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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY CASWELL FILE
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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: EPA ID No.: 16-788. Tolerances For Acephate and Methamidophos Arising from Acephate

Record No.: 251534
HED Project No.: 9-2168
Tox Chem. No.: 2A

FROM: Krystyna K. Locke, Toxicologist Krystyna K. Locke 2/21/90
Section I, Toxicology Branch I (IRS)
Health Effects Division (H7509C)

TO: William H. Miller/Marilyn A. Mautz, PM/RM Team No. 16
Insecticide/Rodenticide Branch
Registration Division (H7505C)

and

Richard D. Schmitt, Chief
Dietary Exposure Branch
Health Effects Division (H7509C)

THRU: Roger Gardner, Acting Section Head
Section I, Toxicology Branch I (IRS)
Health Effects Division (H7509C)

and

Karl Baetcke, Chief
Toxicology Branch I (IRS)
Health Effects Division (H7509C)

BACKGROUND

In the past, when a food tolerance request was submitted for acephate, a certain upper limit (usually about 10% of that tolerance) was allotted to methamidophos; for example, "--- 5 ppm for the residues of acephate, of which no more than 0.5 ppm is methamidophos". A separate application for a definitive methamidophos tolerance was not required by EPA. Methamidophos is also a separately registered pesticide.

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ISSUES OF CONCERN

According to the Registration Standard for acephate, issued in 1987, any tolerance for acephate should be accompanied by a separate and specific tolerance for methamidophos.

According to the Registration Standard for methamidophos, issued in 1982, no further permanent tolerances will be granted until the toxicity data gaps are filled. Although the missing data were submitted in response to the Registration Standard in 1985, cholinesterase activities (brain, plasma and erythrocytes) were inhibited at the lowest levels tested in both the rat and dog chronic feeding studies. The NOEL's for these studies are still missing, although Mobay Chemical Corporation has recently undertaken a 4-week rat feeding/cholinesterase study aimed at providing a definitive NOEL and subsequently RfD (ADI). A report on this study is to be submitted to EPA at the end of February 1990 (personal communications with Dan Peacock). The currently available provisional RfD (PADI) of 0.00005 mg/kg/day is based on the LEL (0.05 mg/kg) for cholinesterase inhibition in the one-year dog feeding study and the uncertainty factor (UF) of 1000.

According to the registrant (Valent), separate tolerances for acephate and methamidophos residues are not needed since the acephate data base and ADI (0.004 mg/kg) are totally sufficient to provide a regulatory basis for the combined residues of acephate and methamidophos which result from using acephate on crops. Valent's position is based on the following observations:

(1) "In addition to being a plant metabolite, methamidophos is also a mammalian metabolite of acephate.

(2) Mammals metabolize acephate to methamidophos in toxicologically significant amounts, and thus, the cholinesterase-inhibiting potency of methamidophos has been included to some extent in all acephate toxicology studies, including those in which no-observed-effect levels (NOELs) occurred.

(3) The results of a study in which mixtures of acephate and methamidophos were fed to human beings demonstrate that there is a sufficient margin of safety in the acephate ADI to allow the Agency to set new tolerances for acephate/methamidophos residues, and that the acephate data base is totally sufficient to support such action."

TOXICOLOGY BRANCH/HED POSITION ON VALENT'S PROPOSAL

Toxicology Branch disagrees with Valent that the acephate toxicity data baseline and the ADI should be used to support methamidophos residues arising from acephate, and that these

residues need not be separated for acephate residues in tolerance requests. Although the cholinesterase inhibiting potency of methamidophos has indeed been included to some extent in all acephate toxicity studies, there is no way to quantitate this extent and to extrapolate this information to the safety of methamidophos - containing crops. It should be kept in mind that methamidophos residues arising from acephate represent new residues (tolerances) for crops (racs) lacking already established methamidophos tolerances. Irrespective of the past practices, these residues should be included in the assessments of human dietary exposures to methamidophos residues and should be supported by methamidophos toxicity data baseline and ADI. Because an ADI is currently lacking for methamidophos and the existing PADI cannot even support published tolerances, and in compliance with the Registration Standard for methamidophos, new tolerances for methamidophos residues cannot be toxicologically supported.

Regarding Valent's observations in support of their proposal, it is true that methamidophos is a plant metabolite of acephate. Plants convert about 10% of acephate to methamidophos which can subsequently be ingested by both humans and animals consuming these plants.

Metabolism studies with rats and goats, referenced by Valent is Appendix II (attached), indicate that acephate is rapidly absorbed from the stomach and rapidly excreted in urine essentially unchanged. In one study (Ref. 4), methamidophos was not detected in urine of rats but O,S-dimethyl phosphorothioate (DMPT; 3-6%), a degradation product of methamidophos and cholinesterase "noninhibitor" was detected. In another study with rats (Ref. 5), the whole carcasses contained 0.6-1.6% and the excreta (chiefly urine) 1.1-1.5% of the administered dose of acephate as methamidophos. The author concluded that mammals did not metabolize acephate to methamidophos (for example, enzymatic conversion in the liver did not occur), but that a portion of the administered acephate could be converted to methamidophos by the intestinal microorganisms. The conversion took place in the small intestine and methamidophos was then absorbed into the blood stream. Similar levels of urinary methamidophos were observed in a study in which rats were exposed dermally to acephate (Ref. 6), but only DMPT (<10% of urinary 14C) was detected in a study in which one goat received seven consecutive doses of acephate (Ref. 7). Considering the above studies, it is difficult to accept Valent's conclusion unequivocally that mammals metabolize acephate to methamidophos in significant amounts.

The study in which mixtures of acephate and methamidophos were fed to humans (Ref. 15), was classified as supplementary and not used in setting an ADI for acephate.

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APPENDIX II

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