MSMA List B File

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

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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Monosodium methanearsonate (MSMA); Disodium methanearsonate (DSMA); Cacodylic acid (CA). Issues to be presented at the 12/19/94 meeting of the HED Metabolism Committee.

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TO: HED Metabolism Committee
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Background

Tolerances are currently established for the selective post-emergence herbicide methanearsonic acid (calculated as As_2O_3) resulting from application of the disodium and monosodium salts of methanearsonic acid in or on cottonseed (0.7 ppm) and in or on 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 methanearsonic acid in cottonseed hulls from application of the disodium and monosodium salts

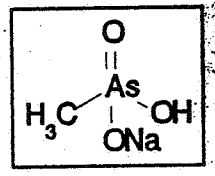
of methanearsonic acid in the production of cotton [40 CFR §186.4050].

The methanearsonic acid salts comprise List B reregistration case no. 2395. A Phase 4 review was completed 3/28/91 (memo, C. Olinger, CBRS Nos. 6974, 7058, 7097, and 7215), in which plant metabolism studies were required for cotton, a grass, and a citrus fruit.

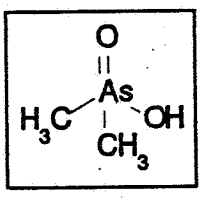
The HED Metabolism Committee has previously discussed the metabolism of MSMA in cotton (memos, C. Swartz, 6/3/92 and 6/19/92). CBRS requested the discussion in order to determine if it is necessary to regulate metabolites that do not contain arsenic, and if there are any arsenic-containing metabolites considered to be more toxic than others, and, therefore, may require separate regulation/quantitation. The Committee could not reach any conclusions on these issues, because of concerns about the different toxicological effects of organic and inorganic forms of arsenic. It was concluded that the Agency needs to determine whether the risks associated with residues resulting from use of arsenic-containing pesticides need to be assessed in terms of two or more different toxicological end points. Also, the residues to be regulated (included in the tolerance expression) must be agreed upon.

Since the 6/8/92 meeting of the Metabolism Committee, the cotton metabolism study has been upgraded to acceptable, and the lemon (citrus) metabolism study has been deemed acceptable; poultry and ruminant metabolism studies are expected to be upgraded to acceptable (studies under review, CBRS No. 10836, DP Barcode No. D184346, MRID Nos. 42525001 and 42525002). Before the registrant can proceed with ruminant and poultry feeding studies (protocols currently under review, CBRS No. 13945, DP Barcode No. D204932), as well as crop field trials, the Agency must determine which residues are to be regulated.

Similar issues exist for cacodylic acid (CA), an arsenic-containing herbicide (defoliant) which is also a plant and animal metabolite of MSMA. Tolerances are established for residues of the defoliant cacodylic acid (dimethylarsinic acid), expressed as As_2O_3, in or on raw agricultural commodities as follows: 2.8 ppm in or on cottonseed; 1.4 ppm in the kidney and liver of cattle; and 0.7 ppm in meat, fat and meat byproducts (except kidney and liver) of cattle [40 CFR §180.311]. Structures of both MSMA and CA are shown below:



MSMA



Cacodylic acid

MSMA Metabolism Studies

All of the metabolism studies were conducted using ^{14}C-MSMA with the label in the methyl group. Cotton plants were treated at 1.1X; lemons were treated at an exaggerated rate. Dairy cattle were dosed for 7 days at 42 ppm, 40X the maximum theoretical beef cattle dietary burden of approximately 1 ppm. The maximum dietary burden for MSMA in dairy cattle is slightly less than that for beef cattle. Total radioactive residues in milk plateaued after days 3 or 5. Laying hens were dosed for 7 days at 42 ppm, 265X the maximum dietary burden; total radioactive residues increased linearly in the egg yolk, but plateaued at day 4 in the white.

The results of the citrus, cotton, and ruminant and poultry metabolism studies are shown in Tables 1 and 2.

Table 1. Results from Citrus (lemon) and Cottonseed Metabolism Studies.[1]

Crop	Matrix	MSMA	CA	Total ID'd
Lemon	Peel (0.44)	40.8 (0.19)	54.7 (0.24)	95.5 (0.43)
	Pulp (0.07)	35.8 (0.03)	61.2 (0.04)	97.0 (0.07)
	Juice (0.12)	48.2 (0.06)	51.8 (0.06)	100.0 (0.12)
Cotton	Seed (1.49)	62.3 (0.93)	6.0 (0.09)	68.3 (1.02)[2]

[1] The TRR in each matrix is presented; for each metabolite, the %TRR (ppm radioactivity, ^{14}C-MSMA equivalents) is presented. Cotton plants were treated at a 1.1X rate.

[2] Only 72% of the cottonseed TRR was recovered through the extraction procedure; two unknowns found in the aqueous and base hydrolysates together constituting 3.7 %TRR (0.06 ppm) were partially characterized by HPLC retention times.

