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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). List B Reregistration Case No. 2395/Chemical ID No. 013803. Submission to Upgrade the Cotton Metabolism Study. MRID No. 43013401. CBRS No. 12891. DP Barcode No. D197117.

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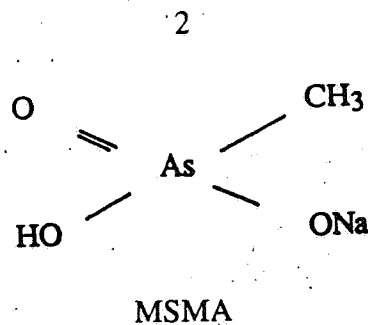
In a letter dated 10/4/93, Chemical Consultants International, Inc. (CCII) on behalf of the MAA Task Force Three has submitted additional information required to upgrade the cotton metabolism study which was reviewed by the Agency in the C. Swartz memo of 5/28/93 (CBRS Nos. 9525, 9942, and 10245).

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 structure of MSMA is:



Recycled/Recyclable
Printed with Soy/Canola Ink on paper that
contains at least 50% recycled fiber



Background

The nature of the residue in citrus (lemon) is adequately understood; the residues of concern in citrus include MSMA and cacodylic acid. In the cotton metabolism study, 33% of the cottonseed TRR was identified as MSMA (27%) and cacodylic acid (7%). An additional 10% of the TRR was characterized as Unknown 1, which the registrant demonstrated contained ¹⁴C-MSMA. Finally, 24% of the cottonseed TRR was characterized as Unknown 2. Additional work conducted with soil metabolites led the registrant to conclude that Unknown 2 also contained MSMA. Based on the registrant's conclusions, 61% of the cottonseed TRR was identified as MSMA, while 7% was identified as cacodylic acid.

CBRS required that the registrant submit more detailed information regarding the soil analytical work. In the mean time, CBRS addressed the following questions to the HED Metabolism Committee (memo, C. Swartz, 6/3/92):

- 1) Is it necessary to regulate metabolites that do not contain arsenic?
- 2) Are there any arsenic-containing metabolites considered to be more toxic than others and, therefore, may require separate regulation/quantitation?

During the 6/8/92 meeting of the HED Metabolism Committee, it was determined that inorganic and organic forms of arsenic may have different TOX endpoints. The Committee decided not to address the CBRS questions until after the RfD committee had discussed MSMA (C. Swartz memo, 6/19/92).

For both the citrus and cotton metabolism studies, the registrant was required to analyze cottonseed and lemon samples using the data collection and enforcement methods, to ensure that the methods detect all residues of concern. The Agency also required that the registrant determine the total arsenic levels in the RACs, in order to ascertain that all ¹⁴C residues are associated with arsenic.

Registrant Response

In response to CBRS questions regarding the soil analytical work, CCII has submitted additional information (MRID No. 43013401), including radiochromatograms from the soil extracts, and

a discussion of the soil analytical work. The registrant intends to complete radiovalidation of the analytical methods by 5/94. Regarding the determination of total arsenic, the registrant is not certain why this was required, and noted that naturally occurring arsenic would be included in such a determination. Furthermore, since cleavage of the methyl group containing the radiolabel is likely to occur to a large extent, there is likely to be a disparity between total ¹⁴C and total arsenic.

CBRS Conclusions

1. The additional information regarding soil extract analyses submitted by the registrant demonstrates that both Unknowns 1 and 2 found in cottonseed extracts in the original study contain MSMA.
2. The additional information is adequate to upgrade the previously submitted study.
3. CBRS concludes that the nature of the residue in cotton is adequately understood. Residues of concern in cottonseed include MSMA and cacodylic acid, MSMA being the primary residue of concern.
4. The Agency's primary reason for requiring the analysis of cottonseed samples for total arsenic was that if the registrant could not further characterize or identify Unknowns 1 and 2, an alternative approach would be to demonstrate that these metabolites either did or did not contain arsenic. Since the registrant has satisfied the Agency regarding the nature of these unidentified metabolites, the requirement to analyze cottonseed for total arsenic is moot. Analysis of cottonseed samples obtained from the metabolism study for total arsenic is no longer required.

