(104)

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

DEC 12 1990

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

Subject: Review of EFGWB/EFED memorandum on toxicological significance of Clethodim Technical residues in crops and fodder
MRID Nos. N/A
ID No. N/A
Tox Chem No. 721F
HED Project No. 0-1966A

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James N. Rowe 12/6/90

To: Ms. Joanne I. Miller/Ms. M. Erumsele-Matzer
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Fungicide-Herbicide Branch
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Thru: Marcia van Gemert, Ph.D., Chief
Toxicology Branch II
Health Effects Division (H7509C)
Marcia van Gemert 12/11/90

ACTION: Review request from Mr. E. Brinson of EFGWB/EFED to assess the toxicological significance of expected residues in rotational crops and related fodders.

BACKGROUND: Uptake has been observed in confined rotated crops replanted at intervals up to 365 days. In an acceptable confined rotational crop study on lettuce, carrots, wheat, some uptake in food and fodder material at exaggerated rates has been observed. About 1/3 of the recovered material was structurally related to Clethodim (imine sulfoxide and oxazole sulfoxide and sulfone derivatives), and the rest apparently came from the soil "carbon pool". At normal use rates total residue would be ca. 1.6 to 4 ppb Clethodim related in food crops and 20 to 53 ppb Clethodim related in fodder crops. In these rotational crops the individual compounds identifiable as derivatives of Clethodim would be well below the limit of quantitation of the analytical method.

DISCUSSION/RECOMMENDATIONS:

A photocopy of chemical structures of possible Clethodim metabolites (not necessarily in crops) is attached. Two metabolites of Clethodim, the imine sulfone and the 5-OH sulfoxide,

114

1/4

have been tested in rat teratology screens, 5 week feeding studies and mutagenicity batteries along with the more extensive testing of the parent compound, Clethodim. In general, although the data is limited, these two metabolites appear less toxic than the parent material. It is not anticipated that the structures of the Clethodim metabolites in the crops would differ significantly in toxicological response from the two tested metabolites.

Perhaps more importantly, it should also be noted that Clethodim is metabolized in vivo in the rat to imine sulfoxide (7-8% of total radiolabel administered; 450 mg/kg) and oxazole sulfoxide (3% of total dose administered; 450 mg/kg) based on urinary and fecal metabolites recovered (MRID No.410301-32). Thus, the metabolites found in the food crops are also found as a significant proportion of mammalian animal metabolites and the toxicological response observed with administration of the parent compound to test animals will incorporate any response produced by the subsequent metabolites formed.

Therefore, it is appropriate to use the toxicity profile of the parent compound, Clethodim Technical, as the basis for a decision on the potential risks of ingestion of these metabolites.

A PADI for Clethodim has been established of 0.01 mg/kg/day by the Health Effects Division ADI Peer Review Committee. This PADI is based upon a NOEL for systemic toxicity in a one-year dog feeding study of 1 mg/kg/day. The daily contribution of Clethodim and its metabolites to human exposure from direct consumption of food (lettuce, carrots, wheat) and/or indirectly from fodder should be determined by Chemistry Branch I- Tolerance Support/HED and a % PADI should be calculated. Percents of the ADI of 100 or less would be considered as acceptable exposures.

cc Francis D. Griffith (H7509C)
E. Brinson Conerly (H7509C)

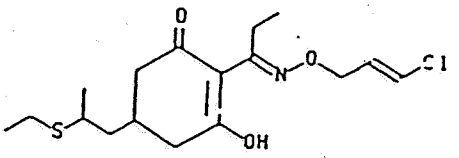
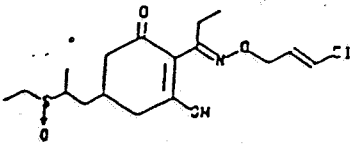
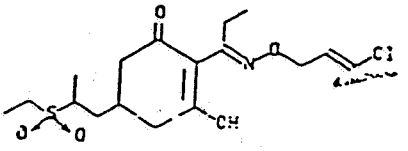
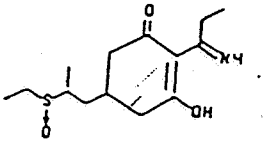
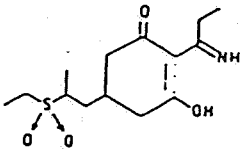
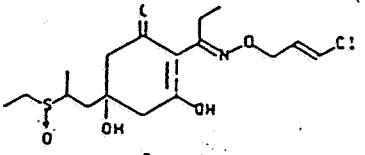
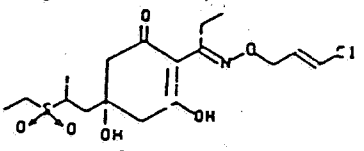
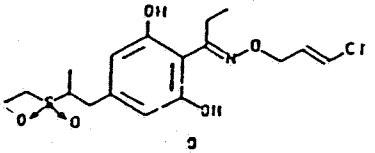
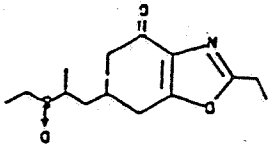
1/5

