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

JAN 24 1995

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Monosodium methanearsonate (MSMA). List B Reregistration Case No. 2395/Chemical ID No. 013803. MAA Task Force Submission to Upgrade Ruminant and Poultry Metabolism Studies [GRN 171-4(b)]. CBRS No. 10836. DP Barcode No. D184346.

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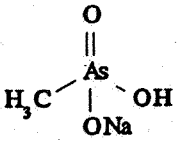
Attached is a review of the Methanearsonate (MAA) Task Force Three submission to upgrade ruminant and poultry metabolism studies. The review was completed by Dynamac under supervision of CBRS, and has been revised to reflect current Agency guidelines.

The poultry and ruminant metabolism studies are tentatively acceptable pending subjection of livestock metabolism study samples to total arsenic method analysis which will serve to validate/confirm results of the livestock metabolism studies. Animal feeding studies are not required at this time, since residues in meat, milk and eggs have been tentatively classified under Category 3 of 40 CFR §180.6(a), i.e. there is no reasonable expectation of finite residues.

cc: CSwartz; MSMA List B file; RF; SF; Circulation
7509C:CBRS:CSwartz:CM#2:Rm 804F:703 305 5877:12/1/94
RDI:WJHazel:12/6/94 MSMetzger:1/18/95 FBSuhre:1/20/95

MONOSODIUM METHANEARSONATE (MSMA)



(Shaughnessy No. 013803; Case No. 2395)

CBRS No. 10836; DP Barcode D184346

REGISTRANT'S RESPONSE TO RESIDUE CHEMISTRY DATA REQUIREMENTS

Task 4

BACKGROUND

In response to the Phase 4 Review for Methanearsonates (MSMA/DSMA) dated 3/91, the Methanearsonate (MAA) Task Force Three submitted [^{14}C]MSMA metabolism studies in ruminants and poultry (1991; MRIDs 42009701 and -02). These studies were reviewed by the Agency (CBRS No. 8647; DP Barcode D168990; 4/7/92; C. Olinger) and judged deficient but upgradeable. Further characterization and identification of insoluble residues in goat and hen muscle and egg white, and confirmation of lipid conjugation of residues in egg yolk were required. The review also required the Task Force to provide copies of literature cited in the original submission describing the methylation of arsenical compounds. The MAA Task Force has submitted additional data from these studies (1992; MRIDs 42525001 and -02) and copies of literature cited in the initial review. These data are reviewed here for adequacy in fulfilling outstanding residue chemistry data requirements. The Agency has concluded that data for MSMA will satisfy requirements for disodium methanearsonate (DSMA). The Conclusions and Recommendations stated herein pertain only to the qualitative nature of the residue in animals.

Tolerances are established for residues of the herbicide methanearsonic acid (calculated as As_2O_3) from application of the disodium and monosodium salts of methanearsonic acid in or on cottonseed (0.7 ppm) and citrus fruit (0.35 ppm) [40 CFR §180.289]; a tolerance of 0.9 ppm (expressed as As_2O_3) is established for residues of the herbicide methanearsonic acid in cottonseed hulls from application of the disodium and monosodium salts of methanearsonic acid in the production of cotton [40 CFR §186.4050(a)]. A colorimetric method is listed as Method I in PAM, Vol. II for the enforcement of methanearsonic acid tolerances in cottonseed. Since Codex MRLs do not exist for residues of MAA, there are no compatibility questions with respect to U.S. tolerances and Codex MRLs.

The qualitative nature of the residue in plants is adequately understood [C. Swartz memos dated 5/28/93 and 5/18/94; CBRS Nos. 9525, 9942, and 10245, and CBRS No. 12891; DP Barcodes D175070, D178793, and D180717, and D197117]. CBRS concludes that MAA

(methanearsonic acid) and cacodylic acid (CA, dimethylarsinic acid) were identified as 62.3 (0.93 ppm) and 6.0 (0.09 ppm) per cent of the cottonseed TRR (1.49 ppm), respectively. Greater than 95% of the TRR was identified in lemon peel, pulp and juice. Most of the radioactivity was found in the peel, of which 40.8 %TRR (0.19 ppm) was identified as MAA, and 54.7 %TRR (0.24 ppm) was identified as CA.

