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MRID 44825201

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

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

Date: 20/July/2000

SUBJECT: **Monosodium Methanearsonate (MSMA) Reregistration.** GLN#: 860.1340: Radiovalidation of the Analytical Method for MSMA in/on Cottonseed.

Reregistration Case No.: 2395.
PC Code: 013803.
DP Barcode No.: D256117.
MRID No.: 44825201.

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Attached is a review of studies submitted for the radiovalidation of the analytical method for MSMA and it's metabolite cacodylic acid (CA) in/on cottonseed commodities. This analytical method has not yet been proposed as the enforcement method; however, the Agency recommends that it be proposed as the enforcement method. This document was prepared by Dynamac Corporation under the supervision of the Health Effect Division (HED) and has been revised to reflect Agency policies.

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EXECUTIVE SUMMARY

1. **860.1340 - *Radiovalidation of the Analytical Method for MSMA in/on Cottonseed (MRID No.:44825201):***

   The radiovalidation data from this study along with the radiovalidation data using samples from a lemon metabolism study (DP Barcode D205012, D205663, D214330, D215133, D217721, D219102, currently under secondary review) are adequate to fulfill the reregistration requirements for radiovalidation studies; they also partially confirm that demethylation is not a significant metabolic pathway of MSMA in plants (MARC 12/19/94; memorandum dated 1/26/95 by C. Swartz and B. Cropp-Kohlligian).

   Analytical Method: The submitted radiovalidation of the analytical method data for MSMA in/on cottonseed is adequate. Residues of MSMA can adequately be quantitated in/on [^{14}C]MSMA-treated cottonseed using a GC/ECD method which has been used as the data-collection method in previous crop field trial submissions.

   Residue Data: Residues of MSMA in/on cottonseed were 0.04 ppm using the HPLC method and 0.05-0.07 ppm using the GC/ECD method. Residues of cacodylic acid in/on [^{14}C]MSMA-treated cottonseed were nondetectable (<0.01ppm) using the HPLC method and GC/ECD method.

DEFICIENCIES

1. **Deficiencies in 860.1340 - *Radiovalidation of the Analytical Method for MSMA in/on Cottonseed (MRID No.:44825201):*** There are no deficiencies that would seriously compromise the interpretation of these data. **The GC/ECD method is considered adequate for data collection purposes.**

cc: Sherrie L. Kinard (RRB2), MSMA/DSMA List B File, MSMA/DSMA Subject File, RF, LAN. RD/I: RRB2 Res. Chem. Team (7/17/00).

7509C: RRB2: S. Kinard: CM#2: Rm 722B: 703-305-0563: 7/20/00.

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MONOSODIUM METHANEARSONATE (MSMA)

(PC Code 013803; Case 2395)

(DP Barcode D256117)

REGISTRANT'S RESPONSE TO RESIDUE CHEMISTRY DATA REQUIREMENTS

BACKGROUND

In support of reregistration, the Meathanearsonic Acid (MAA) Research Task Force Three, comprised of APC Holding Company, GB Biosciences Corporation, and Luxembourg-Pamol, Inc., has submitted a study (MRID 44825201) pertaining to radiovalidation of the analytical method for MSMA and its metabolite cacodylic acid in cottonseed. The HED Metabolism Committee (refer to the 1/25/95 C. Swartz memo) previously concluded that the registrant must submit radiovalidation data using a total arsenic method, as well as develop and provide radiovalidation data for a method capable of quantitating MSMA and cacodylic acid separately. These requirements were imposed in order to confirm that demethylation is not a significant metabolic pathway for MSMA. The radiovalidation data are evaluated herein for their adequacy in fulfilling residue chemistry data requirements for the reregistration of MSMA.

The qualitative nature of MSMA residues in plants is adequately understood based on acceptable cotton and citrus metabolism studies. The HED Metabolism Committee concluded that the residues to be regulated in plants resulting from registered uses of MSMA and disodium methanearsonate (DSMA) include MSMA and cacodylic acid (CA). The molecular structures of MSMA, DSMA, and cacodylic acid are depicted in Figure 1. The qualitative nature of MSMA residues in animals is also adequately understood based on acceptable ruminant and poultry metabolism studies. The Agency has concluded that there is no reasonable expectation of detectable MSMA residues in meat, milk, poultry, and eggs as result of application to cotton; that is, residues in meat, milk, poultry, and eggs can be classified under Category 3 of CFR §180.6(a).

Tolerances have been established under 40 CFR §180.289 and §186.4050 for residues of the selective postemergence herbicide MAA (calculated as As_2O_3) resulting from application of the disodium and monosodium salts of MAA in/on cottonseed, cottonseed hulls and citrus fruit. As Codex MRLs do not exist for residues of MSMA/DSMA, there are no compatibility questions with respect to U.S. tolerances and Codex MRLs.

Tolerances have also been established under 40 CFR §180.311 for residues of the defoliant cacodylic acid, expressed as As_2O_3, in/on cottonseed, kidney and liver of cattle, and in meat, fat, and meat byproducts (except kidney and liver) of cattle.

