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HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

17-JAN-2001

SUBJECT: PP# 9F05092. Imazapic in/on Pasture and Rangeland Grasses. **Request for Petition Method Validation (PMV)**. MRIDs 44817709 and 44817710. Barcode D271474. Chemicals 128943 & 129041. Submission S581930. Case 291904.

FROM: William H. Donovan, Ph.D., Chemist *William H. Donovan*
Registration Action Branch 1 (RAB1)
Health Effects Division (HED) (7509C)

THROUGH: G. Jeffrey Herndon, Acting Branch Senior Scientist *G. Jeffrey Herndon*
RAB1/HED (7509C)

TO: Francis D. Griffith, Jr., Ph.D., Chief
Analytical Chemistry Branch
Biological and Economics Analysis Division (7503C)

American Cyanamid has submitted a petition (PP#9F05092) for the establishment of permanent tolerances for residues of imazapic (also known as CL 263222 or Cadre®) in/on pasture and rangeland grasses. The proposed tolerances, expressed as imazapic [(±)-2-[4,5-dihydro-4-methyl-4-(1-methylethyl)-5-oxo-1H-imidazol-2-yl]-5-methyl-3-pyridinecarboxylic acid] applied either as the free acid or its ammonium salt and its metabolite CL 263284 [(±)-2-[4,5-dihydro-4-methyl-4-(1-methylethyl)-5-oxo-1H-imidazol-2-yl]-5-hydroxymethyl-3-pyridinecarboxylic acid] both free and conjugated [CL 189215], are as follows (see Attachment 1):

Grass, forage	35 ppm
Grass, hay	15 ppm

Indirect tolerances are also being proposed for residues of imazapic and its metabolite CL 263284 in the following livestock commodities (see Attachment 1):

Milk	0.1 ppm
Meat*	0.1 ppm
Fat*	0.1 ppm
Meat byproducts (except kidney)*	0.1 ppm
Kidney*	2.0 ppm

1.

Internet Address (URL) • <http://www.epa.gov>

* Of cattle, sheep, goats, and horses

Plant methods

The petitioner has submitted a capillary electrophoresis (CE) enforcement method (Method M 3114) for the analysis of imazapic and its metabolites CL 263284 and CL 189215 in/on grass forage and hay (MRID # 44817709). The validated limit of quantitation (LOQ) is 0.50 ppm for each analyte in/on grass forage and hay; the reported method limit of detection (LOD) is 0.050 ppm for each analyte. Independent laboratory validation (ILV) conducted by Centre Analytical Laboratories for grass forage and hay, and radiovalidation for Bermuda grass from the metabolism study were included with the method submission which is appended to this memorandum as Attachment 2. Note that this method is similar to CE method M 2379 which has been successfully validated by the Agency for peanut tolerances.

MRID# 44817709 Nejad, H.; Miller, P.; Duan, B. (1999) Independent Laboratory Validation of Capillary Electrophoresis (CE) Determinative Method for CL 263222, CL 263284, and CL 189215 Residues in Grass, Radiovalidation, and Multiresidue Method. Laboratory Project Identification CY241: RES 98-144: RES 99-038. Unpublished study prepared by American Cyanamid Company. 151 p.

Livestock methods

The petitioner has submitted three enforcement methods (MRID 44817710) for the analysis of imazapic and its metabolite CL 263284 in/on ruminant commodities designated as CE Method M 3188 for milk, CE Method M 3222 for livestock tissues (except fat), and LC/MS Method M 3233 for milk fat and tissue fat. The validated method LOQ for each analyte is 0.010 ppm for milk and milk fat, and 0.050 ppm for cattle tissue (kidney, liver, muscle, and fat). Independent laboratory validation (ILV) conducted by Analytical-Bio Chemistry Laboratories for milk, kidney, liver, and muscle, and by XenoBiotic Laboratories for milk fat and tissue fat, and radiovalidation for goat milk and kidney from the metabolism study were included with the method submission which is appended to this memorandum as Attachment 3.

MRID# 44817710 Nejad, H.; Miller, P.; Sweeney, R.A.; Boner, P.L. (1999) CL 263222 (Imazapic): Independent Laboratory Validation of Methods to Measure CL 263222 and CL 263284 Residues in Cattle Muscle, Kidney, Liver Tissue, Milk, Bovine Milk Fat, and Tissue Fat and Multiresidue Method. Laboratory Project Identification CY239: RES 98-201, RES 98-235, RES 99-004, and RES 99-007. Unpublished study prepared by American Cyanamid Company. 251 p.

RAB1 has conducted a preliminary review of all ILVs. Acceptable recoveries were obtained by the laboratories. The results of the ILVs may be found in MRID# 44817709 on pages 47-49 (grass; CE Method M 3114), and in MRID# 44817710 on pages 17-18 (milk; CE Method M 3188), pages 75-80 (tissues; CE Method M 3222), and page 161 (milk and tissue fats; LC/MS

Method M 3233). RAB1 requests that the Analytical Chemistry Branch conduct a PMV on the submitted analytical enforcement methods.

