Department of Pesticide Regulation

Paul Helliker
Director

M E M O R A N D U M

Arnold Schwarzenegger
Governor

TO: Denise Webster, Senior Pesticide Use Specialist **HSM-04012**
Pesticide Registration Branch

VIA: Joseph P. Frank, D.Sc., Senior Toxicologist *[original signed by J. Frank]*
Worker Health and Safety Branch
(916) 324-3517

FROM: Wendy Zhao, Staff Toxicologist (Specialist) *[original signed by W. Zhao]*
Worker Health and Safety Branch
(916) 332-7619

Thomas Thongsinthusak, Staff Toxicologist (Specialist)
Worker Health and Safety Branch *[original signed by T. Thongsinthusak]*
(916) 445-4267

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SUBJECT: COMMENTS ON POSITION PAPER ON THE ESTIMATED HUMAN DERMAL ABSORPTION OF METHAMIDOPHOS, (REGISTRATION TRACKING ID #203141)

In October 2003, Bayer Corporation submitted a document entitled "Position paper on the estimated human dermal absorption of methamidophos" to the Department of Pesticide Regulation (DPR) for review (Sangha, 2003) Registration Tracking ID No. 203141. This document contains summaries of several studies, including *in vitro* and *in vivo* dermal absorption, and metabolism/pharmacokinetics of methamidophos that were conducted from 1953 to 2001. Upon review of this document, we found no new information or data on dermal absorption of methamidophos. Dermal absorption studies conducted in rats, monkeys, and human volunteers were previously reviewed and evaluated by DPR (Thongsinthusak, 2001a,b,c). Since then, a new dermal absorption study has not been conducted. DPR recommends a dermal absorption value of 29% based on a study in human volunteers (topical administration), whereas Bayer Corporation suggested 4.84% based on the same study and a study in monkeys (intravenous injection [IV]). DPR and Bayer used different procedures to derive the dermal absorption values because of the very low mass balance observed in the human and monkey studies.

Bayer Corporation used [$^{14}CH_3S$]-methamidophos in dermal absorption studies in rats, monkeys and human volunteers. In these studies, the labeled carbon could be absorbed, degraded, and lost to CO_2 and other volatile metabolites. The radioactivity of volatile gas and metabolites was not accounted for in the mass balance determination. The results of the cumulative excretion of radioactivity for the low dose in monkeys (IV dose) and human volunteers (topical dose) were 11.35% and 0.54%, respectively. The results indicate the loss of radioactivity.

Because of the loss of radioactivity observed in a rat dermal absorption study, the U.S. EPA after discussing with Bayer, endorsed an approach where radioactivity of untrapped volatile metabolite(s) was added to the percent recovery systemically and the total was used as a conservative estimate of systemic absorption (Sangha, 2003).

It is essential that the compound used in a dermal absorption study be radiolabeled in a position, which is part of the "core" of the compound. The label should follow the compound and its major metabolites until excreted (Zendzian, 1994). The label should not be exchangeable nor should it be metabolically removed to CO_2 or become part of the one-carbon pool of the organism. In the submitted document (Sanga, 2003), Bayer acknowledges that ^{32}P-methamidophos should have been used in dermal absorption studies. However, Bayer indicated difficulty of using ^{32}P in a dermal absorption study. DPR believes that [$^{14}CH_3S$]-methamidophos is inappropriate for use in a dermal absorption study because evaluation of results is extremely difficult and may not be accurate. To illustrate the difference in urinary excretion of radioactivity, about 77% of the administered radioactivity was recovered in the urine 24 hours after oral administration of ^{32}P-labeled methamidophos in rats versus 11.35% in monkeys after intravenous injection of [$^{14}CH_3S$]-methamidophos. This clearly shows that ^{32}P-methamidophos is a much better choice than [$^{14}CH_3S$]-methamidophos.

Wester and Maibach (1983) used the ratios of area under the curve or radioactivity in excreta after dermal administration and intravenous injection to derive the dermal absorption of a compound. If [$^{14}CH_3S$]-methamidophos was used in a dermal absorption study, the dermal absorption should not be determined using the ratios of radioactivity following intravenous injection and dermal administration because total radioactivity of volatile metabolite(s) was not accounted for in the mass balance. Wester and Maibach (1983) also suggested an approach to determine *in vivo* dermal absorption by determining the loss of material from the surface as it penetrates into the skin. DPR estimated dermal absorption of methamidophos based on the applied dose (100%) minus unabsorbed dose or dose recovered from surface washings (Thongsinthusak, 2001c).

Due to uncertainties in using [$^{14}CH_3S$]-methamidophos in the dermal absorption studies in human volunteers and monkeys, DPR recommends a human dermal absorption of 29% (Thongsinthusak, 2001c) for use in exposure assessments, instead of 4.84% as suggested by Bayer Corporation (Sangha, 2003). DPR recommends a new dermal absorption study be conducted in animals, such as nonhuman primates, by using ^{32}P-methamidophos. The dermal dose should be prepared in an aqueous suspension with addition of formulation blank (i.e., ingredients used in the methamidophos formulation minus methamidophos). A probe study

is recommended. A dermal absorption study protocol should be submitted to DPR for review before the study.

References:

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