PM 52 ESB

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

SEP 29 1988

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Ethyl Parathion: Supplement to Final Report (MRID# 402889-02): Nature of the Residue in Livestock-Lactating Goats (MRID# 406238-03), (RCB# 3935).

FROM: Freshteh Toghrol, Ph.D., Chemist F. Toghrol
Dietary Exposure Branch
Health Effects Division (TS-769C)

THRU: Philip Errico, Section Head
Tolerance Petition Section III
Dietary Exposure Branch
Health Effects Division (TS-769C)

TO: Dennis H. Edwards, PM#12
Insecticide/Rodenticide Branch
Registration Division (TS-767)

The Petitioner A/S Cheminova has submitted a supplement to the final report "Ethyl Parathion [O,O-diethyl-p-(acetamidophenyl)phosphate]: Nature of the Residue in Livestock-Lactating Goats" (MRID# 402889-02) identifing the labeled parathion metabolites. The analytical portion of the studies was completed by Hazleton Laboratories America Inc of Madison, WI. The study was completed on 5/10/88.

Tolerances have been established for residues of the insecticide ethyl parathion or its methyl homolog in or on more than one hundred commodities with tolerances ranging between 0.1 to 5.0 ppm (40 CFR 180.121). No food or feed additive tolerances have been established. No tolerances have been established for meat, milk, poultry and eggs.

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Summary of Previously Submitted Metabolism Study in Lactating Goats:(MIRD#402889-02)

The petitioner A/S Cheminova previously (8/4/87) submitted a study of the residue of labeled parathion in ruminants and poultry. The results of ^{14}C distribution in different tissues were submitted in " Final Report: Ethyl Parathion: Nature of the Residue in Livestock - Lactating Goats" (See review of S. Hummel, 10/29/87).

Two lactating goats were fed [Ring-^{14}C]-ethyl parathion at 188 mg/day, equivalent to a dietary level of 96.9 ppm for 5 consecutive days. One control goat received capsules containing an inert carrier. Samples of round muscle, renal, omental fat, kidney, liver and bile were collected after the animals were sacrificed. Milk, urine and feces were collected during the study. The total recovery of radioactivities was 36.6% to 42.4% with 23.5% to 25.6% in urine, 12.1% to 15.5% in feces, 0.18% to 0.2% in milk and <0.01% to 0.16% in the collected tissues kidneys, liver, round muscle, renal fat and omental fat.

Table I

Distribution of Radioactivity in Goat Tissues and Excreta

Matrix	percent of total dose		Residue ppm a Parathion Equivalents)
	Animal 0.092	Animal 0.088	
Kidney	0.08	0.07	4.43-5.46
Liver	0.76	0.57	5.26-6.33
Round Muscle	0.08	0.03	0.32-0.75
Omental Fat	0.03	0.03	0.34-0.86
Renal Fat	<0.01	0.03	0.34-0.90
Milk	0.20	0.18	0.45-1.03
Bile	0.16	0.08	30.9-35.3
Urine	25.6	23.5	
Feces	15.5	12.1	
Total	42.4	36.6	

a: Residue range of radioactivity in both lactating goats.

This report did not identify the labeled metabolites. In addition the amount of labeled residues were not reported in blood and gastrointestinal tract tissues. There was no accountability for 57% to 63% of the dosed radioactivity (in ethyl parathion equivalents). The tissue samples were rinsed with cool water and then frozen.

Summary of the Identification of Ethyl Parathion Metabolites in Lactating Goats:(MIRD# 406238-03)

In the present report "Supplement No. 1 to Final Report", the labeled metabolites in milk and tissues of goat have been identified and characterized.

The matrices from lactating goat # 0.092 was used for this study (table I). The time period from sample collection (tissues) till analysis was 9 months . Milk and homogenized tissues were extracted by chloroform/methanol (1/1) in the presence of zinc sulfite. This extraction recovered 65% to 95% of the ^{14}C compounds, a higher recovery than with methanol alone. The extract was evaporated to dryness, then cleaned up using C-18 Bond-Elut column and was eluted by different solvents, water, methanol, chloroform, acetonitrile and hexane (table II). The extractable radioactivity ranged from 82.6% to 97.1% and the nonextractable radioactivity ranged from 5.8% to 22.4%.

Table II

Distribution of radioactivity in extractable matrices

	% of Radioactivity in Matrix				
Matrix	Water	Methanol	Chloroform	Acetonitril	Hexane
Liver	14.0	58.9	-	-	-
Kidney	36.7	35.7	-	-	-
Renal fat	- -	67.7	5.29	1.25	18.1
Muscle	0.51	64.2	28.8	-	ND

\- Not applicable.
ND Not detectable.

One major metabolite in milk "unknown Y" was hydrolysed by alkaline hydrolysis. One hydrolysate was identified as p-acetamidophenol by HPLC and mass spectrometry, and the other was designated as "unknown X". These two components were also detected in tissue extracts (see table III).

Table III

HPLC Alkaline Hydrolysate Profile

Percentage of Radioactivity in Matrix

Matrix	Unknown X	p-Acetamidophenol	p-Acetamidoparaoxon
Milk extract	15.4	37.5	14.4
Milk	5.38	43.7	28.8
Muscle extract	12.4	33.1	5.6

Identification and quantitation of labeled metabolites were obtained by HPLC and TLC. Ethyl parathion, aminoparathion, nitrophenol, p-acetamidophenol, and O,O-diethyl-p-(acetamidophenyl) phosphate were identified among the terminal ^{14}C-residues in milk and tissue extracts.
The parent compound ethyl parathion (0.019- 0.563 ppm) was found in all examined matrices.