RECOMMENDATION

The nature of the residue in ruminants is now tentatively understood. The only residue identified in ruminant and poultry liver and kidney and in egg whites was cacodylic acid (CA), at approximately 68 to 85 %TRR. The principle residue in ruminant and poultry muscle was CA (80 to 85 %TRR); however, MAA constituted up to 4 %TRR. Approximately 50% of the milk TRR was identified as MAA (34 %TRR) and CA (15 %TRR). In egg yolk, only 35 %TRR was identified as MAA (21.3 %TRR) and CA (13.9 %TRR); approximately 16 %TRR was postulated to be MAA residues associated with the lipid matrix. Inorganic arsenic was not sought.

Based on the maximum theoretical 1X dietary burden, and TRRs found in tissues, eggs and milk in the metabolism studies, CBRS concludes that residues of MAA in livestock can be tentatively classified under Category 3 of 40 CFR §180.6(a), i.e. there is no reasonable expectation of finite residues, pending subjection of livestock metabolism study samples to total arsenic method analysis which will serve to validate/confirm results of the livestock metabolism study. Tolerances and feeding studies are not required at this time.

Tissue, milk and egg samples from both metabolism studies should be tested using a validated total arsenic method to confirm that demethylation is not a significant pathway for MSMA in ruminants.

CONCLUSIONS

1. As required by the Agency, goat leg muscle from the original study was re-analyzed after ~2 years in frozen storage. Fractions containing bound residues were subjected to enzyme (protease) and acid hydrolysis.

2. All radioactivity was lost from the acid-hydrolyzed fraction. Using [^{14}C]MSMA-fortified samples, the registrant demonstrated that a portion of acid hydrolyzed [^{14}C]MSMA residues could be trapped as volatiles in cold organic solvent.

3. Radioactive residues in aqueous-soluble fractions and enzyme hydrolysates were identified and quantified using HPLC under conditions similar to those used in the original study. Supporting sample chromatograms and raw data were provided.

4. The release of additional radioactivity from the bound fraction of goat leg muscle resulted in identification of 84 %TRR (0.087 ppm) as cacodylic acid (81 %TRR) and

MAA (3 %TRR). Approximately 12% of the leg muscle TRR was identified as MAA in the original study; this indicates that either MAA residues were not stable in the frozen muscle, or that extraction/enzyme hydrolysis resulted in methylation of MAA.

5. Hen breast muscle and egg white samples from the original study were re-analyzed after 20 months in frozen storage. Fractions containing bound residues were subjected to enzyme (protease) and acid hydrolysis. All radioactivity was lost from the acid-hydrolyzed fraction of breast muscle; 2.5% of the egg white TRR was recovered as trapped volatiles.

6. Aqueous-soluble residues, including protease hydrolysates, were identified and quantified using HPLC under conditions similar to those in the original study. Adequate sample chromatograms and raw data were submitted.

7. Re-analysis of the radioactivity in hen muscle resulted in identification of ~89% (0.092 ppm) of the total radioactive residue (TRR) as cacodylic acid (~84 %TRR) and MAA (4.55 %TRR).

8. Re-analysis of the radioactivity in egg white resulted in identification of 74% (0.080 ppm) of the egg white TRR as cacodylic acid. MAA was not detected. Lost residues, purportedly un-trapped volatile components, accounted for 23% of the TRR (0.025 ppm).

9. Additional data on lipid conjugates in egg yolks were not submitted. However, The Task Force's assertion that MAA residues tend to adhere to the lipid matrix of egg yolk is reasonable, and is supported by experiments with fortified egg yolk. These residues are appropriately termed lipid matrix-associated residues rather than "lipid conjugates."

10. The only residue identified in ruminant and poultry liver and kidney was cacodylic acid (CA), at approximately 68 to 85 %TRR. The principle residue in ruminant and poultry muscle was CA (80 to 85 %TRR); however, MAA constituted up to 4 %TRR. Approximately 50% of the milk TRR was identified as MAA (34 %TRR) and CA (15 %TRR). In egg yolk, only 35 %TRR was identified as MAA (21.3 %TRR) and CA (13.9 %TRR). Only CA was identified in egg yolk (39 %TRR). Inorganic arsenic was not sought.

