PC 129006 R.F.

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

MAR 7 1995

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Request for a Metabolism Review of Chlorethoxyfos (DPX-43898) and Determination of Residue(s) to be Regulated.

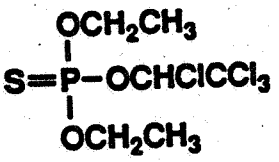
FROM: Jerry B. Stokes, Chemist
Chemistry Branch I/Tolerance Support
Health Effects Division (7509C)

THRU: Ed Zager, Acting Branch Chief
Chemistry Branch I/Tolerance Support
Health Effects Division (7509C)

TO: The Metabolism Committee
Health Effects Division (7509C)

Chlorethoxyfos is a soil insecticide that is applied at planting time either into the planting furrow or as a band application over the planting row.

Structure:



Nature of the Residue in Plants and Animals:

The major components identified in the plant include trichloroacetic acid (TCA), D-glucose, and oxalate. Neither the parent chlorethoxyfos or its oxygen analog are detected in any above-ground portion of the plant at any time during the growing period. Detectable residues (limit of detection, 0.01 ppm) of the parent, oxygen analog, or TCA are not expected in corn grain at the normal label rate. Residues of TCA in fodder or stover at the maximum label rate are expected to be ≤0.03 ppm.

The metabolism of DPX-43898 in the goat was extensive. No significant residues of parent or its oxygen analog were found. The major metabolite of the orally administered 14C DPX-43898 in the goat was 14C-CO_2 which was exhaled. The major components

excreted in the urine were biosynthetic intermediates like 14C-glycine, 14C-serine, 14C-glycine conjugates of benzoic acid and phenyl acetic acid. The main residue in milk was 14C-lactose. Thus all metabolites detected were the result of reincorporation of radioactivity into natural products.

Analytical Methodology:

An analytical method has been validated by the EPA lab (Beltsville) for residues of chlorethoxyfos in corn grain, forage, and fodder. CBTS has requested the registrant to supply validation data for the oxygen analog to be then verified in the Agency lab. No methods have been submitted for meat and milk, because the petitioner the expected amounts of identifiable residues from the proposed use would not be finite (<0.01).

REQUEST TO COMMITTEE:

CBTS requests the Metabolism Committee to determine if only the parent chlorethoxyfos should be regulated, or should the oxon, and/or TCA be included in the tolerance expression and/or dietary risk assessment?

Supplementary Information:

Proposed Use:

Chlorethoxyfos is a soil insecticide that is applied at planting time into the planting furrow or as a 6-8 inch band over the planting row at the rate of 0.32 oz a.i./1000 feet of row (.27 to 0.35 lb a.i./A based upon row spacing of 40 or 30 inches respectively). Rotation to corn at anytime, and to all other crops 30 days after application. No PHI is proposed.

Nature of the Residue in Corn

Corn plants were treated at 2.4 lb a.i./A (**ca. 10X** the proposed field rate) with carbon-14 labeled at the trichloro carbon of chlorethoxyfos. Plants were sampled 30, 60, 119 (mid dough stage), and 151 (mature harvest) days after treatment. The plant tissue analyzed consisted of leaves from day 30 and day 60 and all aerial parts of the plant except grain from the day 119 and day 151 samples.

The major components identified included trichloroacetic acid (TCA), D-glucose, and oxalate; neither the parent compound nor the oxygen analog was detected in any fraction. The radioactivity was distributed as follows and the levels of radioactivity in plant tissues and grain are chlorethoxyfos equivalents.

Radioactivity in Corn Plant Tissues and Corn Grain						
Days	Sample	PPM*	Ext.% of TRR	%TCA	%Glucose	%Oxalate
30	leaves	0.71	92.8	84	NA	NA
60	leaves	1.6	87.5	78.7	NA	NA
119	grain	0.33	99,9	14.2	74	NA
	aerial plant minus grain	1.08	89.2	51.6	3.3	17.8
151	grain	0.32	94.2	4.5	73.4	NA
	aerial plant minus grain	0.65	87.1	19.9	12.4	12.4

* Chlorethoxyfos equivalents
NA: not analyzed or not available

Chlorethoxyfos is converted to diethyl thiophosphate and the trichloroacetate ion and/or trichloracetic acid (TCA) in the soil. The oxygen analog of chlorethoxyfos is not detected in the soil. Trichloroacetate is hydrolyzed to TCA and TCA is then taken up by the plant and metabolized by dehalogenation to oxalate. Oxalate is metabolized by enzymatic decarboxylation by the plant tissues to form carbon dioxide. The carbon dioxide is reincorporated into starch/glucose. There is no concentration of radioactivity in the oil fraction. At least 5 other very minor unknowns were detected during the growing season with no single peak representing greater than 5% of the TRR. Most of this radioactivity was very polar, and presumably these are natural products with C14 from the carbon dioxide reincorporated. At final harvest, a combined 42% of the TRR (total radioactive residue) in all fractions was unidentified; this includes 15+ components each determined at <3% for various extraction/partition fractions. Neither the parent chlorethoxyfos or its oxygen analog were detected in any above-ground portion of the plant at any time during the growing period. Formation of TCA from the parent involves hydrolysis of the phosphate ester which is the major step in the detoxification of the parent. Residues of TCA in fodder or stover at the maximum label rate would be expected to be ≤0.03 ppm based on field trials. Detectable residues (limit of detection, 0.01 ppm) are not expected in corn grain at the normal label rate.

