PM 9/ISB

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

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

AUG 2 6 1989

MEMORANDUM

SUBJECT: Fonofos Registration Standard. Response by ICI Americas, Inc. Qualitative Nature of the Residue in Ruminants and Poultry. MRIDs 40657501 and 40749501. DEB No. 5401.

FROM: William O. Smith, Ph.D., Chemist
Reregistration Section
Dietary Exposure Branch (DEB)
Health Effects Division (H7509C)

THROUGH: William Boodee, Section Head
Reregistration Section
Dietary Exposure Branch
Health Effects Division (H7509C)

TO: William H. Miller, PM #16
Insecticide-Rodenticide Branch
Registration Division (H7505C)

INTRODUCTION

ICI Americas, Inc. has submitted two studies on the nature of [^{14}C]fonofos residues in goat tissues and milk and in poultry tissues and eggs. These studies were submitted in partial response to data requirements identified in the Reregistration Guidance Document (dated 3/84) for fonofos. In the cover letters accompanying these submissions (letter of July 15, 1988; MRID 40749500 and letter of June 10,1988; no MRID assigned), the registrant claimed that these data satisfy the outstanding data gaps for the qualitative nature of the residue in animals and the magnitude of the residue in meat, milk, poultry and eggs. At present there are no established tolerances for fonofos residues in animal commodities.

DATA GAPS OF CONCERN

Guideline 171-4-Qualitative Nature of the Residue in Animals

A lactating ruminant (cow or goat) metabolism study and a poultry metabolism study are required. Should the studies require a change in the existing nature of the tolerance to include other components, new analytical methods may also be necessary.

Guideline 171-4-Magnitude of the Residue in Meat, Milk, Poultry and Eggs

No conclusion can be drawn about the carry-over of residues and the need for tolerances for residues in meat, milk, poultry and eggs until the requested metabolism (poultry and large lactating ruminant) studies, as well as the new feeding studies, have been submitted and evaluated.

THE REGISTRANT'S RESPONSE

The registrant has submitted the following studies in response to these data gaps.

MRID 40657501 L.J. Servatius and L.C. Wilkes (1988) Nature of the Residue in Lactating Goats Orally Dosed with [Phenyl-^{14}C]Dyfonate (Fonofos).

MRID 40749501 L.J. Servatius and L.C. Wilkes (1988) Nature of the Residue in Laying Hens Orally Dosed with [Phenyl-^{14}C]Dyfonate (Fonofos).

CONCLUSIONS

1(a). The qualitative nature of the residue in animals is adequately understood; however, should the potential dietary burden of fonofos for ruminants increase substantially due to future changes in established uses, additional characterization of polar residues in liver and kidney may be necessary.

1(b). The terminal residue of concern in meat, milk, poultry and eggs is methyl phenyl sulfone. It should be noted that the terminal residue in plant commodities consists of fonofos and its oxygen analog.

2(a). Enforcement analytical methods will be required for residue monitoring purposes in meat, milk, poultry and eggs.

2(b). If the need for establishment of tolerances for residues in livestock commodities is determined (see conclusion 6), then additional validated methods for data collection in these commodities will be required.

3. If the need for establishment of tolerances for residues in livestock commodities is determined, then additional data will be required demonstrating the storage stability of the residues of concern in these commodities.

4. Residue field trial data have not been received for potatoes, radishes, sweet potatoes, radish tops, peppers, corn (field/pop/sweet), corn fodder & forage, asparagus, peanuts, sugarcane, and tobacco. Therefore, these requirements are still outstanding.

5. Data have not been received concerning the potential for fonofos residues to concentrate in processed commodities of potatoes, and sorghum. Therefore, these data are still outstanding.

6. The need for tolerances for residues in animal products and/or the need for conventional feeding studies cannot be determined until all of the outstanding data gaps in the magnitude of the residue in livestock feed items (conclusions 4 and 5) have been resolved.

RECOMMENDATIONS

The registrant should be advised of the conclusions reached in this review. A recommendation concerning the need for tolerances for residues in meat, milk, poultry and eggs and/or conventional feeding studies is reserved pending resolution of deficiencies in the data concerning the magnitude of residues in feed items.