DETAILED CONSIDERATIONS

Qualitative Nature of the Residue in Animals: Ruminants

The Methanearsonate (MAA) Task Force Three submitted a ruminant metabolism study (1991; MRID 42009701), which was reviewed by the Agency (CBRS No. 8647; DP Barcode D168990; 4/7/92; C. Olinger). Briefly, two goats were dosed with [^{14}C]MSMA (2.4 Mci/mmole) once daily for 7 days at a rate equivalent to ~42 ppm in the diet. This dosage is equivalent to ~40X the maximum theoretical dietary exposure of ~1 ppm. Various combinations of cottonseed, cottonseed hulls, and wet or dried citrus pulp can be used to estimate a cattle diet ranging from ~0.6-1.2 ppm. An example is shown in Table 1. No data are available regarding the magnitude of the residue in or on cotton gin byproducts, which may constitute up to 20% of the dairy cattle diet and up to 30% of the beef cattle diet; however, in the cotton metabolism study, the total radioactive residue (TRR) in the seed was approximately 1.7 times higher than in the leaves.

Table 1. Calculation of maximum theoretical beef cattle dietary exposure to MSMA.

Commodity	Tolerance (ppm)	% Dry matter	% of Diet	Dietary contribution (ppm)
Cottonseed	0.7	88	15	0.12
Cottonseed hulls	0.9	90	20	0.20
Cotton gin byproducts	0.4[1]	90	5	0.02
Citrus pulp (wet)	0.35	21	40	0.67
Total				1.01

[1] The tolerance level for cotton gin byproducts was determined using the ratio of the seed TRR to the leaf TRR in the cotton metabolism study.

For the goat designated #67 in the original study, TRRs were 0.015-0.038 ppm in milk, 0.012 ppm in fat, 0.215 ppm in liver, 0.292 ppm in kidney, and 0.089-0.104 ppm in muscle. Residues were extracted using a modified Bligh-Dyer procedure with MeOH:H_2O:$CHCl_3$ (11:5:5, v/v). In order to release bound residues, liver was subjected to base hydrolysis. Cacodylic acid was identified as 74, 85, and 31% of the TRR in liver, kidney, and loin muscle, respectively. MAA was detected in leg muscle (34.2 %TRR) and milk (33.6 %TRR). Unidentified residues in the post-extraction solids fraction (bound residues) comprised 58-60% of the radioactivity in muscle.

The Agency required the registrant to conduct additional work to release radioactivity from the post-extraction solids of ruminant muscle using acid, base, and/or enzyme hydrolysis. In response, The MAA Research Task Force Three submitted additional data from the reanalysis of goat #67 leg muscle.

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MRID 42525001. Supplemental data on goat metabolism

Extraction and hydrolysis

Goats used in the initial study were sacrificed on 9/19/90. The leg muscle sample from goat #67 was analyzed for TRR initially (0.104 ppm) and in 2/91 (0.103 ppm). The sample was archived in 10/91 following completion of the original study. The frozen sample was shipped to XenoBiotic Laboratories, Inc. for reanalysis on 5/21/92. Metabolite analyses for the supplemental study were conducted between 7/7/92 and 8/3/92 according to the dates on the chromatograms provided. Just under 2 years elapsed between sacrifice and reanalysis of the muscle sample.

The leg muscle TRR was not determined prior to re-analysis. Residues in leg muscle were extracted with water via sonication for 30 minutes, then centrifuged to separate the aqueous-1 and post-extraction solids-1 (PES-1) fractions. The solids were subjected to enzyme hydrolysis (protease, phosphate buffer, pH ~7.5, 24 hours) and centrifuged to separate aqueous-2 and PES-2 fractions. Aqueous residues were freeze-dried and then reconstituted in a minimum volume of water and centrifuged. Radioactive residues in the fractions were quantitated using liquid scintillation counting (LSC). The distribution of radioactivity in the aqueous-1, PES-1, aqueous-2, and PES-2 fractions is shown in Table 2.