Table 2. Results of ^{14}C-MSMA Metabolism in Ruminants and Poultry.[1]

Study	Matrix (TRR/1X TRR)	MSMA	CA	Total ID'd
Ruminant	Liver (0.215/0.005)	ND	74.24 (0.160)	74.24 (0.160)
	Kidney (0.292/0.007)	ND	85.16 (0.249)	85.16 (0.249)
	Leg muscle (0.103/0.003)	2.9 (0.003)	80.81 (0.084)[2]	83.71 (0.087)
	Loin Muscle (0.089/0.002)	ND	31.47 (0.033)	39.59 (0.041)
	Day 5 Milk (0.038/0.001)	33.6 (0.013)	15.12 (0.006)	48.72 (0.019)[3]
Poultry	Liver (0.101/0.0004)	ND	68.31 (0.069)	68.31 (0.069)
	Kidney (0.158/0.0006)	ND	81.72 (0.129)	81.72 (0.129)
	Breast muscle (0.119/0.0004)	4.20 (0.005)	84.9 (0.101)[4]	89.1 (0.106)

Table 2. Results of ^{14}C-MSMA Metabolism in Ruminants and Poultry.[1]

Study	Matrix (TRR/1X TRR)	MSMA	CA	Total ID'd
Poultry	Thigh muscle (0.083/0.0003)	ND	27.71 (0.023)	27.71 (0.023)
	Skin/Fat (0.023/0.00009)	17.42 (0.004)	11.23 (0.003)	28.65 (0.007)
	Egg yolk (0.340/0.0013)	21.26 (0.072)	13.87 (0.047)	35.13 (0.119)[5]
	Egg white (0.108/0.0004)	ND	74.27 (0.080)	74.27 (0.080)

[1] The TRR in each matrix is presented, along with the TRR extrapolated to a 1X dose; for each metabolite, the %TRR (ppm radioactivity, ^{14}C-MSMA equivalents) is presented. Ruminants and poultry were treated at 40X and 265X, respectively.

[2] In the original study, 34.17 %TRR (0.032 ppm) was identified as MSMA, while 7.86 %TRR (0.007 ppm) was identified as CA. The results shown above were obtained when the study was upgraded, and additional attempts were made to release bound radioactivity. Perhaps during storage, or during enzyme hydrolysis, some of the radioactivity originally ID'd as MSMA was converted to CA. The data show that MSMA and CA are the principal residues of concern.

[3] Unidentified radioactivity was found in the hexane, suspension and 2 solids fractions.

[4] The results shown above were obtained when the study was upgraded; CBRS required the registrant to attempt to release/identify bound residues.

[5] Unidentified radioactivity in the egg yolk consisted of residues associated with the lipid matrix (16.71 %TRR, 0.057 ppm), and bound residues constituting 48.16 %TRR (0.164 ppm).

CA Metabolism Studies

A cotton metabolism study is currently under review by CBRS (MRID No. 42886601; CBRS No. 12459; DP Barcode No. D194647), and therefore the following information is tentative: total radioactive residues (TRRs) in cotton leaves and seeds harvested 7 days after treatment with ^{14}C-cacodylic acid at 2.18 lb ai/A (1.9X) were 6.99-12.31 ppm (ave.= 9.94 ppm) and 0.002-0.05 (ave.=0.015 ppm), respectively. Radioactive residues in leaves were not characterized or identified. In seed containing 0.05 ppm radioactivity (^{14}C-CA equivalents), parent cacodylic acid was identified at 0.02 ppm (approximately 40%TRR). It is likely that radiovalidation data will be required to upgrade the study, since no information is available on the nature of the residue in leaves (and therefore ginned byproducts, which constitute up to 30% of the beef cattle diet).

Ruminant and poultry metabolism studies are currently under review by CBRS (MRID Nos. 42975001 and 43059901; CBRS Nos. 12827 and 13055; DP Barcode Nos. D196657 and D198198). Lactating goats were dosed with methyl-labeled ^{14}C-CA at 52 ppm for 3 days (30X the maximum dietary burden for cattle, calculated based on worst case residues). Laying hens

were dosed with ^{14}C-CA at 60 ppm (75X the maximum dietary burden for poultry) for 3 days. Results of cacodylic acid livestock metabolism studies are shown in Table 3.

