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

1992

AUG 12 1992

MEMORANDUM

SUBJECT: RfD/Peer Review Report of Methamidophos (Monitor)
CAS No. 10265-92-6
EPA Chem. Code 101201
Reg. Group: List A

FROM: George Z. Ghali, Ph.D. G. Ghali 6.9.92
Manager, RfD/Quality Assurance Peer Review
Health Effects Division (H7509C)

TO: Marilyn Mautz, PM
Insecticide/Rodenticide Branch
Registration Division (H7505C)
and
Lois Rossi, Chief
Reregistration Branch
Special Review and Reregistration Division (H7508W)

The Health Effects Division RfD/Peer Review Committee met on May 29, 1992 to reconsider the RfD for Methamidophos. This reevaluation was requested by the registrant based upon new data submitted to the Agency to establish a regulatory "no observable-effect level" for cholinesterase (CHE) inhibition for Methamidophos.

The data base on this chemical has been reviewed and an RfD was established by the HED RfD/Peer Review Committee on June 13, 1986. Subsequently, the chemical was revisited and the RfD was reassessed by the HED RfD/Peer Review Committee on April 3, 1987 and verified by the Agency RfD Work Group on May 20, 1987. At that time the Committee recommended that the RfD should be established based upon an LEL of 0.05 mg/kg/day (LDT) for inhibition of plasma, RBC and brain cholinesterase in a one-year feeding study in dogs using an uncertainty factor of 1000 (100 to account for the intra- and inter-species differences, and an additional 10 to account for the lack of NOEL for brain cholinesterase inhibition).

At that time, studies listed as data gaps, for being absent or inadequate, included: 1) a multi-generation reproduction study (the existing study failed to establish a NOEL), 2) special studies in rats and dogs to establish a NOEL for cholinesterase inhibition.

Subsequently, and based on additional information (reproductive historical control data submitted by the registrant Mobay report No. 88686-1), the reproduction study was upgraded to Core-minimum data (K. Locke, memo dated May 4, 1990, HED Doc. No, 007891). A "no-observable effect level" of 10 ppm (0.5 mg/kg/day) was established for reproductive and systemic toxicity.

The registrant, Mobay Corporation, has recently submitted a subchronic study (60 days) in rat (Mobay Report No. 100667, MRID No. 41867201) with the purpose of establishing a regulatory NOEL for cholinesterase inhibition to be used as a basis for the RfD. This subchronic study demonstrated a "lowest-effect level" of 0.5 ppm (0.025 mg/kg/day) for plasma, erythrocyte and brain cholinesterase inhibition. The registrant has also submitted a position document entitled "Discussion of the Toxicological Basis for Revising the Reference Dose (RfD) for Chronic Dietary Exposure for Monitor (Methamidophos)" outlining the registrant position on the RfD issue. The data evaluation records of the rat subchronic study and the registrant's position paper were provided to the HED RfD Committee for consideration.

In their meeting of May 29, 1992, taking into consideration all available information on this chemical, and considering the rationale used in setting the RfD for the parent compound, acephate, the Committee concluded that the lowest dose level of 0.5 ppm (equivalent to 0.05 and 0.06 mg/kg/day for males and females respectively) in the new subchronic study in the rat represents a threshold level. The Committee concluded that the rationale used in setting the RfD for acephate, the parent compound of monitor, can be applied in the case of monitor. Human studies with acephate and monitor were considered. The Committee concluded that the existence of such supporting human data diminishes the need for an uncertainty factor to account for the interspecies variability. Data from comparative in vitro studies with human brain, RBC or plasma cholinesterase also showed differences of less than 10-fold. On this basis, the Committee recommended to modify the customary 100-fold uncertainty factor used for cholinesterase inhibition. This 100-fold factor was reduced to 10 (e.g., the 10-fold factor from animal to man was not considered necessary). Furthermore, a 3-fold factor was used because a NOEL was not determined in the critical study. This intermediate factor of 3 was considered more appropriate than 10 because the LEL dose was concluded to represent a threshold dose. Finally, the 10-fold factor normally used to estimate an RfD using subchronic data was not considered necessary, since the results after subchronic exposure are similar in both severity and magnitude as for chronic studies.

Based on the above, the RfD for this chemical was calculated to be 0.001 mg/kg/day.

A. Individuals in Attendance

1. Peer Review Committee (signature indicates concurrence with the peer review unless otherwise stated).

William L. Burnam _____

Reto Engler _____

Karl Baetcke _____

Marcia Van Gemert _____

Henry Spencer _____

Stephen Dapson _____

Roger Gardner _____

Gary Burin _____

George Ghali _____

Rick Whiting _____

2. Peer Review Members in Absentia (committee members who were unable to attend the discussion; signatures indicate concurrence with the overall conclusions of the committee).

Laurence Chitlik —

Esther Rinde —

James Rowe _____

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

Krystyna Locke _____

B. Conclusions and Recommendations:

In their meeting of May 29, 1992, taking into consideration all available information on this chemical, and considering the rationale used in setting the RfD for the parent compound, acephate, the Committee concluded that the lowest dose level of 0.5 ppm (0.05 and 0.06 mg/kg/day for males and females respectively) in the new subchronic study in the rat represents a threshold level. The Committee concluded that the rationale used in setting the RfD for acephate, the parent compound of monitor, can be applied in the case of monitor. There are human studies conducted with acephate and monitor (MRID 093672). The Committee concluded that the existence of such supporting human data diminishes the need for an uncertainty factor to account for the interspecies variability. Data from comparative in vitro studies with human brain (taken from an accident victim), RBC or plasma CHE also showed differences of less than 10-fold. On this basis, the Committee recommended to modify the customary 100-fold uncertainty factor used for cholinesterase inhibition. This 100-fold factor was reduced to 10 (e.g., the 10-fold factor from animal to man was not considered necessary). Furthermore, a 3-fold factor was used because a NOEL was not determined in the critical study. This intermediate factor of 3 was considered more appropriate than 10 because the LEL dose was concluded to represent a threshold dose. Finally, the 10-fold factor normally used to estimate an RfD using subchronic data was not considered necessary, since the results after subchronic exposure are similar in both severity and magnitude as for chronic studies.

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