Samples should be run in duplicate per the experimental design specified in Appendix 1. Please complete and return this attachment as part of your report. Also, please include with your report, copies of the standard curves, sample calculations, and representative chromatograms for controls and fortified samples. Any deficiencies in the method, as written, should also be noted and reported. Please comment on the length of time necessary to complete a set of samples.

One of the purposes of conducting a PMV is to determine whether all necessary instructions are included in the submitted method. For this reason, we are requesting that laboratory staff scientists have minimal contact with the petitioner during this PMV. Any problems encountered should be documented and included in your report. The petitioner will be informed of any deficiencies in the method and asked to resolve them.

Please obtain the necessary analytical reference standards from the EPA Repository. If the analytical reference standard of imazapic and its metabolites CL 263284 and CL 189215 are not available from the Repository, then please contact Janet M. Overholt (609-716-2410), the Registration Specialist at American Cyanamid Company, directly requesting that several hundred milligrams of each standard along with the required MSDS be provided directly to ACL. In your final report please note which standards are available from the Repository as of (date). Also confirm the Repository ordering codes for imazapic, CL 263284 and CL 189215.

The Registration Division Product Manager for imazapic is Jim Tompkins (703-305-5697). He should be contacted directly concerning the priority for completion of the PMV.

Please address your written reports to: Clark Swentzel, Acting Branch Chief, Registration Action Branch 1, Health Effects Division (7509C).

Appendix 1. Reporting form for analytical results.

Attachment 1- Section F for PP# 9F05092 (not available electronically).

Attachment 2- ILV and Radiovalidation of Proposed Enforcement Method for Grass, forage and hay, MRID# 44817709 (not available electronically).

Attachment 3- ILV and Radiovalidation of Proposed Enforcement Methods for Ruminant Commodities, MRID# 44817710 (not available electronically).

Attachment 4- Bean sheet (D271928) for PMV (not available electronically).

cc (with Appendix 1 only): W. Donovan, J. Tompkins (7505C)
RDI: RAB1 Chemists (04-JAN-2001), G. Kramer (05-JAN-2001)
W. Donovan:CM#2:Rm 806R:703-305-7330

APPENDIX 1

METHOD: MRID# 44817709 Nejad, H.; Miller, P.; Duan, B. (1999) Independent Laboratory Validation of Capillary Electrophoresis (CE) Determinative Method for CL 263222, CL 263284, and CL 189215 Residues in Grass, Radiovalidation, and Multiresidue Method. Laboratory Project Identification CY241: RES 98-144: RES 99-038. Unpublished study prepared by American Cyanamid Company. 151 p.

Please: (i) Indicate the LOD and LOQ; (ii) Do not use control values for recovery calculations; and (iii) Do not report control values as zero; if less than the limit of detection, report as such.

Commodity	Chemical Added	ppm Added	ppm Found	Percent Recovery
CE Method M 3114 for Grass, forage and hay				
Grass, forage	Imazapic	Control		N/A
		0.50		
		17.5		
		35		
	CL 263284	Control		N/A
		0.50		
		17.5		
		35		
	CL 189215	Control		N/A
		0.50		
		17.5		
		35		

Commodity	Chemical Added	ppm Added	ppm Found	Percent Recovery
Grass, hay	Imazapic	Control		N/A
		0.50		
		7.5		
		15		
	CL 263284	Control		N/A
		0.50		
		7.5		
		15		
	CL189215	Control		N/A
		0.50		
		7.5		
		15		

METHOD: MRID# 44817710 Nejad, H.; Miller, P.; Sweeney, R.A.; Boner, P.L. (1999) CL 263222 (Imazapic): Independent Laboratory Validation of Methods to Measure CL 263222 and CL 263284 Residues in Cattle Muscle, Kidney, Liver Tissue, Milk, Bovine Milk Fat, and Tissue Fat and Multiresidue Method. Laboratory Project Identification CY239: RES 98-201, RES 98-235, RES 99-004, and RES 99-007. Unpublished study prepared by American Cyanamid Company. 251 p.

Please: (i) Indicate the LOD and LOQ; (ii) Do not use control values for recovery calculations; and (iii) Do not report control values as zero; if less than the limit of detection, report as such.

Commodity	Chemical Added	ppm Added	ppm Found	Percent Recovery
CE Method M 3188 for Milk				
Milk	Imazapic	Control		N/A
		0.010		
		0.05		
		0.10		
	CL 263284	Control		N/A
		0.010		
		0.05		
		0.10		
CE Method M 3222 for Tissues (except fat)				
Kidney	Imazapic	Control		N/A
		0.050		
		1.0		
		2.0		
	CL 263284	Control		N/A
		0.050		
		1.0		
		2.0		

Commodity	Chemical Added	ppm Added	ppm Found	Percent Recovery
Liver	Imazapic	Control		N/A
		0.050		
		0.10		
	CL 263284	Control		N/A
		0.050		
		0.10		
LC/MS Method M 3233 for Milk Fat and Tissue Fat				
Tissue fat	Imazapic	Control		
		0.050		
		0.10		
	CL 263284	Control		
		0.050		
		0.10		