chemical was associated with significant reproductive or developmental toxicity under the testing conditions.