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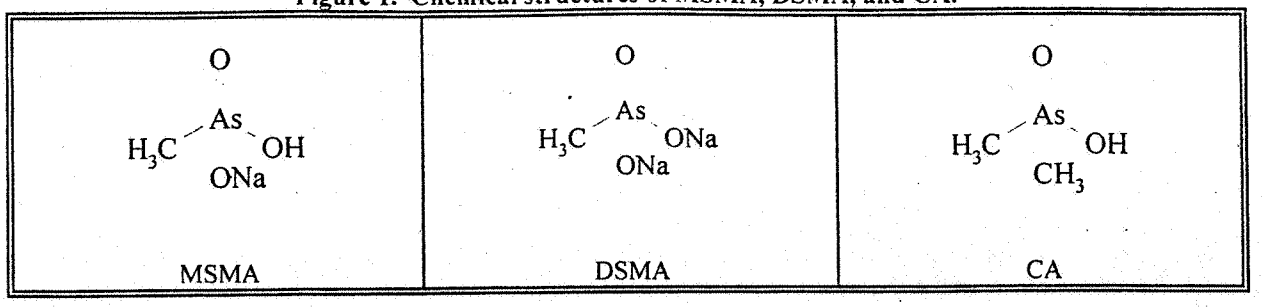
Figure 1. Chemical structures of MSMA, DSMA, and CA.



The enforcement methods listed in Pesticide Analytical Manual (PAM) Volume II are colorimetric methods for the determination of residues of MAA (Section 180.289) and CA (Section 180.311). The methods involve extraction of residues using nitric and sulfuric acids, conversion of residues to arsine gas (AsH_3) followed by determination of the AsH_3 as As_2O_3 using colorimetric methods. A recently submitted orange field study (DP Barcode D214330 and D216740) describes a GC/ECD method for quantitating MSMA and CA residues in/on citrus fruits. The method has not, as yet, been proposed as an enforcement method. The Agency recommends that this be proposed as the enforcement method.

CONCLUSIONS AND RECOMMENDATIONS

Residues of MSMA can adequately be quantitated in/on [^{14}C]MSMA-treated cottonseed using a GC/ECD method which has been used as the data-collection method in previous crop field trial submissions. Residues of MSMA in/on cottonseed were 0.04 ppm using the HPLC method and 0.05-0.07 ppm using the GC/ECD method. Residues of cacodylic acid in/on [^{14}C]MSMA-treated cottonseed were nondetectable (<0.01ppm) using the HPLC method and GC/ECD method. The radiovalidation data from this study along with the radiovalidation data using samples from a lemon metabolism study (DP Barcode D205012, D205663, D214330, D215133, D217721, D219102, currently under secondary review) are adequate to fulfill the reregistration requirements for radiovalidation studies; they also partially confirm that demethylation is not a significant metabolic pathway of MSMA in plants.

DETAILED CONSIDERATIONS

Discussion of radiovalidation study (1998; MRID 44825201)

To generate samples for the study, cotton plants were treated with [^{14}C]MSMA at PTRL East, Incorporated (Richmond, KY). The radioactive test substance, [^{14}C]MSMA labeled on the methyl group (specific activity 17.0 mCi/mmole, radiochemical purity 98%), was formulated with non-labeled MSMA in an aqueous solution with Triton X-100 surfactant. Cotton plants were planted in pots with sandy loam soil and maintained in a greenhouse. Mature cotton was harvested 154 days following the last of two topical broadcast spray applications of the formulated test substance at 2.27 lb ai/A/application for a total application rate of 4.54 lb ai/A. The first and second applications were made when cotton plants were 10-15 and 24-36 inches in

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height, respectively using a manual trigger sprayer; the retreatment interval was 21 days. Twelve additional plants were treated with an aqueous Triton X-100 surfactant solution for control samples. At harvest, seed was manually pulled from the bolls and delinted by scraping the lint from the seed with a razor blade and/or tweezers. A subsample of the delinted cottonseed was chopped with dry ice in a coffee grinder, and stored frozen in plastic bags until combustion analysis. Triplicate samples were analyzed for total radioactive residues by combustion LSC. The reported LOQ for combusted samples was <0.01 ppm and for solvent extractable residues was ≤0.02 ppm in MSMA equivalents.

Radioactive residues in/on cottonseed were extracted using similar procedures employed in the cottonseed metabolism study (DP Barcode D175070, D178793, and D180717; C. Swartz; 5/28/93). Briefly, samples were homogenized sequentially with water, methanol, and hexane. The aqueous extract was cleaned up by C18 solid phase extraction; residues were eluted with pH 2 water. The pH of the eluate was adjusted to 12 with 10% NaOH, and residues were concentrated for radioassay. Nonextractable residues were hydrolyzed sequentially with acid (refluxed with 0.1 N HCl for ~5 hours) and base (refluxed with 0.1 N NH_4OH for ~5 hours). All extracts, hydrolysates, and nonextractable residues were radio assayed by direct or combustion LSC. Analysis of the aqueous cottonseed extract was conducted via HPLC using a Supelcosil amino (normal phase) column, and a gradient mobile phase of methanol and 1% acetic acid in water. Radioactivity was quantitated by a radioactivity flow-through monitor, and residues were identified by comparison with nonlabeled reference standards by UV detection at 230 nm. The TRR in cottonseed, extracts, hydrolysates, and nonextractable residues are presented in Table 1.

