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

JUL 8 1996

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Fonofos: Reconsideration of the Reference Dose

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

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

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

TO: Robert Forrest, PM 14
Insecticide-Rodenticide Branch
Registration Division (7505C)

Chief, Reregistration Branch
Special Review and Reregistration Division (7508W)

The Health Effects Division-RfD/Peer Review Committee met on June 20, 1996 to reconsider its position on the Reference Dose (RfD) for Fonofos in light of additional information provided to the Committee. In this meeting, the Committee was also requested to evaluate additional information on neurotoxicity recently submitted to the Agency in support of Fonofos re-registration.

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A. Background:

The health effects Division-RfD Peer Review Committee met on August 12, 1993 to evaluate the toxicology data available in support of Fonofos re-registration and to reassess the Reference Dose for this chemical.

In the meeting of August 12, 1993, the Committee recommended that an RfD be established based on two co-critical studies: a subchronic neurotoxicity study and a chronic feeding study in rats. The overall NOEL for the two studies was 0.75 mg/kg/day. Clinical signs of neurotoxicity and brain cholinesterase inhibition were observed at the next higher dose level of 2.5 mg/kg/day in the subchronic study and 2.4 and 2.8 mg/kg/day for males and females, respectively, in the chronic study. An uncertainty factor (UF) of 100 was applied to account for both the interspecies extrapolation and intraspecies variability. On this basis, the RfD was calculated to be 0.0075 mg/kg/day.

Subsequently, an acute delayed neurotoxicity study in hens and additional supplemental data on the acute and subchronic mammalian neurotoxicity studies were submitted to the Agency and a chronic toxicity study in dogs was reevaluated resulting in a lower NOEL which could affect the RfD as it currently exists. The RfD Peer Review Committee was requested to assess the impact of the additional neurotoxicity information and the reevaluation of the dog study on the RfD for this chemical.

B. Committee's Conclusions and Recommendations:

The Committee agreed with the reviewer's reevaluation and interpretation of the chronic dog study. Based on the reevaluation, the NOEL is 0.2 mg/kg/day and the LOEL is 1.0 mg/kg/day based on plasma and red blood cell cholinesterase inhibition. Marginal inhibition of plasma cholinesterase was observed at 0.2 mg/kg/day, the lowest dose level tested in the chronic dog study, but was considered to be of no biological significance.

Since the reevaluation of the dog study resulted in a lower NOEL than the NOEL generated in the subchronic neurotoxicity study and chronic toxicity studies in rats which were previously used as the basis for the setting of the RfD, the Committee, therefore, recommended that the RfD for Fonofos be based on the chronic toxicity study in dogs with a NOEL of 0.2 mg/kg/day. An uncertainty factor (UF) of 100 was applied 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 0.002 mg/kg/day.**

The Committee also agreed with the reviewer's evaluation and interpretation of the acute (81-8, MRID No. 42777801) and

subchronic neurotoxicity studies (82-6, MRID No. 42792601) in rats and the acute (81-7, MRID No. 43161301) and subchronic delayed neurotoxicity studies in hens (82-5, MRID No. 40150120).

C. Individuals in Attendance:

Peer Review Committee members and associates present (in one or more meetings) were William Burnam (Chief, SAB; chairman, RfD/QA Peer Review Committee), Mike Ioannou (Acting Chief, TB II), George Ghali (Manager, RfD/Peer Review Committee), Albin Kocialski (Senior Science Advisor, HED), Rick Whiting, Henry Spencer, James Rowe, and Guruva Reddy.

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

& Pam Hurley

Roger Gardner

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

Karl Baetcke

CC: Stephanie Irene
Debra Edwards
Albin Kocialski
Karl Baetcke
Roger Gardner
Pam Hurley
Marion Copley
Paula Deschamp
Beth Doyle
Amal Mahfouz
RfD File
Caswell File