

MEMORANDUM

SUBJECT: Imazalil. Hen and Ruminant Metabolism Studies. To be Presented to The HED Metabolism Committee on August 8, 1994.

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TO: HED Metabolism Committee
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Jenssen has submitted hen and goat metabolism studies to satisfy GLN 171-4(b) for reregistration of imazalil.

In poultry (66 ppm, 360x exaggerated dose), mean concentrations of TRR in the egg, egg shell, muscle, skin, and fat were as follows: 0.25 ppm (day 1) to 0.81 ppm (day 6) in yolk and white; 0.02-0.58 ppm in egg shells; 10.2 ppm in liver; 0.13 ppm (breast) and 0.165 ppm (thigh) in muscle; 0.435 ppm in skin; and 0.12 ppm (abdominal) and 0.126 ppm (skin) in fat.

The distribution and characterization of imazalil residues in various matrices is tabulated below. See Attachment for structures (L. Cheng, 7/14/94, CBRS 13374).

Table 1. Distribution and characterization of imazalil residues in hen matrices by HPLC.

Fraction	% TRR	ppm	Characterization/identification
Liver, 10.2 ppm			
Ethyl acetate	20.5	2.08	>14 components: FK 858 (4.0%), FK 861 (0.7%), FK 772 (1.3%), FK 326 (1.1%)
Soxhlet	12.9	1.31	>9 components: FK 259 (2.7%), FK 858 (1.3%), FK 839 (0.8%), FK 772 (0.6%)
Aqueous*	46	4.88	>16 components: FK 839 (4.4%), FK 772 (7.3%), FK 858 (3.2%)
PES**	21.1	2.15	4 fractions: 1.1%, 3.4%, 10.1%, 6.3%
Muscle, 0.15 ppm			
Ethyl acetate	50.5	0.075	>10 components: FK 858 (14.7%), FK 326 (6.7%), FK 259 (6.9%)
Soxhlet	8	0.012	N/A (not analyzed)
Aqueous*	13	0.019	N/A
PES	32.6	0.048	3 fractions: 7.2%, 22.4%, 3%

Fat, 0.14 ppm			
Ethyl acetate	39.1	0.048	>13 components: parent (10.7%), FK 284 (9.8%) N/A
Aqueous*	15	0.018	3 fractions: 15.2%, 37.1%, 9.9%
PES	62.2	0.076	
Eggs, 0.78 ppm			
Ethyl acetate	51.5	0.40	>7 components: parent (7.7%), FK 858 (11.1%), FK 326 (7.8%), FK 259 (7.3%), FK 772 (5.2%), FK 839 (3.2%), FK 284 (1.8%)
Aqueous*	33.3	0.26	>5 components: FK 839 (3.4%), FK 861 (0.6%), FK 772 (0.9%); one non-hydrolyzed fraction (15.2%) consisted of several components 4 fractions: 4.4%, 2.5%, 4.8%, 3.1%
PES	14.7%	0.115	

*before and after hydrolysis; **post-extractions solids

Parent was found only in eggs and fat. Metabolite FK 858 (bishydroxylated imazalil) and FK 259 (1-(2,4-dichlorophenyl)-2-aminoethanol) seem to be the most prevalent components which were found in liver, muscle, and eggs. FK 284 was found in fat and eggs. Metabolites deriving from oxidation and ring opening of the imidazole ring were also detected. In their proposed metabolic pathway, the registrant pointed out that FK 411 (despropenyl imazalil) was not found.

	Liver	Muscle	Fat	Eggs
Parent			10.7%	7.7%
FK 858	8.5%	14.7%		11.1%
FK 861	0.7			0.6
FK 772	9.2			6.1
FK 326	1.1	6.7		7.8
FK 259	2.7	6.9		7.3
FK 839	5.2			6.6
FK 284			9.8	1.8

In ruminant, parent imazalil was identified as 6.6% of TRR in fat, and smaller portions in other tissues. Major metabolites identified or characterized were FK1524, 29.7% of TRR in fat; FK284, 14.4% of TRR in muscle and 11.0% of TRR in fat; FK772, 15.1% of TRR in kidney and 20.2% of TRR in muscle; and MS4, 10.9% of TRR in milk. Unextracted and unanalyzed residues in tissues represented less than 10% of TRR or less than 0.05 ppm (J. Abbotts, 2/17/93, CBRS No. 10589 & 11220; 8/17/93, CBRS No. 12303).

Table 2. Overall Assignment of Imazalil Goat Metabolites.

Metabolite	% of TRR in: (TRR for each tissue in parentheses)				
	Milk (0.99 ppm)	Liver (19.8 ppm)	Kidney (9.6 ppm)	Muscle (0.36 ppm)	Fat (0.09 ppm)

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Parent	ND	6.4	3.6	2.5	6.6
FK 1524	ND	ND	ND	ND	29.7
FK 1454	ND	5.0	ND	6.6	ND
FK 274	0.9 (C)	0.6	ND	ND	6.6
FK 411	3.3 (C)	1.0	ND	ND	ND
FK 284	6.2	2.3	ND	14.4	11.0
FK 326	2.2	4.5	2.7	8.0	ND
FK 582	1.3	ND	ND	ND	ND
FK 258	2.9	ND	2.9	ND	ND
FK 858	3.3	2.9	1.5	ND	ND
FK 772	5.3	4.4	15.1	20.2	ND
FK 839	7.0	2.2	0.5	ND	ND
FK 861	0.9 (C)	0.6	ND	ND	ND
MS 1	8.0				
MS 3	1.3				
MS 4	10.9				
Total % TRR Identified	53.5	29.9	26.3	51.7	53.9

Table notes:

ND = nondetectable. (C) = detected only as conjugate.

For structures of parent and metabolites, see Figures 2-4.

MS1, MS3, and MS4 were determined only in milk.