Nature of the Residue in the Lactating Goat:

Three lactating goats were employed in the metabolism study: One goat was dosed at 0.5 ppm carbon-14 chlorethoxyfos (labeled at the trichloro carbon) for 5 consecutive days while another one was dosed at 10 ppm for 3 consecutive days for metabolite

characterization purposes, and the third animal served as an untreated control.

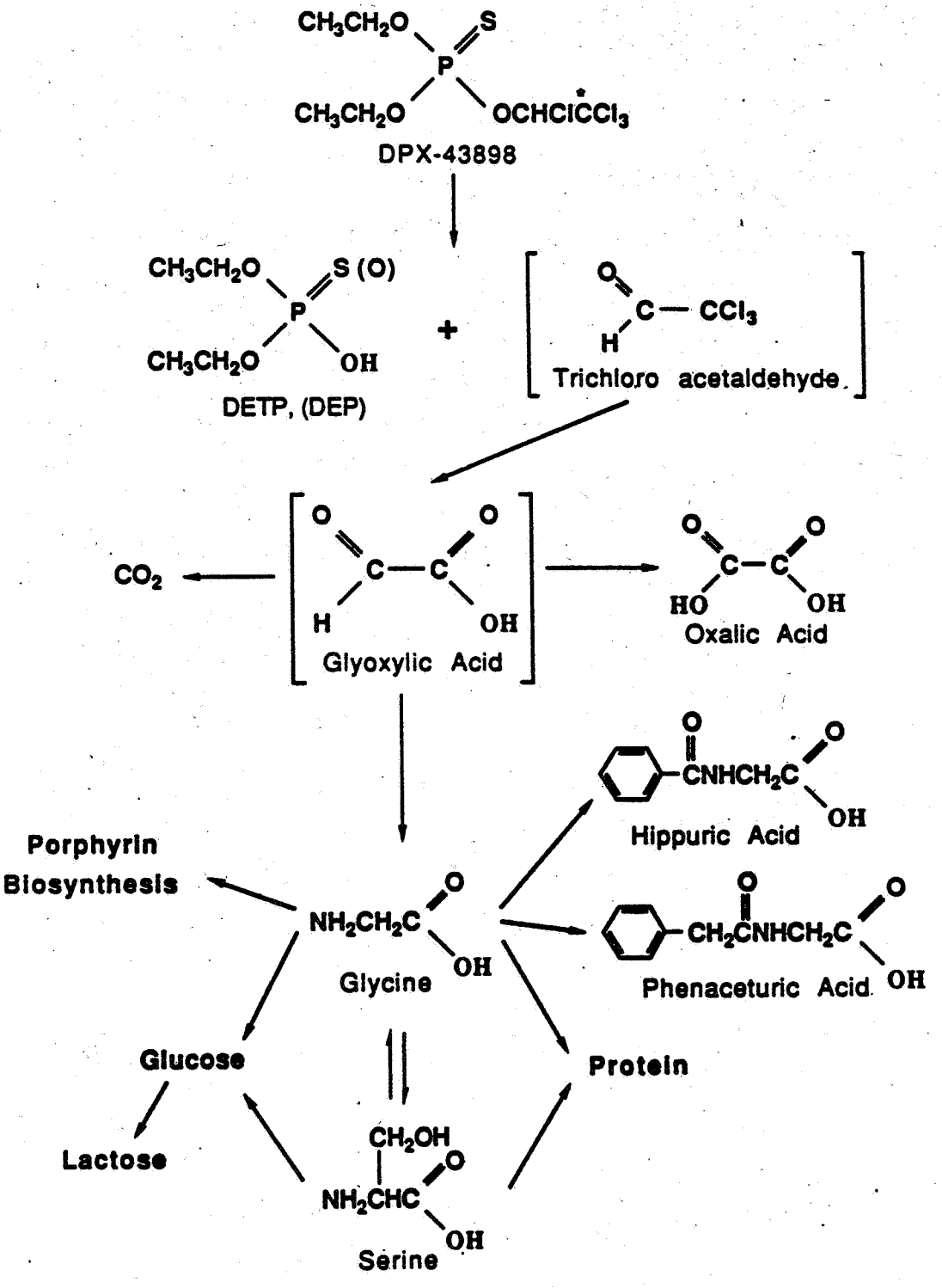
The metabolism of DPX-43898 in the goat was extensive. No significant residues of parent or its oxygen analog were found. Essentially all metabolites detected were the result of reincorporation of radioactivity into natural products. The major metabolite was carbon dioxide. Metabolism of DPX-43898 was more extensive in the goat than in the rat. The major metabolite of the orally administered 14C DPX-43898 in the goat was 14C-CO_2 which was exhaled. The major components excreted in the urine were biosynthetic intermediates like 14C-glycine, 14C-serine, 14C-glycine conjugates of benzoic acid and phenyl acetic acid. The main residue in milk was 14C-lactose. These get incorporated into proteins, etc., and take longer to clear from the animal than chlorinated metabolites that represented well over half of the administered dose in the rat. (See proposed metabolic pathway, p. 5, this memo). In the rat chlorethoxyfos is metabolized primarily through the hydrolysis of the tetrachloroethyl ester bond, and the subsequent formation and excretion of the glucuronide of trichloroethanol. In the goat, only a trace amount (0.08% of the total dose) of a chlorinated metabolite was found in the goat (feces only) and this was identified as TCA.

