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

EXPEDITE

MAY 11 1989

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: PP7F3540. DPX-L5300 (Express®) on Grain and Straw of Wheat and Barley. DEB Nos. 5134, 5135. MRID 41043101

FROM: R. W. Cook, Chemist
Tolerance Petition Section I
DEB/HED (H7509C)

TO: L. Schnaubelt, Acting PM 23
Fungicide-Herbicide Branch
Registration Division (H7505C)

and

Toxicology Branch, Fungicide-Herbicide Support
Health Effects Division (H7509C)

THRU: R. D. Schmitt, Acting Chief
DEB/HED (H7509C) Richard D Schmitt

DEFICIENCIES OUTSTANDING

Magnitude of the Residue

The deficiency regarding the magnitude of the residue on barley and wheat, as discussed in our memorandum of 4/26/88 and 4/21/89 has not been resolved. No new residue data was included in this submission to respond to this question.

CONCLUSION

A ruminant (goat) metabolism study has been submitted. At this time we are not requiring additional ruminant feeding studies nor are we requiring tolerances for residues of DPX-L5300 in meat or milk of cattle, hogs, horses, goats, or sheep. Ruminant animal feeding studies, and poultry metabolism and feeding studies may be required when tolerances at higher numerical levels are required for animal feed items than are currently required for wheat and barley grain (0.05 ppm) and wheat and barley straw (0.1 ppm).

Recommendation

We recommend against the proposed tolerances based upon the unresolved deficiency regarding the magnitude of the residue on barley and wheat.

DETAILED CONSIDERATIONS

The petitioner has responded in part to our previous reviews in which we have requested both ruminant metabolism and ruminant feeding studies in support of the proposed use on wheat and oats, and therefore on the straws of these commodities. The petitioner has contended that low residue levels in grain preclude the need for animal metabolism studies. However, based upon detectable residues in nature straw, we have requested ruminant metabolism and feeding studies.

In our initial screen of this subject petition, we noted that no information on the nature of the residue in animals was submitted (see New Chemical Screen, memorandum of 7/17/87). Further, we recommended (PP5G3296, 10/18/85) that animal feeding studies would be required if studies showed presence of residues in treated wheat or barley.

Nature of the Residue in Animals: Goat Metabolism MRID 41042101

The petitioner initiated a goat metabolism study in November 1986 and completed final analyses in January 1989. We can find no record of any protocol for this goat metabolism study in our files. The usual practice is to obtain RCB response regarding any particular protocol, prior to initiation of study; this did not happen in the current situation.

Two lactating nonpregnant goats of unspecified breed were purchased from a local farmer on 10/27/86. Goats were acclimated until being placed in metabolism cages. Goats were given a single capsule after the morning milking for 5 days. Urine, fecal, and milk samples were obtained. Milk samples were from morning and evening milkings for days 2, 3, and 4 and the evening of day 1 and morning of day 5. Urine and fecal samples were collected daily. Animals were fed dairy feed during milking, and water and alfalfa hay all other times. Dairy feed consumed was measured but not reported, and alfalfa consumption was not measured. The petitioner reports that usual consumption of food would be 1.5 kg/day; if the goats in this study consumed this amount (not reported), then the daily administered dose was 6.7 ppm of DPX-L5300. Additional details of animal husbandry are provided in the report.

Gelatin capsules were prepared to contain 10.02 mg of DPX-L5300 with 99.8 μCi of triazine-2-^{14}C-DPX-L5300 or 9.98 mg DPX-

L5300 with 95.5 μCi of phenyl-(U)-^{14}C-DPX-L5300. Dosing capsules were then placed inside larger capsules of feed. Additional details of capsule preparation are provided in the report.

The goats were sacrificed about 24 hours after last dose and samples of the following tissues were obtained.

Blood
Lungs
Liver with attached gall bladder
Kidney
Pancreas
Heart
Muscle: Flank
Loin
Leg
Fat: Back
Omental
Peripheral
Renal
Rumen/stomach contents
Intestinal contents

Sample weights were recorded and samples were frozen in plastic bags until analysis.

Results

The overall recovery of triazine-2-^{14}C and phenyl-(U)-^{14}C from goat tissues and excretions was 82 and 87 percent, respectively.

Excretion of both phenyl-(U)-^{14}C and triazine-2-^{14}C labels occurred primarily in urine 71 and 61 percent, respectively, and feces 15 and 20 percent, respectively. The ^{14}C labels occurred rapidly, within the first 24 hours after initial dosing. Excretion in combined urine and feces accounted 86 and 81 percent of the phenyl-(U)-^{14}C and triazine-2-^{14}C labels respectively.