DETAILED CONSIDERATIONS

ICI Americas, Inc. (1988; MRID 40657501) submitted data from a study of fonofos metabolism in three lactating goats. The test animals received twice-daily oral capsular doses of [phenyl-^{14}C]fonofos (specific activity 30 μCi/mg; radiochemical purity 98%) for 4 consecutive days. Two of the animals received doses of ca. 0.5 mg/kg body wt./day (equivalent to 3 ppm in the feed) and one animal received ca. 2.8 mg/kg body wt./day (equivalent to 15 ppm in the feed). Samples of milk were collected twice a day; urine and feces were sampled once a day. Blood, gut contents, muscle, liver, kidney, and fat tissues were sampled at sacrifice, ca. 13 hours following the final dose. Total ^{14}C-activity was quantified in milk and urine by direct liquid scintillation

counting (LSC) and in milk fat, gut contents, tissues, and feces by combustion/LSC.

^{14}C-Residues were extracted from tissue samples with acetone (milk, muscle), 1 N HCl/acetone (fat), methanol (liver), or water (kidney) and fractionated via solvent partitioning into various organic- and aqueous-soluble fractions. Residues from fat samples were further cleaned up by chromatography on an XAD-4 column. Aqueous extracts of kidney and liver were subjected to enzyme (glucuronidase/sulfatase) and acid hydrolysis. ^{14}C-Residues were identified by their Rf values on silica gel thin layer chromatography (TLC) plates. Identities were confirmed by additional TLC in one or more 2-dimensional solvent systems. Standards used for comparison (see attachment 1) were dyfonate (fonofos), dyfonate oxon, p-hydroxy oxon, methyl phenyl sulfoxide, methyl phenyl sulfone, 2-hydroxy methyl sulfone, 4-hydroxyphenyl methyl sulfone, and benzene sulfonic acid.

A total of 73-87% of the ^{14}C-activity administered to the animals was recovered from the urine (38-57%), feces (11-14%), milk (2.2-2.9%), and tissue samples (14-20%). Fonofos-equivalent residues in fat (0.58 ppm), muscle (0.43 ppm), kidney (1.42 ppm), and liver (1.39 ppm) tissues collectively accounted for 7.4% of the total dosage recovered in the goat receiving 15 ppm fonofos in its feed. Total ^{14}C-residues in the milk increased to ca. 0.1 ppm fonofos equivalents on the fourth day in goats receiving the 3 ppm dosage and to ca. 0.5 ppm in the goat receiving 15 ppm.

Two samples of milk from the higher-dose goat were analyzed for metabolites. Approximately 96-100% of the ^{14}C-activity in milk was soluble in acetone. Methyl phenyl sulfone (see attachment 1 for structure), the only metabolite detected, comprised 96-100% of the extractable ^{14}C-residues in these samples.

Methyl phenyl sulfone was the major metabolite in all of the tissue samples (Table 1), comprising 32-97% of the total radioactive residue (TRR). The only other metabolite identified was 3-hydroxyphenyl methyl sulfone, present as 6.5% of the TRR in kidney. There was no significant insoluble radioactivity in fat, muscle, and kidney but ca 17% of the residues in liver were un-extractable. The registrant reported that considerable losses of radioactivity were incurred via volatility during early attempts at cleanup procedures. These losses were reduced by including mineral oil in extracts before evaporation and not completely drying samples.

Approximately 20-30% of the ^{14}C-activity in the liver and kidney was of a polar, presumably conjugated, nature which was unaffected by either enzyme or acid hydrolysis.

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Table 1. Partial characterization of ^{14}C-residues in tissues of lactating goats following oral dosing for 4 days with [phenyl-^{14}C]fonofos.

^{14}C-Residues	Percent of TRR in sample			
	fat	muscle	kidney	liver
Extractable	95	98	92	73
Solubility[1]				
Nonpolar	96	98	44	6.9
Polar	0.4	1.1	44	74
Final recovery[2]				
Nonpolar	84	99	41	-[3]
Polar	-	-	28	70
Metabolites[4]				
methyl phenyl sulfone	82	97	32	50
3-OHPhSO$_2$Me	N.D.[5]	N.D.	6.5	N.D.
nonpolar unknowns	2	2.5	3	-
polar unknowns	-	-	28	20
Total identified	82	97	38	50

[1] The partitioning of radioactive residues between methylene chloride/water (fat and muscle), ethyl acetate/water (kidney), or pentane/methanol (liver).
[2] Radioactive residues remaining after sample cleanup.
[3] Not analyzed.
[4] See attachment 1 for structures of metabolites.
[5] Nondetectable.