Table 3. Results of ^{14}C-Cacodylic Acid Metabolism in Ruminants and Poultry.[1]

Study	Matrix (TRR)	Cacodylic Acid	Unidentified/Bound
Ruminant	Liver (0.861)	92.0 (0.792)	8.0 (0.069)
	Kidney (0.712)	92.8 (0.661)	7.2 (0.051)
	Muscle (0.208)	97.3 (0.202)	2.7 (0.006)
	Fat (0.044)	81.4 (0.036)	18.6 (0.008)
	Milk (0.055)	41.9 (0.023)	58.1 (0.032)[2]
Poultry	Liver (0.273)	90.3 (0.247)	9.7 (0.026)
	Muscle (0.152)	77.0 (0.117)	23.0 (0.035)
	Fat (0.018)	97.5 (0.018)	2.5 (<0.001)
	Egg yolk (0.237)	84.6 (0.201)	15.4 (0.036)
	Egg white (0.471)	75.3 (0.355)	24.7 (0.116)

[1] The TRR in each matrix is presented, along with, parenthetically, ppm radioactivity in ^{14}C-CA equivalents.

[2] Residues were adequately characterized as unidentified polar (0.013 ppm), unidentified apolar (0.010 ppm) and bound (0.009 ppm) residues.

Analytical Method Considerations

The current enforcement methodology for both MSMA and CA involves oxidation of arsenic in samples to arsine gas (AsH_3), followed by determination of the AsH_3 as As_2O_3 using either colorimetric or atomic absorption methods. A recently submitted study, currently under review in CBRS, describes a GLC method for quantitating MSMA and CA residues in citrus. The method has not, as yet, been proposed as an enforcement method. Several HPLC methods are also cited in the literature as useful for differentiating between arsenicals in biological samples.

Although radiovalidation of enforcement/data collection methods is clearly stated as a requirement, none of the metabolism studies discussed above included validation of the existing/proposed data collection or enforcement methods using samples obtained from the cotton or ruminant/poultry metabolism studies.

Other Considerations

There is a good understanding of uptake and translocation of arsenic by plants. In general,

relatively small amounts of arsenic are involved; however, some plants accumulate arsenic at higher levels than others. The average arsenic level in various food/feed items ranges from 0.06 ppm in cottonseed to 2.83 ppm in sugarbeets. Fish and seafood naturally contain As levels of up to 15 ppm, with an average of approximately 5 ppm; arsenic levels in meats ranged from <0.1 ppm to 1.4 ppm, with an average of 0.5 ppm for all meats. Finally, vegetables and grain averaged 0.4 ppm As [Arsenical Pesticides, ACS Symposium Series, Volume 7, American Chemical Society, 1975].

There is no evidence that demethylation of MSMA or CA occurs to a significant extent in either plants or animals. Therefore, CBRS would expect little inorganic arsenic to be available to humans and livestock as a result of consumption of food/feed items containing arsenic residues resulting from registered uses of MSMA or DSMA.

The reference dose (RfD) for arsenic acid is 0.0042 mg/kg/day, based on a chronic feeding study in the dog. This RfD was taken from the Integrated Risk Information System (IRIS), which lists the Agency-wide accepted risk. Currently, however, there are no food uses of arsenic acid being supported through reregistration. The RfD currently used by OPP in risk assessments for CA is 0.00075 mg/kg/day; an RfD has not been established for MSMA.

CBRS Conclusions/Questions to the Committee

Based on the available data, does the HED Metabolism Committee concur with the following conclusions/courses of action for the active ingredients MSMA and CA?

MSMA/DSMA

- The residues of concern (i.e. those that should be included in the tolerance expression and are of toxicological concern) associated with the use of MSMA and DSMA are MSMA and CA. [This conclusion is based on the low rate or lack of demethylation, and on the inability to distinguish between background As and arsenic resulting from pesticidal use].

- In order to confirm that demethylation is not a significant metabolic pathway for MSMA, the registrant must submit "radiovalidation" data from the metabolism studies using a total arsenic method, as well as develop and provide radiovalidation data for a method capable of quantitating MSMA and CA separately.

- Based on TRR values in tissues from ruminant and poultry metabolism studies, and on 1X feeding levels, there is no reasonable expectation of detectable MSMA residues in livestock tissues, milk and eggs resulting from the currently registered uses. Residues resulting from application of MSMA to cotton can be classified under Category 3 of 40 CFR §180.6(a); feeding studies in ruminants and poultry will not be required.

Cacodylic Acid (CA)

- The residue of concern (i.e. that which is of toxicological concern and requires regulation) associated with the use of cacodylic acid is cacodylic acid, *per se*.

Note: For consistency, residues of CA and MSMA resulting from use of MSMA/DSMA and CA would continue to be calculated as As_2O_3.

cc: CSwartz; MSMA List B Reregistration File; MSMA SF; Cacodylic Acid List A Reregistration File; Cacodylic Acid SF; RF; HED Metabolism Committee; L. Edwards (CBRS/HED); Barbara Briscoe (SRRD/7508W).

7509C:CSwartz:CBRS:CM2:RM804F:703 305 5877:11/14/94
RDI:WJHazel: 11/17/94 MSMetzger:12/5/94 EZager:12/5/94