Fat had the highest percentage of total activity. The amount of radioactivity identified in the various tissues and milk were reported as follows: milk, 75%; liver, 54.5%; kidney, 58.8%; renal fat, 47.6%; and muscle, 54.7%.

The major metabolite reported, O,O-diethyl-p-(acetamidophenyl)phosphate(p-acetamidoparaoxon), was detected in all examined matrices from 19.3% to 70.7% of total activity, with milk containing the most. The levels ranged from 0.208 to 2.02 ppm. Liver had the highest level (2.02 ppm). In milk (0.723 ppm), kidney (1.05 ppm), muscle (0.291 ppm) and fat (0.208 ppm) were found (see table IV).

Based on the identification of the metabolites, the petitioner has proposed a metabolic pathway. Ethyl parathion is reduced to aminoparathion, which through desulfuration and acetylation will produce diethyl-p-acetoamidoparaoxon (main metabolite in this study). Hydrolysis of this compound will change the phenol-phosphate to the corresponding phenol.(see figure 1)

DEB COMMENTS/CONCLUSION:

1. The study results have only accounted for 37-42% of the label radioactivity. The protocol included in the goat metabolism report with MIRD#402889-02 (HLA 6222-101) states that blood and gastrointestinal tract will be collected. The

amount of radioactivity for these samples was not reported. In any case, the petitioners should account for the remaining ^{14}C-radioactivity fed. We note that the protocol calls for rinsing the tissues after sacrifice. The amount of radioactivity in the wash water should also be included.

2. The petitioner has only identified 48-59% of the radiolabeled residues in tissue and 75% in milk. The petitioner must identify the remaining labeled residues. The major terminal residues reported in tissue and milk, so for, are the parent compound, ethyl parathion and its metabolites, p-acetamido paraoxon and p-acetamidophenol; p-nitrophenol and p-amino-parathion are minor metabolites.

3. The tolerance expression should consist of at least the parent compound ethyl parathion and its metabolite, p-acetamidoparaoxon. We will defer to Tox on the remaining metabolites after the nature of the residue in lactating ruminants is adequately discerned.

4. The Residue Chemistry Chapter of the Parathion Registration standard (4/8/85) indicates that residues of parathion in or on plants will decrease by 50 percent after 6 months in frozen storage. In lactating goat metabolism studies, the samples have been in the freezer for about 16 months and yet there is no storage stability data. Additional characterization of residues must be accompanied by storage stability data with known standards to ensure that the metabolites found are not resulting from degradation in storage.

5. We reiterate the conclusion in our memo by S. Hummel (10/29/87). Residues of ethyl parathion and its major metabolites do transfer to milk and tissue; A feeding study in a lactating ruminant is needed. Feeding levels should be high enough to cover the established tolerances and any future tolerance requests, together with two exaggerated levels of 3X and 10X.

6. Assuming no additional residues will require inclusion in the tolerance expression, analytical methodology adquate for enforcement purposes should be submitted to determine p-acetamidoparaoxon in tissues and milk. Any proposed enforcement method must pass a method validation by the Agency. The petitioner should also be aware that any proposed method for enforcement submitted after 8/1/88 must be accompanied by an independent laboratory confirmation. The metabolite must also be run through the FDA multiresidue methods. A copy of PR notice 88-5 (Independent laboratory confirmation by petitioner) and the multiresidue method testing protocol are included with this review for the petitioner's convenience. Stability studies in stored samples must also be submitted to support the results of the feeding study.

Note: In table 2 of this report (under extractable portion of milk) the value 58.9 appears to be a typographical errors. The petitioner should verify that this is a typo and give the correct value.

Tables and figure used in this memo have been taken from the nature of the residue studies in livestock-lactating goats (MIRD #, 402889-02, 406238-03, HLA6222-101, dated 8/4/87, 5/10/1988).

cc: with all attachments: Dennis Edwards /PM#12
Attachment # 1 - PR notice 88-5
Attachment # 2 - Multiresidue Method Testing Protocol
Attachment # 3 - Decision Free for MRM Testing

cc: without attachments: Freshteh Toghrol, Ethyl parathion, Circ., SF, RF, Reg. S. File, PMSD/ISB
RDI: PE 9/28/88 RDS:9/28/88
TS-769C: DEB: FT: CM#2, RM:803, 557-7561, (9/28/88).

Table IV

HPLC Metabolite Profile of Milk and Tissues

Matrix	Unknown X	p-Acetamidophenol	p-Nitrophenol	p-Acetamido-paraoxon	p-Amino-Parathion	Ethyl Parathion
			Percentage of Radioactivity in Matrix			
Milk	ND	ND	ND	70.7	2.50	1.83
Liver	ND	9.90	ND	31.9	3.79	8.90
Kidney	8.25	17.2	1.73	19.3	3.53	8.80
Renal fat	3.30	2.94	ND	23.0	2.24	16.1
Muscle	1.74	0.73	9.18	40.4	ND	2.66
			ppm [Ring ^{14}C]-Ethyl Parathion Equivalent			
Milk	ND	ND	ND	0.723	0.026	0.019
Liver	ND	0.627	ND	2.02	0.240	0.563
Kidney	0.450	0.938	0.094	1.05	0.193	0.480
Renal fat	0.030	0.027	ND	0.208	0.020	0.146
Muscle	0.013	0.005	0.066	0.291	ND	0.019

ND Not detectable.

Figure 1

Proposed metabolism pathway of ethyl parathion administered orally to lactating goats