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

JAN 17 1996

MEMORANDUM

SUBJECT: THIRD RfD/Peer Review Report of Ethion [O,O,O',O'-tetraethyl-S,S'-methylene bis phosphorodithoate]: Reassessment of the Reference Dose.

CASRN. 563-12-2
EPA Chem. Code: 058401
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THRU: William Burnam
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TO: Robert Forrest, PM 14
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and

Chief, Reregistration Branch
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The Health Effects Division-RfD/Peer Review Committee met on August 31, 1995 to address issues raised by FMC regarding the basis used in the assessment of the Reference Dose (RfD) and margin of exposure (MOE) determined by the Agency.

A. Background:

The health effects Division RfD/Committee met on October 14, 1993 and again on May 19, 1994 to evaluate the toxicology data available in support of Ethion reregistration and to reassess the Reference Dose for this chemical.

The RfD for Ethion was originally established by the Health Effects Division/RfD Peer Review 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 21-day human study with a no-observable effect level (NOEL) of 0.05 mg/kg/day. Depression of plasma cholinesterase activity was observed at 0.075 mg/kg/day, the next higher dose level. An uncertainty factor (UF) of 100 was applied to account for intraspecies variability and lack of chronic toxicity data in a non-rodent species. On this basis, the RfD was calculated to be 0.0005 mg/kg/day.

Subsequently, the Committee reconvened on October 14, 1993 and again on May 19, 1994 to reassess the RfD for ethion for reregistration purposes and in light of additional information submitted to the Agency. The Committee recommended that the RfD for Ethion remain unchanged, as previously established/verified by the Agency Work Group. The RfD was based on a 21-day human study with a no-observable effect level (NOEL) of 0.05 mg/kg/day. An Uncertainty Factor (UF) of 10 would have been appropriate in this case to be used to account for intraspecies variability. However, since the NOEL/LOEL for plasma cholinesterase depression were comparable in both man and dogs, and since brain cholinesterase inhibition was observed in dogs at dose levels comparable to those causing inhibition of plasma cholinesterase, the Committee felt that brain cholinesterase inhibition in man could also occur at relatively comparable doses. Therefore, the Committee recommended an additional UF of 10 to account for possible brain cholinesterase inhibition in the human study. In determining the appropriate UF, the Committee took in consideration the steep dose-response curve and the fact that the duration of exposure was not a major factor in the progression or magnitude of cholinesterase inhibition.

B. Registrant's Rebuttal:

The registrant, FMC Corporation, has submitted a rebuttal to the Agency to reconsider its position on the RfD for ethion (FMC letter dated August 3, 1995). In their rebuttal, the registrant lists the points of contention and addresses two issues relating to the RfD assessment:

1) The Choice of the NOEL in the human oral toxicity study,

2) The Choice of the UF applied to the NOEL in generating the RfD for this chemical.

The registrant also expressed disagreement with the Agency's evaluation of the Margin of Exposure (MOE) for dermal exposure. In the same letter, FMC corporation indicated that the use of a NOEL of 0.8 mg/kg/day from a 21 day rabbit dermal study (MRID No. 00155499, 00155498) and the default dermal absorption value of 100% were inappropriate for the calculation of Margin of Exposure (MOE) values for field workers.

FMC corporation also indicated that an unpublished oral 21-day

study in humans, previously reviewed by the Agency (IBT Report No. F8948, MRID No. 00073157) and a published experimental value for human dermal absorption of ethion (R.J. Feldmann and H.I. Maibach (1974), entitled "Percutaneous Penetration of some Pesticides and Herbicides in Man". Toxicol. Appl. Pharmacol. 28: 126-132) should be used instead for the calculation of MOE values.

C. Committee's Conclusions and Recommendations:

The HED/RFD Peer Review Committee as well as members of the less than life time (LTL) risk assessment Committee convened on August 31, 1995 to re-examine the toxicity database of ethion and to reconsider its position on the RfD and MOE previously established for this chemical in light of the registrant's rebuttal.