The residues in the PES-2 fraction were hydrolyzed by refluxing with 6 N HCl under argon for 12 hours, and then neutralized with NaOH. No radioactivity was recovered after the acid hydrolysis.

Characterization/Identification of radioactive residues

Radioactive residues in the aqueous fractions were characterized using high performance liquid chromatography (HPLC) under the same conditions used in the original study, substituting a Supelco LC-18 column. The retention times of MAA and cacodylic acid standards were ~9.58 and ~6.27 minutes, respectively. Retention times of metabolites in the extracts shifted due to matrix effects. Metabolites were identified by co-injection of radioactive standards with samples.

The chromatogram of the aqueous-1 fraction indicated two peaks between 4.5 and 7.5 minutes. The registrant obtained two peaks in similar proportions when additional [^{14}C]cacodylic acid was added, demonstrating that the split peak was attributable to cacodylic acid. Two peaks detected at 4.5 and 8 minutes on the chromatogram of the aqueous-2 fraction were shown to be cacodylic acid and MAA, as addition of [^{14}C]cacodylic acid increased only the 4.5 minute peak.

The registrant investigated the hypothesis that the radioactivity lost following acid hydrolysis of the PES-2 fraction was due to formation of volatile components. Radioactive MAA and cacodylic acid standards were subjected to acid hydrolysis as described above; an attempt

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was made to trap volatiles in cold MeOH, toluene, and/or EtOH. Hydrolysis of [^{14}C]MAA yielded 20-22% of the radioactivity in the EtOH trap and 6-10% in the toluene; 12-15% of the radioactivity was lost. No volatile radioactivity was recovered from hydrolysis of [^{14}C]cacodylic acid, whereas 18-23% was lost. Although the fate of the acid hydrolyzed protease insoluble residues could not be entirely explained, the low concentration of the residues remaining in this fraction did not warrant further study.

Table 2. Extraction and characterization of ^{14}C-residues in leg muscle (TRR 0.104 ppm) of goat #67 dosed with [^{14}C]MSMA.

Fraction	% TRR	ppm	Characterization/identification
Aqueous-1	55.59	0.058	HPLC: Split peaks, both identified as cacodylic acid 55.59% (0.058 ppm)
PES-1	44.41	0.046	Enzyme hydrolysis
Aqueous-2	28.44	0.029	HPLC: Cacodylic acid 25.22% (0.026 ppm) MAA 2.9% (0.003 ppm)
PES-2	15.97	0.017	Acid hydrolysis 6 N HCl; all ^{14}C-activity lost

Table 3 presents a comparison of the initial analysis and re-analysis of goat leg muscle. Approximately 84% of the radioactive residues in muscle, consisting of both cacodylic acid and MAA, were identified in the supplemental study.

Table 3. Comparison of MAA and cacodylic acid quantified in goat leg muscle in the initial analysis and re-analysis.

	Initial analysis	Re-analysis
Sampling-to-analysis	2 months	2 years
Extraction	Bligh-Dyer	H_2O/sonication extraction
Hydrolysis	None	Protease I
Residues identified		
MAA	34.17% TRR; 0.032 ppm	2.9% TRR; 0.003 ppm
Cacodylic acid	7.86% TRR; 0.007 ppm	80.81% TRR; 0.084 ppm
Percent TRR identified	42.03%	83.7%

As shown in Table 3, MAA constituted a significantly greater percentage of the leg muscle TRR in the initial analysis than in the subsequent analysis. Although the supplemental study made note of this difference, no explanation was provided. There is no way to know if MAA was converted to CA during storage, or if the different extraction procedure used in the supplemental study had an effect on the relative amounts of MAA and CA. Additional uncertainty is attributed to the lack of a TRR determination prior to the re-analysis.