Table 1. Summary of total radioactive residues in/on cottonseed samples treated with [^{14}C]MSMA.

Sample Description	Total Radioactive Residues (TRR)	
	Percent	ppm
Cottonseed, control	--	<0.01
Cottonseed, treated	--	0.20
-aqueous extract	63	0.12
-methanol extract	7.0	0.01
-hexane extract	<0.1	<0.01
-acid hydrolysate	13.4	0.03
-base hydrolysate	17.7	0.03
-nonextractable	21.6	0.04

To radiovalidate the analytical method, subsamples of [^{14}C]MSMA treated cottonseed were extracted and analyzed using a similar GC/ECD method which had been used as the data-collection method in many field trial submissions. Briefly, residues were extracted (3x) with water. The filtered extract was acidified, washed with hexane (3x) and diethyl ether (3x), made basic (pH 11-13) with 10% NaOH, and concentrated by rotary evaporation. The concentrated aqueous extract was acidified (~pH 2) with 50% HCl and refluxed for 16-18 hours. The extract

was further purified by C-18 solid phase extraction. Residues were eluted with pH 2 water and derivatized with methylthioglycolate. The derivatized residues of MSMA and cacodylic acid were partitioned into hexane (2x). The aqueous:hexane mixture was centrifuged to eliminate any emulsion for phase separation. The hexane phase was analyzed for residues of MSMA and cacodylic acid using GC/ECD. Although the stated LOQ for MSMA and cacodylic acid using the GC/ECD method was 0.05 ppm, residue values were calculated by the registrant down to 0.01 ppm. The results of the radiovalidation study are presented in Table 2.

Table 2. Summary of data obtained from the radiovalidation trial for MSMA and cacodylic acid in cottonseed.

Sample Description	Metabolism Method: HPLC (ppm)	Residue Method: GC/ECD (ppm)
MSMA		
Cottonseed, control	<0.01 (determined by combustion/LSC)	0.03
Cottonseed, ^{14}C-treated	0.04	0.05, 0.07
Cacodylic acid		
Cottonseed, control	ND	ND
Cottonseed, ^{14}C-treated	ND	<0.01, <0.01

[a] Percent recovery was only calculated when detectable residues were found with both methods.
[b] TRR determined by combustion LSC.
[c] ND = not detected.

Conclusions: Residues of MSMA can adequately be quantitated in/on [^{14}C]MSMA-treated cottonseed using a GC/ECD method which had been used as the data-collection method in previous crop field trial submissions. Residues of MSMA in/on cottonseed were 0.04 ppm using the HPLC method and 0.05-0.07 ppm using the GC/ECD method. Residues of cacodylic acid in/on [^{14}C]MSMA-treated cottonseed were nondetectable (<0.01ppm) using the HPLC method and GC/ECD method. The radiovalidation data from this study along with the radiovalidation data using samples from a lemon metabolism study (DP Barcode D205012, D205663, D214330, D215133, D217721, D219102, currently under secondary review) are adequate to fulfill the reregistration requirements for radiovalidation studies; they also partially confirm that demethylation is not a significant metabolic pathway of MSMA in plants.

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EPA MEMORANDA CITED IN THIS REVIEW

DP Barcode: D175070, D178793, and D180717
Subject: Monosodium methanearsonate (MSMA). List B Reregistration Case No. 2395. Metabolism Studies in Cotton and Citrus (Lemon).
From: C. Swartz
To: B. Briscoe
Dated: 5/28/93
MRID(s): 42216101, 42324401, and 42391201

DP Barcode: D205012, D205663, D214330, D215133, D217721, D219102
Subject: Monosodium methanearsonate (MSMA). List B Reregistration Case No. 2395. (I) analytical methods for quantitation of residues of MSMA and its metabolite cacodylic acid in/on cottonseed (1995; MRIDs 43630101 and 43802501) and oranges (1995; MRIDs 43279301, 43630201, 43769101, and 44125501); (ii) magnitude of the residue in/on cottonseed (1995; MRID 43720701); and (iii) magnitude of the residue in the processed commodities of cottonseed (1995; 43959801) and oranges (1995; MRID 43803701).
From: S. Kinard
To: K. Depukat
Date: 7/20/00
MRIDs: See those listed under subject

MASTER RECORD IDENTIFICATION NUMBERS

The citations for the MRID documents referred to in this review are presented below.

44825201 O' Neal, S. And Howard, J. (1998) Radiovalidation of the Analytical Method for Monosodium Methanearsonate (MSMA) in Cottonseed: Growth and Treatment of Cotton with ^{14}C-MSMA and Method Validation: PTRL project No. 1050, PTRL Report No. 1995. Unpublished study prepared by PTRL East, Inc. 142 p.