ICI Americas, Inc. (1988; MRID 40749501) submitted data from a study of fonofos metabolism in 10 laying leghorn hens. The animals received twice-daily oral capsular doses of [phenyl-^{14}C]fonofos (specific activity 30 μCi/mg; radiochemical purity 98%) for 4 consecutive days. One group of 4 hens received doses of ca. 3 ppm in the feed and another group of 6 hens received doses of ca. 15 ppm in the feed. Eggs were collected twice daily and separated into whites and yolks, which were pooled for analysis. Total excreta was collected daily. Muscle, liver, kidney, blood, contents of the G.I. tract, and fat tissues were sampled when the chickens were sacrificed 14 hours following the last dose. ^{14}C-Residues were extracted from tissue samples with water/acetone (muscle and kidney), 1 N HCl/acetone (fat), methanol (liver), or acetonitrile (egg whites and yolks). Extracts from liver, muscle, fat and egg yolks were further

cleaned up for analysis by solvent partitioning. Total ^{14}C-residues were determined by LSC or combustion/LSC and metabolites were identified by the same TLC systems as described above for the goat study (MRID 40657501).

A total of 73-76% of the ^{14}C-activity administered to the two groups of animals was recovered from excreta (62-65%), eggs (1-1.4%), and tissue samples (9.1-9.2%). Fonofos-equivalent residue concentrations in the edible tissues from hens receiving doses of 3 ppm and 15 ppm were as follows: fat, 0.19 and 1.2 ppm; muscle, 0.14 and 0.82 ppm; and liver, 0.23 and 1.59 ppm. TRR in egg whites and yolks, respectively, increased to ca. 0.12 ppm and 0.19 ppm on the fourth day in hens receiving the 3 ppm dosage and to ca. 0.64 ppm and 1.03 ppm in the hens receiving 15 ppm.

The radioactive residues in tissues and eggs were soluble in the initial extracts (88-104% recovery) but, as was the case with the lactating goat study, significant losses occurred via volatility during preparation of some of the samples for analysis. The final recoveries of radioactivity were as follows: 96% from fat, 94% from muscle, 74% from liver and kidney, 82% from egg white, and 103% from egg yolk. TLC analysis of the remaining radioactive residues identified only one metabolite, methyl phenyl sulfone. This metabolite accounted for 81-103% of the radioactivity in the cleaned up samples. The only significant unidentified radioactive zone on the TLC plates, presumably of polar nature, remained at the origin in the analysis of residues in kidney. This unidentified material accounted for 6.8% of the TRR in the kidney.

In summary, the fonofos residue of concern in ruminant tissues and milk is methyl phenyl sulfone. From 40% to 100% of the terminal residue was identified in goat tissues and milk and the only other metabolite identified was 3-hydroxyphenyl methyl sulfone, accounting for 6.5% of the TRR in kidney. Residues in milk, fat, and muscle were present in organosoluble (nonconjugated) form. Kidney and liver contained polar conjugates, which were resistant to either enzyme or acid catalyzed hydrolysis. Because the presently established uses of fonofos should not result in detectable levels of residues in meat or milk, further characterization of these metabolites will not be required. However, should the potential dietary burden of fonofos for ruminants increase due to concentration in feed items or due to future registration requests, additional characterization of residues may be necessary.

The qualitative nature of the residue in poultry is adequately understood. The residue of concern is the methyl phenyl sulfone metabolite.

OTHER CONSIDERATIONS

The registrant has claimed in cover letters accompanying the ruminant and poultry metabolism submissions (letter of July 15, 1988; MRID 40749500 and letter of June 10,1988; no MRID assigned) that the data indicate no need for tolerances for residues on meat, milk, poultry and eggs. This argument was based on the assumption that the highest level of residue in any potential feed item would not exceed 0.1 ppm. Linear extrapolation of the residue levels occurring in meat, milk, poultry and eggs as the result of 4-day metabolism studies conducted at feeding levels of ca. 3 ppm and 15 ppm indicated that nondetectable levels of residues would occur in these commodities even in the worst-case exposure of livestock to feeds that had been treated with fonofos. DEB cannot accept this claim and defers any further consideration of the need for tolerances and/or further data concerning the magnitude of the residue in animal commodities until data gaps concerning the magnitude of the residue in feed items has been resolved.

Attachment

cc: RF, SF, Fonofos Registration Standard File, Reviewer (W. Smith), PMSD/ISB (Eldridge).

RDI: WB: 08/26/89: RP: 08/26/89: EZ: 08/26/89.
H7509C: DEB: WS: ws: CM #2: RM 812D: 557-4353: 06/07/89.