CBRS tentatively concludes that the supplemental data are adequate; the major residues identified in ruminant tissues and milk are MAA and CA. In general, a greater percentage of the radioactivity in tissues was attributed to CA than to MAA, except in milk. An amended summary table, incorporating the leg muscle re-analysis, is presented below:

Table 4. Results of ^{14}C-MSMA Metabolism in Ruminants.[1]

Matrix (TRR)	MAA	CA	Unknown	Not Analyzed	Bound	Total ID'd
Liver (0.215)	ND	74.24 (0.160)	--	N/A	25.76 (0.055)	74.24 (0.160)
Kidney (0.292)	ND	85.16 (0.249)	9.76 (0.028)	N/A	5.08 (0.015)	85.16 (0.249)
Leg Muscle (0.103)	2.9 (0.003)	80.81 (0.084)[2]	--	N/A	15.97 (0.017)	83.71 (0.087)
Loin Muscle (0.089)	ND	31.47 (0.033)	8.12 (0.008)	N/A	60.41 (0.063)	31.47 (0.033)
Day 5 Milk (0.038)	33.6 (0.013)	15.12 (0.006)	--	48.97 (0.019)[3]	2.34 (0.001)	48.72 (0.019)

[1] The TRR in each matrix is presented; for each metabolite, the %TRR (ppm radioactivity, ^{14}C-MSMA equivalents) is presented. ND = none detected; N/a = not applicable.

[2] In the original study, 34.17 %TRR (0.032 ppm) was identified as MAA, while 7.86 %TRR (0.007 ppm) was identified as CA.

[3] Represents a combination of hexane, suspension, and 2 of the solids fractions.

Qualitative Nature of the Residue in Animals: Poultry

The Methanearsonate (MAA) Task Force Three submitted a poultry metabolism study (1991; MRID 42009702), which was reviewed by the Agency (CBRS No. 8647; DP Barcode D168990; 4/7/92; C. Olinger). Briefly, 10 laying hens were dosed with [^{14}C]MSMA (2.4 mCi/mmole) once daily for 7 days at a rate equivalent to ~42 ppm in the diet. This dosage represents >265X the maximum theoretical dietary exposure of 0.157 ppm, based on a diet consisting of 20% cottonseed meal with cottonseed tolerance-level residues of 0.7 ppm.

Total radioactivity accumulated to 0.340 ppm in egg yolk and 0.108 ppm in egg white and did not plateau over the 7-day dosing period. Total radioactive residues (TRRs) in other tissues were 0.023 ppm (fat), 0.083 ppm (thigh muscle), 0.119 ppm (breast muscle), 0.101 ppm (liver), and 0.158 ppm (kidney).

Radioactivity in tissue samples was extracted using water and sonication. Residues in egg yolk and egg white were extracted with hexane:acetonitrile:H_2O (6:5:1, v/v); hexane fractions were saponified by refluxing in KOH. Residues in fat were extracted sequentially with hexane and MeOH:H_2O (11:5, v/v).

Residues were identified and quantified using HPLC and thin layer chromatography (TLC). MAA was the predominant residue in skin/fat (17%) and egg yolk (21%). Cacodylic acid constituted the major portion of the residue in liver (68%), kidney (82%), thigh muscle

(28%), and egg white (39%), and was also identified as a component in breast muscle (12%) and egg yolk (14%). The Agency required the registrant to further analyze an unknown soluble component, constituting 25% of the residue in breast muscle and 28% in egg white. Furthermore, the registrant was required to confirm that 17% of the egg yolk TRR consisted of lipid conjugates.

MRID 42525002. Supplemental data on poultry metabolism

Extraction and hydrolysis

The hens in this study were sacrificed on 12/11/90. The hen egg and tissue samples were archived in 11/91 following completion of the original study. The frozen breast muscle and egg white samples were shipped to XenoBiotic Laboratories, Inc. for reanalysis on 5/21/92. Metabolite analyses for the supplemental study were conducted between 7/9/92 and 8/3/92 according to the dates on the chromatograms provided. Approximately 20 months elapsed between sacrifice and analysis of poultry tissues for the supplemental study.

The TRRs in breast muscle and egg white were not determined again prior to re-analysis. The TRR values from the original study, 0.119 ppm in breast muscle and 0.108 ppm in day-7 egg white, were used to calculate concentrations of radioactivity in fractions and to quantify metabolites.

