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

6F4664

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

DATE: 9/18/97

SUBJECT: PP# 6F04664. Isoxaflutole in/on Field Corn and Animal RACs. Request for Revised Anticipated Residues. Barcode D238727. Chemical 123000. Case 287353.

FROM: George F. Kramer, Ph.D., Chemist
RABI/HED (7509C)

THROUGH: Melba Morrow, Branch Senior Scientist
RABI/HED (7509C)

TO: Barbara Madden, RCAB
Health Effects Division (7509C)

Rhône-Poulenc Ag Company has proposed permanent tolerances for the combined residues of the herbicide isoxaflutole and its metabolites 1-(2-methylsulfonyl-4-trifluoromethylphenyl-2-cyano-3-cyclopropyl propane-1,3-dione (RPA 202248) and 2-methylsulfonyl-4-trifluoromethyl benzoic acid (RPA 203328), calculated as the parent compound, in/on:

Field Corn, Grain -- 0.20 ppm | Field Corn, Fodder -- 0.50 ppm
Field Corn, Forage -- 1.0 ppm

Tolerances are also proposed for the combined residues of the



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herbicide isoxaflutole and its metabolite RPA 202248, calculated as the parent compound, in/on:

Milk	--	0.02 ppm		Liver*	--	2.0 ppm
Poultry, Liver	-	2.0 ppm		Kidney*	--	0.40 ppm
Meat Byproducts (except liver and kidney)*	--	0.20 ppm				

*of cattle, goat, hogs, poultry and sheep

The DRES run using tolerance level residues resulted in a cancer risk (3×10^{-6}) which exceeded HED's level of concern. RCAB has requested that RAB1 provide anticipated residues for isoxaflutole in corn and animal RACs and processed commodities. These anticipated residues were provided to RCAB in our Memo of 8/20/97 (G. Kramer, D237699). However, in a subsequent HED Metabolism Assessment Review Committee Meeting (9/4/97), it was determined the isoxaflutole metabolites RPA 207048 and RPA 205834 need to be included in the risk assessment for animal commodities. RCAB has thus requested that RAB1 provide revised anticipated residues which reflect this decision.

Anticipated Residues

Table 1. Summary of Isoxaflutole Anticipated Residues for Dietary Risk Assessment (Acute Endpoints).

Commodity	Required Tolerance (ppm)	Anticipated Residue for DRES Run (ppm)
Corn Grain	0.20	0.015
Corn grits	-	0.014
Corn oil	-	0.005
Corn sugar	-	0.022
Liver	0.50	0.85 ¹
Meat	0.20	0.26 ¹
Fat	0.20	0.48 ¹
Meat by-products (except liver)	0.20	0.23 ¹
Milk ²	0.02	0.0014
Eggs ³	0.01	0.021
Poultry meat	0.20	2.1
Poultry fat	0.20	0.35
Poultry meat by-products	0.30	0.30

- 1 These anticipated residues should be used for beef, horses, hogs, goats and sheep in the DRES run.
- 2 Based on the results of the feeding studies and the chemical nature of isoxaflutole and its metabolites, concentration of residues in milk fat is not expected.
- 3 Based on the results of the feeding study, residues in egg whites are not expected.

Table 2. Summary of Isoxaflutole Anticipated Residues for Dietary Risk Assessment (Chronic Endpoints).

Commodity	Value for TMRC Calculation (ppm)	Anticipated Residue for DRES Run (ppm)
Corn Grain	0.20	0.015
Corn grits	0.20	0.014
Corn oil	0.20	0.005
Corn sugar	0.20	0.022
Liver	0.85 ¹	0.041 ¹
Meat	0.26 ¹	0.0017 ¹
Fat	0.48 ¹	0.00048 ¹
Meat by-products (except liver)	0.23 ¹	0.0056 ¹
Milk ²	0.036	0.00022
Eggs ³	0.021	0.000089
Poultry meat	2.1	0.000023
Poultry fat	0.36	0.000017
Poultry meat by-products	0.30	0.015

- 1 These anticipated residues should be used for beef, horses, hogs, goats and sheep in the DRES run.
- 2 Based on the results of the feeding studies and the chemical nature of isoxaflutole and its metabolites, concentration of residues in milk fat is not expected.
- 3 Based on the results of the feeding study, residues in egg whites are not expected.