Distribution of Extractable 14C Activity in Goat Tissue, Milk, and Body Fluids

Matrix	Low Dose		High Dose	
	ppm	% total	ppm	% total
liver	0.184	3.9	3,83	5.7
kidney	0.051	0.2	0.776	0.2
muscle	0.01	2.6	0.165	3.6
fat	≤0.002	-	0.02	0.3
milk	0,054	6.7	.81	5.5
urine	-	21.7	-	19.2
feces	-	10.7	-	13.2
CO_2	-	-	-	15 (day 1)
Total		45.8		62.7

The milk was fractionated into milk fat (4.5% of total activity in milk), milk supernatant (56.5%) and milk proteins (39%). The fat fraction was not further analyzed. The supernatant was analyzed by HPLC to show 3 significant components (M1, 46.2%; M2, 5.1%; and M3, 2.2%). M1 had the same retention time as lactose, and upon beta-

Proposed Metabolic Pathway for DPX-43898 in the Lactating Goat



galactosidase treatment resulted in a component that had the same retention time of galactose and glucose (not resolved under the HPLC conditions). Parent was not found in milk supernatant fraction. The protein fraction after TFA precipitation and derivatization with phenylisothiocyanate (PITC) yielded HPLC retention times same as those of serine PITC (13.9%) and glycine PITC (8.2%) derivatives. The remaining activity was not further characterized.

Insignificant amounts (<0.1% of tissue total or <0.01 ppm parent equivalent) of the parent or its oxygen analog were detected in tissues. Components identified in various tissues (liver, kidney, and muscle) showed incorporation of the TCA in the serine and glycine ranging from 0.3 to 38%. The remaining amounts of radioactivity (1.5 to 17%) consisted of possibly 4 other components, but were not readily available for identification.

Activities in urine were identified to include serine, glycine, oxalic acid, and glycine conjugates of benzoic acid and phenylacetic acid; and in feces appeared to consist of predominantly bile pigments and <0.7% TCA.

Analytical Method (MRID # 412906-03)

The petitioner's GC/EC Method #AMR-1507-89 on corn grain, forage, and fodder has been validated for parent compound by the EPA lab at fortification levels of 0.02 and 0.05 ppm. A successful validation was completed with good recoveries for both fortification levels of chlorethoxyfos only: corn grain, 78-93%; corn forage, 86-97%; corn fodder, 73-85%. (The method can be used to determine both chlorethoxyfos and its oxygen analog, but the oxygen analog was not included in the validation run since non-detectable (<0.01 ppm) residues were in the corn commodities.) This method is suitable for residue analysis and enforcement of chlorethoxyfos. The limit of quantification is 0.01 ppm. Since the oxygen analog of these types of compounds may show higher toxicity, CBTS has now requested the registrant to supply validation data for the EPA lab to validate this method for the oxygen analog.

Another residue method for determining chlorethoxyfos and its oxygen analog is a capillary GC Method #AMR-1195-88 equipped with a mass spectrometric detector with a limit of quantification of 0.01 ppm. A capillary GC/EC method is also available for the analysis of TCA with a limit of quantification of 0.01 ppm.

No methods have been submitted for meat and milk, because the petitioner expected amounts of identifiable residues from the proposed use would not be finite (<0.01). This argument is supported by the petitioner's data.

cc: J. Stokes (CBTS); chlorethoxyfos S. F.; R.F.; Circu.
RDI: PErrico:12/20/94:RLoranger:01/03/95
7509C:CBTS:JStokes:js:Rm 803:CM#2:305-7561:03/07/95