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

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OFFICE OF
INTERNATIONAL ACTIVITIES

MEMORANDUM

SUBJECT: Terbufos: Reconsideration of the Reference Dose

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

FROM: George Z. Ghali, Ph.D.
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G. Ghali 7.1.96

THRU: William Burnam
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TO: Robert Forrest, PM 14
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The Health Effects Division-RfD/Peer Review Committee met on May 22, and again on May 23, 1996 to reconsider the basis used in the assessment of the Reference Dose (RfD) for Terbufos, evaluate other alternative toxicological end-points as possible basis for the RfD setting, and to address issues raised by the registrant, American Cyanamid Co., in their letter of April 13, 1995. The Committee recommended that the RfD for terbufos remain unchanged.

In this meeting, the Committee was also requested to evaluate a new reproductive toxicity study in rats recently submitted to the Agency in support of Terbufos re-registration. The Committee considered this study (83-4, MRID No. 43649402) to be acceptable. The Committee also agreed with the reviewer's evaluation and interpretation of data and classification of the study.

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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

blood cell cholinesterase was inhibited at comparable or slightly higher dose levels than those required to cause plasma cholinesterase inhibition in this species.

The Committee, therefore, recommended that the RfD for Terbufos remain unchanged and be based on the three studies in dogs. The RfD for terbufos, as currently exists, is based on a NOEL of 0.005 mg/kg/day with an uncertainty factor (UF) of 100 to account for both the interspecies extrapolation and intraspecies variability (i.e. the differences in sensitivity within the human population). **On this basis the RfD was calculated to be 0.00005 mg/kg/day.**

In view of the above, the Committee believes that adequate and thorough consideration has been given to the registrant's rebuttal of April 13, 1995 and in the absence of additional or new data, there will be no justification for any further reconsideration of the RfD of Terbufos.

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.