The nature of the ^{14}C in urine and feces was examined. The primary residues, when urinary and fecal metabolites are considered together, were metsulfuron-methyl, saccharin, DPX-L5300, O-demethyl-N-demethyl-triazine-amine, DPX-L5300 acid, and hydroxylated metsulfuron methyl. The presence of such metabolites as saccharin and O-demethyl-N-demethyl-triazine amine are indicative of cleavage to fragments which could derive from several sources, i.e., other pesticides [triazines], artificial sweeteners, etc. The presence of metsulfuron methyl, and DPX-L5300 acid indicate relatively unmetabolized DPX-L5300 (or metsulfuron methyl) is excreted by ruminants.

In milk, the excretion of both triazine-2-^{14}C and phenyl-(U)-^{14}C varied according to the milking cycle; since the

daily capsule was administered after the morning milking, the evening milking showed higher ^{14}C residues than did the morning milking. The phenyl-(U)-^{14}C radiolabel totaled 0.05% of the administered dose, with the concentration of ^{14}C equivalent to DPX-L5300 ranging from 0.002 to 0.006 ppm in the daily milk. The triazine-2-^{14}C radiolabel residues were much higher, totaling 0.79% of the administered dose. The concentration of triazine-2-^{14}C in the study milk ranged from 0.03 to 0.09 ppm.

Samples of skim milk and cream, as separated from whole milk, were analyzed; skim milk contained 85 percent of the ^{14}C while cream was about 15 percent. The nature of the ^{14}C in skim milk (from triazine-2-^{14}C-DPX-L5300) was examined. The major identified ^{14}C metabolite was N-demethyltriazine amine, ranging from 0.01 to 0.02 ppm calculated as DPX-L5300 (14 to 29 percent of the total ^{14}C). Other identified milk metabolites, at <0.01 ppm calculated as DPX-L5300, were O-demethyltriazine amine (3.2 to 7.4% of total ^{14}C), α-hydroxytriazine amine (0.7 to 8.7 percent) and triazine amine (0.6 to 2.5 percent). DPX-L5300, metsulfuron methyl, DPX-L5300 acid and hydroxylated metsulfuron methyl were not observed. However, unextracted ^{14}C at 0.01 ppm calculated as DPX-L5300 constituted 12 to 21 percent of the total ^{14}C, and an unknown milk metabolite constituted 0.02 to 0.03 ppm calculated as DPX-L5300, or 42 to 54 percent of the ^{14}C present in skim milk. The petitioner concludes that since phenyl-(U)-^{14}C residues were about 1/10 the triazine-2-^{14}C residues and also given the absence of intact sulfonyl urea bridge, the unknown milk metabolite arises from the triazine portion of the molecule. The unknown milk metabolite was not cleaved by lipase or B-glucuronidase enzymatic treatment; this treatment showed both N-demethyl-triazine and the unknown milk metabolite were present at 0.02 ppm calculated as DPX-L5300.

The nature of the residue in livestock is adequately understood for this use unless Toxicology Branch is concerned with this 0.02 ppm of unknown metabolite equivalent to DPX-L5300. If that is the case, it may be necessary for the petitioner to more fully elucidate the nature of the residue in milk.

The petitioner analyzed other tissues and organs for ^{14}C. The nature of the ^{14}C was examined for tissues with adequate amounts of ^{14}C. A total of less than 0.5 percent of the administered dose was found in the assayed tissues and organs. Some tissues and organs contained ^{14}C levels below twice the background levels and these tissues and organs were not included in total recovery calculations. Levels of triazine-2-^{14}C and phenyl-(U)-^{14}C were not calculated in fat samples and phenyl-(U)-^{14}C was not calculated in muscle samples.

^{14}C in Goat Tissues and Organs

	Phenyl-^{14}C		Triazine-2-^{14}C	
	ppm	% dose	ppm	% dose
Blood	0.005	<0.01	0.012	0.02
Lungs	0.005	<0.01	0.017	0.02
Liver	0.084	0.23	0.029	0.09
Kidney	0.023	0.01	0.023	0.01
Pancreas	--	--	0.013	<0.01
Heart	0.003	<0.01	0.013	0.01
Gall Bladder	0.022	<0.01	0.022	<0.01
Muscle [1]	--	--	0.013	--
Fat [2]	--	--	--	--
Total		0.24%		0.15%

[1] Flank, Loin, Leg
[2] Back, Omental, Peripheral, Renal

From Tables 13 and 14.