Radioactivity in breast muscle and egg white was extracted as described in the original study. Bound residues were hydrolyzed sequentially with protease enzyme and 6 N HCL as described above for goat leg muscle. The distribution of radioactivity in soluble and solid fractions is reported in Table 5. All radioactivity was lost from the PES-2 fraction after acid hydrolysis of muscle PES-2. Although trapping volatiles from acid hydrolyzed PES-2 from egg white was not described, a small percentage (~2.5%) was reported as trapped.

Table 5. Extraction and characterization of ^{14}C-residues in breast muscle and egg white from hens dosed with [^{14}C]MSMA.

Fraction	% TRR	ppm	Characterization/identification
Breast Muscle (TRR 0.119 ppm)			
Aqueous-1	56.40	0.067	HPLC: Cacodylic acid 51.8% (0.062 ppm) MAA 4.55% (0.005 ppm)
PES-1	43.60	0.052	Enzyme hydrolysis
Aqueous-2	32.46	0.039	HPLC: Cacodylic acid 32.46% (0.039 ppm)
PES-2	11.14	0.013	6 N HCl hydrolysis; all radioactivity lost
Egg white day 7 (TRR 0.108 ppm)			
ACN/H_2O	26.07	0.028	HPLC: Cacodylic acid 26.07% (0.028 ppm)
PES-1	73.93	0.080	Enzyme hydrolysis
Aqueous-1	37.23	0.040	HPLC: Cacodylic acid 37.23% (0.04 ppm)

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Table 5. Extraction and characterization of ^{14}C-residues in breast muscle and egg white from hens dosed with [^{14}C]MSMA.

Fraction	% TRR	ppm	Characterization/identification
PES-2	36.70	0.040	6 N HCl hydrolysis
Aqueous-2	10.97	0.012	HPLC: Cacodylic acid 10.97% (0.012 ppm)
PES-3	0.30	<0.001	Not further analyzed
Trapped volatiles	2.47	0.003	Not further analyzed
Lost volatiles	22.96	0.025	

Table 6 presents a comparison of the initial analysis and re-analysis of breast muscle and egg white. Greater than 84% of the radioactivity in muscle, consisting primarily of cacodylic acid with a minor amount of MAA, was identified in the supplemental study when enzyme hydrolysis was employed. After re-analysis of egg white, 77% of the TRR was characterized, with 74% of the egg white TRR identified as cacodylic acid.

Table 6. Comparison of MAA and cacodylic acid quantified in hen breast muscle and egg white in the initial analysis and re-analysis.

	Initial analysis	Re-analysis
Hen Breast Muscle (0.119 ppm TRR)		
Sampling-to-analysis	4 months	20 months
Extraction	Hexane:ACN:H_2O	Hexane:ACN:H_2O
Hydrolysis	None	Protease I
Residues identified		
MAA	--	4.55% TRR; 0.005 ppm
Cacodylic acid	12.10% TRR; 0.014 ppm	84% TRR; 0.101 ppm
Percent TRR identified	12.10%	88.55%
Egg White (0.108 ppm TRR)		
Sampling-to-analysis	4 months	20 months
Extraction	Hexane:ACN:H_2O	Hexane:ACN:H_2O
Hydrolysis	None	Protease I; 6 N HCl
Residues identified		
MAA	--	--
Cacodylic acid	39.08% TRR; 0.042	74.27% TRR; 0.080 ppm
Trapped volatiles	--	2.47% TRR; 0.003 ppm

Table 6. Comparison of MAA and cacodylic acid quantified in hen breast muscle and egg white in the initial analysis and re-analysis.

	Initial analysis	Re-analysis
Total characterized	39.08%	76.74%

[a] -- = None detected.

Lipid-associated residues in egg yolk

No additional work was conducted to identify residues in egg yolk. The Task Force cited data from the original study indicating that the proportions of identified soluble components, lipid matrix-associated radioactivity, and bound radioactive residues were similar in treated samples and [^{14}C]MSMA-fortified egg yolk (see Table 7). The report stated that MAA residues tend to adhere to matrices, including glassware. It was concluded that upon contact with the egg yolk matrix, a portion of MAA residues tends to bind to the lipid matrix and that "lipid matrix-associated" is more appropriate than "lipid-conjugated," as stated in the initial report, for describing these residues.