DETAILED CONSIDERATIONS

In our review of 8/20/97, the following ARs were calculated:

Table 3. Summary of Isoxaflutole Anticipated Residues for Dietary Risk Assessment (Chronic Endpoints) initially calculated by RAB1.

Commodity	Required Tolerance (ppm)	Anticipated Residue for DRES Run (ppm)
Corn Grain	0.20	0.015
Corn grits	-	0.014
Corn oil	-	0.005
Corn sugar	-	0.022
Liver	0.50	0.024 ¹
Meat by-products (except liver)	0.02	0.0049 ¹
Milk ²	0.02	0.00012
Poultry meat by-products	0.30	0.015

¹ These anticipated residues should be used for beef, horses, hogs, goats and sheep in the DRES run.

² Based on the results of the feeding studies and the chemical nature of isoxaflutole and its metabolites, concentration of residues in milk fat is not expected.

In order to adjust the ARs for the presence of the isoxaflutole metabolites RPA 207048 and RPA 205834, the percentage of the total toxic residue (TTR) occupied by these metabolites must be determined. The tolerance values and previous ARs were based on the combined residues of isoxaflutole and its metabolite RPA 202248. The adjustment factor is determined by dividing the TTR by the sum of isoxaflutole and RPA 202248:

$$\frac{[\text{isoxaflutole} + \text{RPA 202248} + \text{RPA 207048} + \text{RPA 205834}]}{[\text{isoxaflutole} + \text{RPA 202248}]}$$

Table 4- Adjustment factors for animal commodities.

Animal	Commodity	% of TTR Comprised of Isoxafutole + RPA 202248	Adjustment Factor
Ruminant	Liver	59	1.7
	Kidney	88	1.1
	Muscle	77	1.3
	Fat	42	2.4
	Milk	56	1.8
Poultry	Liver	100	1.0
	Muscle	9.5	10.5
	Fat	57	1.8
	Egg Yolk	49	2.1

Ideally, the results of the animal feeding studies should be used to calculate the adjustment factors. However, in the isoxafutole feeding studies, ruminant liver was the only commodity which contained quantifiable residues of RPA 207048 and RPA 205834. The results of the animal metabolism studies were thus used to calculate adjustment factors for all other commodities.

Ruminant Commodities

The acute ARs (Table 1) are determined by multiplication of the required tolerances by the adjustment factors, except for milk which is considered to be a blended commodity. For milk, the acute AR is based on a diet (0.76 ppm) comprised of corn grain with average residues (0.015 ppm, blended commodity) and corn silage with the highest average field trial value (0.75 ppm, non-blended commodity).

For liver, meat by-products (except liver), and milk chronic ARs (Table 2), our previously calculated ARs were multiplied by the adjustment factors shown above. The tolerance values also must be adjusted for calculation of the TMRC.

Based on the decision of the HED Metabolism Assessment Review Committee, tolerances are now required for ruminant meat and fat. The required tolerance for these commodities, 0.20 ppm, is based on the LOQ of the proposed analytical enforcement method. The anticipated residues for the chronic dietary risk assessment were calculated by adjusting the residues of isoxaflutole + RPA 202248 + RPA 207048 + RPA 205834 found in the ruminant metabolism study at a 10 ppm feeding level for the anticipated dietary burden of 0.12 ppm.

Poultry Commodities

For the meat by-products acute (Table 1) and chronic ARs (Table 2), our previously calculated AR is unchanged as the adjustment factor is 1.0.

Based on the decision of the HED Metabolism Assessment Review Committee, tolerances are now required for poultry meat, eggs and fat. The required tolerances for these commodities, 0.20 ppm for meat and fat and 0.01 ppm for eggs, are based on the LOQ of the proposed analytical enforcement method. The anticipated residues for the chronic dietary risk assessment were calculated by adjusting the residues of isoxaflutole + RPA 202248 + RPA 207048 + RPA 205834 found in the poultry metabolism study at a 10 ppm feeding level for the anticipated dietary burden of 0.012 ppm. The acute ARs for poultry meat, eggs and fat (Table 1) are determined by multiplication of the required tolerances by the adjustment factors.

cc: PP#6F04664, G. Kramer (RAB1), Dan Kenny (RD)
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