The nature of the residue in liver and kidney samples was examined by extraction, proteinase K enzyme incubation and further, by acid or base hydrolysis of unextracted ^{14}C. For both triazine-2-^{14}C and phenyl-(U)-^{14}C in kidney, solvent extraction released the major portion of the residue, yielding 72 and 41 percent respectively. Kidney from the phenyl-(U)-^{14}C had about equal amounts of enzyme-extractables and unextractable materials 28 to 31 percent respectively, while for triazine-2-^{14}C goat kidney the figures are 11 to 17 percent, respectively.

Liver samples were analyzed in both freeze-dried (FD) and nonfreeze-dried (NFD) conditions. For the triazine-2-^{14}C goat liver there is no apparent difference in the effectiveness of extraction based on the freeze-drying process. The amount of triazine-2-^{14}C remaining unextractable in liver was high, 36 to 44%, although additional acid or base hydrolysis left only <15 percent unextractable.

Results for the phenyl-(U)-^{14}C goat liver were different. Only small amounts of phenyl-(U)-^{14}C were solvent extractable $\leq$6.3 percent in both freeze-dried and non-freeze-dried liver. In the freeze-dried liver, only 28 percent of the phenyl-(U)-^{14}C was enzyme extractable leaving 68 percent unextractable. For the non-freeze-dried liver, the results were reversed with 64 percent enzyme extractable and 30 percent unextractable. Freeze-dried unextractable phenyl-(U)-^{14}C was about half extractable by acid hydrolysis but 81 percent extractable by base hydrolysis. Non-freeze-dried liver showed much more acid-solubilized

phenyl-(U)-^{14}C than did freeze-dried liver. There is no ready explanation for the difference of extractability of phenyl-(U)-^{14}C between freeze-dried and non-freeze-dried goat liver.

In summary, the major pathway of metabolism in goats treated with phenyl-(U)-^{14}C-DPX-L5300 or triazine-2-^{14}C-DPX-L5300 was excretion via urinary and fecal processes, accounting more than 80 percent of the administered dose. Excretion via milk (lactation) was <1 percent of the administered dose. Metabolites with intact sulfonylurea bridge were metsulfuron methyl, DPX-L5300 per se, DPX-L5300 acid and hydroxylated metsulfuron methyl. Cleavage of the sulfonylurea bridge produced as metabolites saccharin, O-demethyl-N-demethyltriazine amine, N-demethyltriazine amine, triazine amine, sulfonamide, and acid sulfonamide.

In milk, triazine containing moieties were the predominant metabolites and no DPX-L5300 or other metabolites with intact sulfonylurea bridge were found. Residues in edible portions of meat (muscle) and fat were <0.013 ppm. In the organ meats, kidney, and liver residues were 0.023 to 0.084 ppm (calculated as DPX-L5300) with up to 35 percent unextractable by solvents, enzyme incubation, and acid hydrolysis (phenyl-(U)-^{14}C in liver).

Residues in grain are reportedly non-detectable at exaggerated application rates and in straw are occasionally present at levels less then the proposed 0.1 ppm tolerance level. Livestock consuming straw at a level of 10% in the diet would ingest <0.01 ppm DPX-L5300 per day. The goat metabolism adequately represents an exaggerated feeding level.

Based upon the submitted goat metabolism study, at this time we are not requiring additional ruminant feeding studies or tolerances on the raw agricultural commodities milk meat fat and meat byproducts of cattle, goats, hogs, horses, and sheep. This conclusion is based upon excretion rates in urine and feces, extraction rates in milk, and tissue residue levels. Even though the submitted study is not considered a feeding study, the study can substitute for the required ruminant feeding study.

When residues of DPX-L5300 occur in livestock animal feed items at finite levels higher than those contemplated herein, a ruminant feeding study may be required. Additionally, when residues of DPX-L5300 occur in poultry feed items, poultry metabolism and poultry feeding studies may be required.

If and when tolerances for residues of DPX-L5300 in meat, milk, poultry, or eggs are contemplated, we would consider the compounds containing the intact sulfonyl urea bridge as candidates for the tolerable residue. These would include, from this study, DPX-L5300, DPX-L5300 acid, metsulfuron-methyl, and

hydroxylated metsulfuron-methyl, plus any intact sulfonylurea bridge metabolites uncovered in a poultry metabolism study if required.

cc: RF,Circ,RCook,PP7F3540,DPX-L5300 Registration Standard File, TOX(RGardner),ISB/PMSD(EEldredge)
H7509C:DEB:RWCook:05/3/89:Rm810H:CM2:5577324:
RDI: SecHead:RSQuick:5/5/89:Acting Senior Branch Scientist: RALoranger:5/8/89
Draft KENCO Typing corrected 5/3/89:RWCook:5/9/89:RWCook 5/11/89:RWCook
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