The Task Force's rationale is reasonable. Since MAA and cacodylic acid are the only residues identified in animal commodities and MAA is shown to immediately adhere to the hexane-soluble fraction, it can be concluded that the lipid-associated residues in treated samples are MAA and/or cacodylic acid. No additional work is required for egg yolk. Distribution of radioactivity in treated egg yolk and fortified egg yolk is shown in Table 7, while a summary of metabolism results in poultry is shown in Table 8.

Table 7. Comparison of [^{14}C]MSMA fortified and treated egg yolk.

	^{14}C-Residues (ppm)	
Component/fraction	Treated egg yolk	[^{14}C]MSMA fortified egg yolk
MAA	0.072	0.159
Cacodylic acid	0.047	--
Lipid matrix-associated	0.057	0.038
Non-extractable	0.164	0.147
Total	0.340	0.344

Table 8. Results of ^{14}C-MSMA Metabolism in Poultry.[1]

Matrix (TRR)	MAA	CA	Unknown	Not Analyzed	Bound	Total ID'd
Liver (0.101)	ND	68.31 (0.069)	13.8 (0.014)	--	17.89 (0.018)	68.31 (0.069)

Table 8. Results of ^{14}C-MSMA Metabolism in Poultry.[1]

Matrix (TRR)	MAA	CA	Unknown	Not Analyzed	Bound	Total ID'd
Kidney (0.158)	ND	81.72 (0.129)	–	–	18.28 (0.029)	81.72 (0.129)
Breast muscle (0.119)	4.20 (0.005)	84.9 (0.101)[2]	–	–	11.14 (0.013)	89.1 (0.106)
Thigh muscle (0.083)	ND	27.71 (0.023)	9.54 (0.008)	–	62.75 (0.052)	27.71 (0.023)
Skin/Fat (0.023)	17.42 (0.004)	11.23 (0.003)	–	12.61 (0.003)	58.74 (0.014)	28.65 (0.007)
Egg yolk (0.340)	21.26 (0.072)	13.87 (0.047)	16.71 (0.057)[3]	–	48.16 (0.164)	35.13 (0.119)
Egg white (0.108)	ND	74.27 (0.080)	–	25.43 (0.0.028)[4]	0.3 (<0.001)	74.27 (0.080)

[1] The TRR in each matrix is presented; for each metabolite, the %TRR (ppm radioactivity, ^{14}C-MSMA equivalents) is presented.

[2] The results were obtained when the study was upgraded; CBRS required the registrant to attempt to release/identify bound residues. There was no attempt to release bound residues in the thigh muscle, but the results would most likely have been similar.

[3] Unknown residues consisted of 16.71 %TRR (0.057 ppm), which the Task Force maintains are MSMA residues associated with the lipid matrix.

[4] Consists of volatiles, either lost or trapped following acid hydrolysis of bound residues.

Literature References

As stated above, the Task Force was requested to submit literature articles referenced in the original study, which describe methylation of arsenical compounds. The cited references were provided by the Task Force in the subject submission to upgrade the animal metabolism studies. There were several articles about analytical methods, a summary of a hamster metabolism study, and excerpts from the publication Arsenical Pesticides [ACS Symposium Series, Volume 7, American Chemical Society, 1975]. The information supports methylation as the major metabolic pathway for arsenicals.

CBRS Comments

The additional information provided by the Task Force is tentatively sufficient to upgrade the previously submitted livestock metabolism studies. The qualitative nature of the residue in animals is therefore tentatively understood. The only residue identified in ruminant and poultry liver and kidney was cacodylic acid (CA), at approximately 68 to 85 %TRR. The principle residue in ruminant and poultry muscle was CA (80 to 85 %TRR); however, MAA constituted up to 4%TRR. Approximately 50% of the milk TRR was identified as MAA (34 %TRR) and CA (15 %TRR). In egg yolk, only 35 %TRR was identified as MAA (21.3 %TRR) and CA (13.9 %TRR); approximately 16 %TRR was postulated to be MAA residues

associated with the lipid matrix. Only CA was identified in egg yolk (74.3 %TRR). Inorganic arsenic was not sought.