Recommendation

The registrant has satisfied the Agency's requirements, and CBRS now concludes that the nature of the residue in cotton is adequately understood. While analysis of cottonseed samples for total arsenic is no longer required, CBRS notes that this issue may eventually need to be readdressed, since there are other arsenic containing pesticides [with similar uses] being supported through reregistration. We urge that radiovalidation of the regulatory method continue to be pursued actively by the registrant (due 5/94).

If you need additional input, please advise.

DETAILED CONSIDERATIONS

In the current submission, the registrant has provided more details regarding the soil analytical work. The performing laboratory was in the process of conducting a rotational crop study, when

it became apparent that soil extracts contained two unidentified peaks eluting at 3.5 and 30.5 minutes, respectively; the similarity between these peaks and the two unidentified peaks isolated from cottonseed extracts was noted. Since the peaks were found in an extract from soil which had been fortified the same day, and since MSMA is known to be fairly stable, it was assumed that the two unidentified peaks were artifacts of the HPLC system (i.e. the peaks were due to matrix effects).

Since greater quantities of the soil extract were available, additional work to characterize these metabolites was conducted using the soil extracts. More soil extracts were subjected to HPLC, and showed that the retention time of Unknown 2 varied between 31 and 34 minutes; radioactivity in extracts from soil fortified with ^{14}C -MSMA was present only as Unknown 2 at times, but at other times MSMA and Unknown 1 were also present. Multiple injections of the soil extracts were made, and sufficient quantities of Unknowns 1 and 2 were eluted, evaporated, and the residues reconstituted in water. The residues were then analyzed using HPLC, TLC, and (after derivatization) GC/MS.

As stated in the original report, HPLC analysis of Unknown 2 demonstrated a shift in the retention time from 31 to 34 minutes to 12 to 15 minutes; CBRS notes that the peak was much more broad than typical MSMA peaks. Normal phase TLC analysis of the fractionated Unknown 2 showed that the R_f of Unknown 2 was the same as that of MSMA. Analysis using GC/MS indicated the presence of MSMA. Sample radiochromatograms and spectra were provided. Similar analysis of Unknown 1 demonstrated that Unknown 1 also contained MSMA. As with Unknown 2, the MSMA peak on the HPLC radiochromatogram was more broad than typical MSMA peaks. GC/MS results of Unknown 1 were not conclusive, as sufficient quantities were not available.

Regarding analysis of the cottonseed samples for total arsenic, the registrant stated some confusion as to what correlation the Agency intends to make between total arsenic and ^{14}C -associated arsenic. The registrant points out that a disparity between total arsenic and total ^{14}C would be possible, through cleavage of the radiolabeled methyl group, and due to the presence of naturally-occurring arsenic.

CBRS Comments

The additional information submitted by the registrant regarding the identities of Unknowns 1 and 2 is sufficient to upgrade the cottonseed metabolism study. CBRS can now conclude that the registrant has identified 67% of the cottonseed TRR as MSMA and cacodylic acid; bound residues constituted 9% of the cottonseed TRR, and the remaining radioactivity was either unidentified or was not recovered through the extraction and hydrolysis procedure.

The Agency's primary reason for requiring the analysis of cottonseed samples for total arsenic was that if the registrant could not further characterize or identify Unknowns 1 and 2, an alternative approach would be to demonstrate that these metabolites either did or did not contain arsenic. Since the registrant has satisfied the Agency regarding the nature of these unidentified

metabolites, the requirement to analyze cottonseed for total arsenic is moot. However, this issue may eventually need to be readdressed, since there are other arsenic-containing pesticides [with similar uses] being supported through reregistration. We urge that radiovalidation of the regulatory method continue to be pursued actively by the registrant (due 5/94).

cc: CSwartz; List B File; RF; SF; Circulation.

7509C:CSwartz:CBRS:CM2:Rm804F:703 305 5877:3/9/94

RDI:RBPerfetti:5/10/94 WJHazel:5/10/94 MSMetzger:5/12/94

EZager:5/16/94