Attachment

HED # 0-1966A

TABLE I

CHEMICAL NAMES, DESIGNATIONS AND STRUCTURES
OF POSSIBLE CLETHODIM METABOLITES

DESIGNATION	CHEMICAL NAME	STRUCTURE
CLETHODIM (RE-45601)	2-[1-[[(E-3-chloro-2-propenyl)oxy]-imino]propyl]-5-[2-(ethylthio)propyl]-3-hydroxy-2-cyclohexen-1-one	
CLETHODIM SULFOXIDE (RE-45924)	2-[1-[[(E-3-chloro-2-propenyl)oxy]-imino]propyl]-5-[2-(ethylsulfoxo)propyl]-3-hydroxy-2-cyclohexen-1-one	
CLETHODIM SULFONE (RE-47253)	2-[1-[[(E-3-chloro-2-propenyl)oxy]-imino]propyl]-5-[2-(ethylsulfonyl) propyl]-3-hydroxy-2-cyclohexen-1-one	
IMINE SULFOXIDE (RE-47718)	2-[[1-imino]propyl]-5-[2-(ethylsulfoxo) propyl]-3-hydroxy-2-cyclohexen-1-one	
IMINE SULFONE (RE-47719)	2-[[1-imino]propyl]-5-[2-(ethylsulfonyl) propyl]-3-hydroxy-2-cyclohexen-1-one	
5-OH SULFOXIDE (RE-51229)	2-[1-[[(E-3-chloro-2-propenyl)oxy]-imino]propyl]-5-[2-(ethylsulfoxo)propyl]-5-hydroxy-3-hydroxy-2-cyclohexen-1-one	
5-OH SULFONE (RE-51228)	2-[1-[[(E-3-chloro-2-propenyl)oxy]-imino]propyl]-5-[2-(ethylsulfonyl)propyl]-5-hydroxy-3-hydroxy-2-cyclohexen-1-one	
AROMATIC SULFONE (RE-50419)	2-[1-[[(E-3-chloro-2-propenyl)oxy]-imino]propyl]-5-[2-(ethylsulfonyl) propyl]-1,3-dihydroxybenzene	
OXAZOLE SULFOXIDE (RE-47795)	6,7-dihydro-6-[2-(ethylsulfoxo)propyl]-2-ethyl-4(5H)-benzoxazolone	

17

116

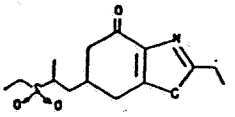
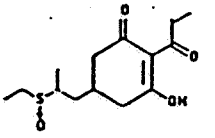
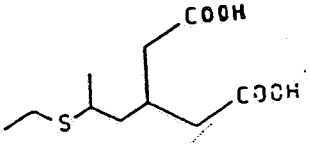
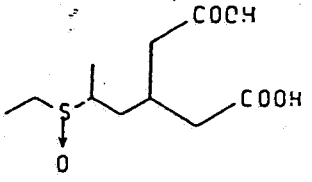
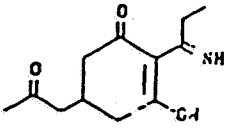
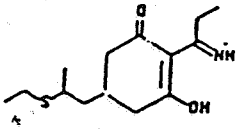
2-3

Attachment

HED # 0-1966A

TABLE I (CONTINUED)

CHEMICAL NAMES, DESIGNATIONS AND STRUCTURES
OF POSSIBLE CLETHODIM METABOLITES

DESIGNATION	CHEMICAL NAME	STRUCTURE
OXAZOLE SULFONE (RE-47797)	6,7-dihydro-6-[2-(ethylsulfonyl)propyl]-2-ethyl-4(5H)-benzoxazolone	
TRIONE SULFOXIDE (RE-47386)	2-[1-one]propyl]-5-[2-(ethylsulfoxo) propyl]-3-hydroxy-2-cyclohexen-1-one	
DME SULFIDE (RE-52420)	3-[2-(ethylthio)propyl] pentanedioic acid	
DME SULFOXIDE (RE-52453)	3-[2-(ethylsulfoxo)propyl] pentanedioic acid	
IMINE KETONE	2-[1-[imino]propyl]-5-[propyl-2-one]-3-hydroxy-2-cyclohexen-1-one	
IMINE (RE-47686)	2-[[1-imino]propyl]-5-[2-(ethylthio) propyl]-3-hydroxy-2-cyclohexen-1-one	
OXAZOLE (RE-47365)	6,7-dihydro-6-[2-(ethylthio)propyl]-2-ethyl-4(5H)-benzoxazolone