Based on the maximum theoretical 1X dietary burden, and TRRs found in tissues, eggs and milk in the metabolism studies, CBRS tentatively concludes that residues of MAA in livestock can be classified under Category 3 of 40 CFR §180.6(a), i.e. there is no reasonable expectation of finite residues, pending subjection of livestock metabolism study samples to total arsenic method analysis which will serve to validate/confirm results of the livestock metabolism studies. Tolerances and feeding studies are not required at this time.

Tissue, milk and egg samples from both metabolism studies should be tested using a validated total arsenic method to confirm that demethylation is not a significant pathway for MAA in ruminants.

MASTER RECORD IDENTIFICATION NUMBERS

Citations for the MRID documents referenced in this review are presented below.

42525001 Robinson, R. (1992) Metabolism of [^{14}C]-MSMA in Lactating Goats: Dosing, Sample Collection, Quantitation of Radioactivity and Metabolite Analysis in Milk and Edible Tissues: Lab Project Number: 90060: RPT0059. Unpublished study prepared by XenoBiotic Laboratories, Inc. 43p.

42525002 Robinson, R. (1992) Metabolism of [^{14}C]-MSMA in Laying Hens: Metabolite Analysis and Quantitation in Eggs and Tissues: Lab Project Number: 90061: RPT0060. Unpublished study prepared by XenoBiotic Laboratories, Inc. 55 p.

AGENCY MEMORANDA CITED IN THIS DOCUMENT

CBRS No.:	8647
DP Barcode:	D168990
Subject:	Methanearsonate (MSMA/DSMA) Livestock Metabolism Studies
From :	C. Olinger
To:	B. Compton/B. Briscoe
Date:	4/7/92
MRIDs:	42009701 and -02

CBRS Nos.:	9525, 9942, 10245
DP Barcodes:	D175070, D178793, D180717
From:	C. Swartz
To:	B. Briscoe
Date:	5/28/93
MRIDs:	42216100, 42216101, 42324400, 42324401, 42391200, and 42391201

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

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

CERTIFIED MAIL

E. M. Bellet, Ph.D.
Chemical Consultants International, Inc.
7270 West 98th Terrace, Suite 100
Overland Park, Kansas 66212

Subject: Submission to Upgrade Ruminant and Poultry Metabolism Studies Supporting the Reregistration of Monosodium Methanearsonate (MSMA) and Disodium Methanearsonate (DSMA) Case# 2395, AI#'s 13803 and 13802.

Dear Dr. Bellet:

You submitted additional data from your 1992 studies (MRID#s 42525001 and -02) and copies of literature cited in the initial review. These data were reviewed for outstanding residue chemistry data requirements for guideline 171-4(b)(Nature of Residue in Animals). The Agency has concluded that data for MSMA may satisfy requirements for disodium methanearsonate (DSMA).

The Agency also determined that the nature of the residue in ruminants is now tentatively understood. The only residue identified in ruminant and poultry liver and kidney and in egg whites was cacodylic acid (CA). However, inorganic arsenic was not sought.

The Agency did conclude that there is no reasonable expectation of finite residues. However, you are still required to test tissue, milk and egg samples from both metabolism studies using a validated total arsenic method to confirm that demethylation is not a significant pathway for MSMA in ruminants. The subjection of

CONCURRENCES								
SYMBOL	RCB	1508W						
SURNAME	Rieder	WILHITE						
DATE	2/8/95	2/8/95						

livestock metabolism study samples to total arsenic method analysis will serve to validate/confirm results of the livestock metabolism study. Tolerances and feeding studies are not required at this time though the Agency will review any submissions that would better refine our knowledge of MSMA.

I have enclosed a copy of the Agency evaluation of your suplemental submission. If you have any questions please contact Ron Kendall in the Accelerated Reregistration Branch at (703) 308-8068.

Sincerely,

Jay S. Ellenberger, Chief
Accelerated Reregistration Branch
Special Review and
Reregistration Division

cc: Dolphine Wilson, PM22

7508W:R.Kendall:rk:02/02/95:Rm:4L3:308-8068:Disk:cy95:MSMA14

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