



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

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

DATE: 11/26/97

SUBJECT: PP# 6F04664. **Isoxaflutole in/on Field Corn and Animal RACs**. Amendments of 8/12/97 & 9/25/97. Revised Sections B & F. MRID# none. Barcode D238240. Chemical 123000. Case 287353.

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

THROUGH: Melba Morrow, Branch Senior Scientist *Melba Morrow*
RAB1/HED (7509C)

TO: Barbara Madden
RCAB/HED (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

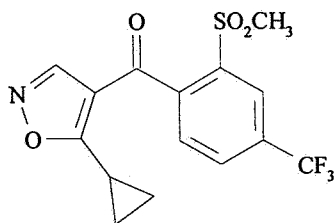
the parent compound, in/on:

Milk	--	0.02 ppm		Liver*	--	0.05 ppm
Poultry, Liver	-	0.3 ppm				
Meat Byproducts (except liver)*	--	0.10 ppm				

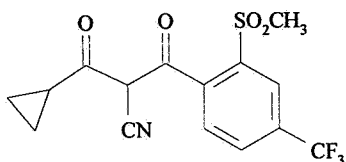
*of cattle, goat, hogs, and sheep

The current amendment addresses deficiencies identified in RAB1's previous review (Memo, G. Kramer 7/14/97; D232139). The structure of isoxaflutole and its metabolites are shown below:

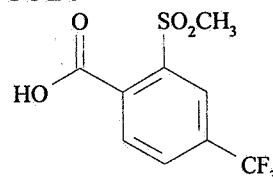
ISOXAFLUTOLE



RPA 202248



RPA 203328



Executive Summary of Chemistry Deficiencies

- Limited field accumulation studies in rotational crops.
- Revised version of the analytical enforcement method for plants.
- Revised version of the analytical enforcement method for animals.
- Revised Section F.

RECOMMENDATIONS

RAB1 continues to recommend against the proposed permanent tolerances for isoxaflutole and its metabolites in/on field corn and animal RACs for reasons detailed in Conclusions 1 - 5, below. RAB1 would, however, be willing to recommend in favor of time-limited tolerances while these deficiencies are resolved.

CONCLUSIONS

1. As residues in rotational crops in the confined study were very low (<0.05 ppm) in crops with a plantback interval of 4 months and residues were not found in human food items, RAB1 is willing to recommend in favor of a conditional registration and time-limited tolerances while the requisite limited field trials for rotational crops are performed.
2. Based on the decision of the HED Metabolism Assessment Review Committee, tolerances are now required for meat and fat of cattle, goat, hogs, and sheep; and for meat, eggs and fat of poultry (Memo, G. Kramer 9/18/97; D238727). 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. **A revised Section F is required.**
3. The petitioner has submitted standards of isoxaflutole to the EPA repository in RTP. However, submission of a revised version of the proposed analytical enforcement method for plants is still required. Until the revised method, the requirements for analytical enforcement methodology in plant matrices will remain unfulfilled.
4. The proposed analytical enforcement method for animal RACs has been validated by ACL, Beltsville (Personal Communication, F. Griffith 11/17/97). However, minor revisions of the method will be required. Until the receipt of the revised method for animal RACs, the requirements for analytical enforcement methodology will remain unfulfilled.
5. The proposed tolerance for liver of cattle, goat, hogs, and

sheep (0.05 ppm) is incorrect. The appropriate value is 0.50 ppm. **A revised Section F is required.** RAB1 also notes that the tolerances for corn commodities should be expressed as: "Corn, field, grain"; "Corn, field, forage" and "Corn, field, stover."

DETAILED CONSIDERATIONS

Deficiencies - Conclusion 1b & 2b (from Memo, G. Kramer 7/14/97)

1b. Field accumulation studies in rotational crops are required to determine the appropriate plantback intervals and/or the need for rotational crop tolerances. These studies should be performed in accordance with OPPTS Test Guidelines 860.1900.

2b. RAB1 is unable to assess the adequacy of the proposed rotational crop restrictions until the requisite limited field trials for rotational crops are performed and submitted for our review.

Petitioner's Response: Submission of a revised label in which the planting of all rotational crops is limited to 6 months. The petitioner has also initiated limited field trials and proposed that registration of isoxaflutole be made conditional pending completion of these trials.

RAB1's Conclusion: As residues in rotational crops in the confined study were very low (<0.05 ppm) in crops with a plantback interval of 4 months and residues were not found in human food items, RAB1 is willing to recommend in favor of a conditional registration and time-limited-tolerances while the requisite limited field trials for rotational crops are performed.