1. RfD Considerations

Upon re-evaluation of the results of the 21-day oral toxicity study in humans (MRID No. 00073157), the Committee further concluded that the study did not demonstrate a clear NOEL for cholinesterase inhibition and that the lowest dose level tested, 0.05 mg/kg/day, could be defined as an LOEL for plasma cholinesterase inhibition. This conclusion was based on clinical signs of cholinesterase inhibition observed in one subject towards the end of the administration period of the low-dose, and in another subject on the first day of the initiation of the next higher dose period (0.075 mg/kg/day). The first subject was reported to suffer headache and blurred vision on days 19-21 of the low-dose period and on day 1 of the administration of 0.075 mg/kg/day period; lightheadedness and dizziness were reported by this subject on the following day. The second affected subject reported partial blindness and lightheadedness twice on the first day of receiving 0.075 mg/kg/day and on the first day of receiving 0.15 mg/kg/day. These results show the occurrence of cholinergic signs in 2 out of 6 subjects and taken together, can be interpreted as a reflection of a cumulative effect of the test material administered at the dose of 0.05 mg/kg/day and higher doses.

It was noted that in the initial review of the 21-day oral study in humans, the reviewer had discussed the cholinergic symptoms presented by the two subjects but had concluded that the symptoms were not treatment-related (HED Doc. 007033, August 30, 1983). Thus, the LOEL was defined, at that time, as 0.075 mg/kg/day based on inhibition of plasma cholinesterase activity with a NOEL of 0.05 mg/kg/day. In the present re-evaluation of the study the HED/RFD Peer Review Committee felt that the cholinergic signs are sufficiently consistent in the two subjects to indicate a treatment-related effect at the low dose.

The HED/RFD Peer Review Committee, therefore, concluded that an RfD for ethion should be established based upon an LOEL of 0.05

mg/kg/day with an uncertainty factor (UF) of 10 to account for intraspecies variability (i.e. the differences in sensitivity within the human population), and an additional UF of to compensate for the lack of a well defined NOEL and the possibility that brain cholinesterase could be inhibited at dose levels comparable to or less than those causing plasma cholinesterase inhibition as it has been demonstrated in other species. **On this basis the RfD was calculated to be 0.0005 mg/kg/day.**

2. MOE Considerations

In the evaluation of the published experimental value for human dermal absorption of ethion [Toxicol. Appl. Pharmacol. 28: 126-132 (1974)] it was concluded that the absorption value of 6.6% of the dose (i.e. the reported mean 3.3% plus 3 times the standard deviation, which encompasses most of the population) is adequate for risk assessment.

The HED/RFD Peer Review Committee re-examined the 21-day rabbit dermal toxicity data (MRID Nos. 00155499 and 00155498) and noted that the data suggest that after dermal dosing with ethion, rabbit brain cholinesterase is significantly inhibited at lower doses than those required to inhibit significantly plasma and erythrocyte cholinesterase. It was also noted that these results contrast with findings in oral studies with rats and dogs that show significant inhibition of plasma and erythrocyte cholinesterase at dose levels comparable to or comparable to those required to inhibit brain cholinesterase significantly. The Committee concluded that it was unclear, with the available data, whether the effect observed in the 21-day rabbit dermal study reflected a route effect valid for other species or was a species specific effect.

The Committee recommended that an MOE of 100 define the minimally acceptable exposure level if the 21-day oral human study (MRID No. 00073157) is used as the critical study for the purpose of risk assessment of short or intermediate term occupational or residential exposure. As indicated above, an MOE of 100; i.e. 10 to account for the lack of a NOEL and 10 to account for the intraspecies variability would be necessary.

In the case of ethion, the use of an MOE of 100 when using an oral study is additionally supported by the results of the 21-day dermal rabbit study, which suggest that upon dermal dosing, brain cholinesterase may be inhibited at lower doses than those required to cause plasma or erythrocyte cholinesterase inhibition.

D. Individuals in Attendance:

Peer Review Committee members and associates present were William Burnam (Chief, SAB; chairman, RfD/QA Peer Review Committee), Karl Baetcke (Chief, TB I), Marcia Van Gemert (Chief, TB II), George Ghali (Manager, RfD/Peer Review Committee), Rick Whiting, William Sette, Henry Spencer, Roger Gardner and Guruva Reddy. In attendance also were Kit Farwell, Laura Morris, Elizabeth Doyle, Larry Dorsey and Jane Smith of HED as observers.

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

Alberto Protzel

James Rowe

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

Karl Baetcke

CC: Stephanie Irene
Debra Edwards
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