3-18-98

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

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

DATE: 18-MAR-1998

SUBJECT: PP# 6F04664. Isoxaflutole in/on Field Corn and Animal RACs. **Request for Anticipated Residues for Tier 3 Risk Assessment.** Barcode D244004. Chemical 123000. Case 287353.

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

THROUGH: Melba Morrow, D.V.M., Branch Senior Scientist
RAB1/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 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, horses, poultry and sheep

The DRES run using tolerance level residues resulted in an acute dietary risk 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. **Note: This Memo will address acute ARs only, further refinements to the chronic ARs are not possible at this time.**

Anticipated Residues

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

Commodity	Anticipated Residue for Acute DRES Run (ppm)
Corn, grain- endosperm	0.015
Corn, grain- bran	0.015
Corn, oil	0.005
Corn, sugar	0.005
Liver	0.26[1]
Meat	0.0011[1]
Fat	0.0065[1]
Meat by-products (except liver)	0.034[1]
Milk[2]	0.0011
Eggs[3]	0.00069
Poultry meat	0.0035
Poultry fat	0.00059
Poultry meat by-products	0.020

[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

CORN RACs

HED reviewed a total of 32 corn residue trials. Isoxaflutole was applied prior to emergence at a rate of 0.223 lbs. ai/A (1.2X). For samples with residue levels below the LOQ (0.01), a value of ½ LOQ used in calculating average residues. The average level of isoxaflutole and its metabolites in grain was 0.015 ppm; in silage, was 0.11 ppm; in forage, was 0.087 ppm; and in stover, was 0.057 ppm. As corn is a blended commodity, the average value can be used in a Tier 3 acute assessment.

Corn was treated with isoxaflutole at a rate of 4X and the grain processed after harvest. The following concentration factors were observed: grits, 0.9X; meal, 0.9X; starch, <0.3X; and oil, <0.3X. The data for starch will be translated to corn sugar. These factors were used in conjunction with the average value for corn grain to derive the ARs for corn processed commodities (Table 1).

Meat, Milk & Eggs

The acute ARs are based on a diet 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):

Table 2. Anticipated Dietary Burden for Beef and Dairy Cattle.

Feed Item	AR/%DM[1]	% in Diet[2]		Anticipated Dietary Burden[3]	
		Beef	Dairy	Beef	Dairy
Corn Grain	0.017	60	40	0.01	0.01
Corn Silage	1.88	40	50	0.75	0.94
Total				**0.76**	**0.95**

1 AR/%DM = average of anticipated residues in feed items divided by the % dry matter (%DM) for the feed item. %DM: 88% for corn grain and 40% for silage.

2 The % of each feed type assumed to be included in the diet was based on information contained in Table I of the OPPTS Test Guidelines Series 860.

3 The anticipated dietary burden is calculated by multiplying the AR/%DM by the % of the feed item in the diet.

The dosing levels used in the ruminant feeding study correspond to 6X, 18X and 61X the anticipated dietary burden for beef cattle and

5X, 15X and 48X the anticipated dietary burden for dairy cattle. Based on this information, and based on the residues found in meat, meat by-products, fat and milk in the ruminant feeding study (average tissue/feed ratio for milk, maximum for all others), the anticipated residues of parent + RPA 202248 in livestock commodities to be used in the acute dietary risk assessments are shown below:

liver	0.15 ppm
meat by-products (except liver)	0.031 ppm
fat	0.0027 ppm
meat	0.00084 ppm
milk	0.00061 ppm

Table 3. Anticipated Dietary Burden for Poultry.

Feed Item	AR	% in Diet[1]	Anticipated Dietary Burden[2]
Corn Grain	0.015	80	0.012

[1] The % assumed to be included in the diet was based on information contained in the revised Table I of the OPPTS Test Guidelines Series 860.

[2] The anticipated dietary burden is calculated by multiplying the average AR by the % of the feed item in the diet.

The dosing levels used in the poultry feeding study correspond to 15X, 45X and 150X the anticipated dietary burden for poultry. Based on this information, and based on the residues found in meat, liver, eggs, and fat in the poultry feeding study (maximum tissue/feed ratio), the anticipated residues of parent + RPA 202248 in poultry commodities to be used in the acute dietary risk assessments are shown below:

meat by-products	0.020 ppm
fat	0.00033 ppm
meat	0.00033 ppm
eggs	0.00033 ppm

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 (Memo, G. Kramer 9/25/97). The above ARs are 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:

[isoxaflutole + RPA 202248 +RPA 207048 + RPA 205834] ÷ [isoxaflutole + RPA 202248]

The acute ARs (Table 1) are determined by multiplication of the above values by the adjustment factors (Table 4).

Table 4- Adjustment factors for animal commodities.

Animal	Commodity	% of TTR Comprised of Isoxaflutole + 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 isoxaflutole 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.

cc: PP#6F04664, G. Kramer (RAB1), Dan Kenny (RD)
RDI: M. Morrow (3/13/98), A. Rathman (3/12/98), Chem SAC (3/18/98)
G.F. Kramer:804V:CM#2:(703)305-5079:7509C:RAB1