Deficiencies - Conclusions 3b & 4b (from Memo, G. Kramer 7/14/97)

3b. RAB1 need not defer to the HED Metabolism Committee on the toxicological significance of isoxaflutole metabolites identified in corn and rotational crops as the only metabolites identified, RPA 202248 and RPA 203328, are included in the tolerance expression. However, the HED Metabolism Committee will consider the possible formation of metabolites of toxicological concern which were not identified in these studies.

4b. RAB1 will defer to the HED Metabolism Committee on the toxicological significance of metabolites in animal commodities. A decision concerning which residues to regulate will then follow. A tolerance based on the parent and RPA 202248 may not be appropriate; in such an instance a revised Section F and additional feeding studies, analytical methodology, and storage stability data may be needed.

Petitioner's Response: none.

RAB1's Conclusion: It was determined at an Ad Hoc Metabolism Committee Pre-meeting (7/17/97) that there is no scientific objection to establishing the plant tolerances in terms of isoxaflutole and its metabolites RPA 202248 and RPA 203328, calculated as the parent compound. At the HED Metabolism Assessment Review Committee Meeting of 9/4/97, it was concluded that the identified metabolites RPA 207048 and RPA 205834 are likely to be of comparable toxicity to the parent. Since RPA 207048 and RPA 205834 are a major portion of the residue in animal commodities, these metabolites need to be included in the risk assessment (Memo, G. Kramer 9/25/97; D238728). However, since another major metabolite, RPA 202248 is measured by the proposed enforcement method, RPA 207048 and RPA 205834 need not be included in the tolerance expression for animals. Based on the decision of the HED Metabolism Assessment Review Committee, tolerances are now required for meat and fat of cattle, goat, hogs, and sheep; and for meat, eggs and fat of poultry (Memo, G. Kramer 9/18/97; D238727). 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. **A revised Section F is required.**

Deficiency - Conclusion 5 (from Memo, G. Kramer 7/14/97)

5. The proposed analytical enforcement method for corn RACs has been validated by ACL, Beltsville (Memo, G. Kramer 8/20/96; D228481). However, the petitioner should submit standards of isoxaflutole (including metabolites and the GC standard) to the EPA repository in RTP along with the MSDS, and a revised version of the proposed analytical enforcement method as specified in conclusions 1-5 of the aforementioned Memo. Until the receipt of the standard and the revised method, the requirements for analytical enforcement methodology will remain unfulfilled.

Petitioner's Response: Submission of proof of shipment of reference standards.

RAB1's Conclusion: The petitioner has submitted standards of isoxaflutole to the EPA repository in RTP. However, submission of a revised version of the proposed analytical enforcement method for plants is still required. Until the revised method, the requirements for analytical enforcement methodology in plant matrices will remain unfulfilled.

Deficiency - Conclusion 6b (from Memo, G. Kramer 7/14/97)

6a. A new HPLC/UV enforcement method for meat, milk and eggs (EC-96-340) has been submitted by the petitioner. Adequate validation data (recovery, ILV and radiovalidation) were also submitted. The method and ILV have been sent to Beltsville for PMV (Memo, G. Kramer 1/16/97).

6b. RAB1 will withhold a final conclusion on the adequacy of this method as an analytical enforcement method pending receipt of the PMV report.

Petitioner's Response: none.

RAB1's Conclusion: The proposed analytical enforcement method for animal RACs has been validated by ACL, Beltsville (Memo, M. Law 11/4/97). However, minor revisions of the method are required. Until the receipt of the revised method for animal RACs, the requirements for analytical enforcement methodology will remain unfulfilled.

Deficiency - Conclusion 9 (from Memo, G. Kramer 7/14/97)

9. The samples from the feeding studies were stored for a maximum of 3 months. The results of the feeding study have been recalculated, correcting for the ~50% extraction efficiency of the LC-MS-MS data gathering method and the decline of residues observed in some tissue/metabolite combinations. The appropriate tolerances are:

Milk	--	0.02 ppm		Liver*	--	0.50 ppm
Meat Byproducts (except liver)*	--	0.10 ppm				
Poultry, Liver	--	0.30 ppm				

*of cattle, goat, hogs, horses and sheep

Petitioner's Response: Proposed tolerances 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*	--	0.05
ppm						
Poultry, Liver	-	0.3 ppm				
Meat Byproducts (except liver)*	--			0.10 ppm		

*of cattle, goat, hogs, poultry and sheep

RAB1's Conclusion: The proposed tolerance for liver of cattle, goat, hogs, and sheep (0.05 ppm) is incorrect. The appropriate value is 0.50 ppm. **A revised Section F is required.** RAB1 also notes that the tolerances for corn commodities should be expressed as: "Corn, field, grain"; "Corn, field, forage" and "Corn, field, stover."

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