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

JAN 4 1993

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: SAN-582H (Dimethanamid/Frontier®). Metabolism and Residue Data. Submission dated 10/15/92.

DP Barcode: D183772. CBTS # 10763.
MRID # 425162-01, -02; 425160-00, -03.

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The present submission, dated 10/15/92 consists of Sandoz Agro Inc.'s response to metabolism questions in our 7/29/92 review and analyses of corn samples for residues of the sulfonate metabolite of SAN-582H.

Conclusions (Pertaining to this memo only)

1. The nature of the residue in ruminants is adequately understood. The parent compound is extensively metabolized in ruminants. No one compound is present at more than 10% of the total SAN-582H residue. The HED Metabolism Committee has concluded that tolerances for SAN-582H in ruminants and poultry commodities are not necessary at this time.

2. The nature of the residue in corn is basically understood. SAN-582H is extensively metabolized. The sulfonate conjugate of SAN-582H is the principal

metabolite. The HED Metabolism Committee concluded that the tolerance expression for SAN-582H in/on corn need only include the parent compound. However, that conclusion was based on preliminary information that the sulfonate conjugate was not present in corn racs at levels exceeding 0.05 ppm. (See following conclusion.)

3. Residue data from field trials held during 1991 and 1992 generally show sulfonate levels <0.05 ppm in corn racs. Higher levels were found in samples from the 1992 South Dakota field trial, but these levels could be due to an interference. Portions of the check sample (0.068 ppm), the preemergence treated sample (0.094 ppm) and early postemergence treated sample (0.101 ppm) should be fortified with the sulfonate conjugate at 0.05 ppm and chromatograms compared with those from the unspiked samples. If we cannot conclude that the peaks in the unfortified samples are due to interferences, it will be necessary to reevaluate the HED Metabolism Committee's conclusions using a sulfonate conjugate level of 0.2 ppm rather than 0.05 ppm.

Recommendation

CBTS recommends against the proposed tolerances for reasons given in Conclusion 3 of this memo.

Detailed Considerations

Deficiencies in our 7/29/92 review are listed along with Sandoz's response and CBTS' comments.

Deficiency 1a,1b (Conclusions 1a,1b from our 7/29/92 memo)

The nature of the residue in corn plants is not as yet adequately understood. Additional characterization of the very polar components of the methanol soluble fraction (A5) from forage is necessary. Refer to discussion in text of this memo, page 13.....

Conclusions in this memo concerning the nature of the residue in corn plants as well as the need for residue data on two metabolites...are provisional, pending review by the HED Metabolism Committee.

Sandoz Response

The following report has been submitted:

"Response to the EPA's Concerns (CBTS # 9880 of 7/29/92) on the Corn Metabolism of SAN-582H Study;" P.A. Moore; 10/9/92; Sandoz Agro Inc. Report 414105-14B. (MRID # 425162-01)

Forage treated in 1988 with 1.5 lbs ai/acre ^{14}C-SAN-582H was extracted and partitioned in a manner similar to that described

previously (see our 7/29/92 memo, Attachment 1) except that hexane and neutral methylene chloride partitioning steps were omitted. The aqueous fraction was acidified to pH 1 and extracted with methylene chloride, as before. The aqueous fraction was freeze dried, then solubilized with methanol to give fraction A5 and with water to give fraction A6.

Fraction A5 was characterized by TLC using the solvent system ethyl acetate/isopropanol/formic acid/water, 60/30/5/5. The lowest Rf radiocarbon band was scraped, reconcentrated in methanol and rechromatographed. The low Rf component represented 3.4% of total radioactive residue (TRR) or 0.0112 ppm. This same component when incubated in 3N HCl at 90°C for 6 hours "carmelized". The carmelization was possibly due to sugar coextractives and did not occur when the temperature was held at 50°C. TLC after the milder hydrolysis showed a very diffuse band. Because the sulfonate conjugate could be recovered intact from sucrose solutions under the 50°C hydrolysis conditions, the low Rf component is not likely to be the sulfonate conjugate. Previous work, summarized in our 7/29/92 memo, showed that neither α- or β-glucosidase, nor sulfatase, nor glucuronidase rendered components of A5 organosoluble.

Work was also done on A5 from a 1990 corn forage radiolabeled study (rotational crops). In this case the TRR was much lower than the earlier study, even though the rate was exaggerated (4 lb ai/A); and the low Rf component of A5 was only 0.005 ppm.

CBTS Comment

At this time no further work on this fraction is advisable. This deficiency (1a) is resolved.

The HED Metabolism Committee, in its meeting of 11/3/92, concluded that only the parent compound should appear in the tolerance expression for corn grain, forage and fodder. This conclusion was based in part on the preliminary report of residue data which showed absence of the sulfonate conjugate of SAN-582H at a level of 0.05 ppm.

Deficiency #2a

The nature of the residue in ruminants is not as yet adequately understood. Additional characterization of liver metabolites L15a, L15b and L15c is required -- at least to the point of demonstrating that they are not the same metabolite.

Sandoz Response

The following report has been submitted:

"SAN-582 H: Addendum to Previous Goat Metabolism

Studies;" A.S. Guirguis and C.C. Yu; 10/7/92; Sandoz Agro Inc. Report No. 414105-6B. (MRID # 425162-02)

Metabolites L15a, L15b and L15c were respectively found in the organosoluble fraction released by base hydrolysis, in the free solvent extract and in the organosoluble fraction released from acid hydrolysis. Their retention times were almost identical in the TLC solvent system used for characterization (n-butanol/acetic acid/water 60:15:25), and we suggested that they might be the same compound. If that were the case, that compound would constitute more than 10% of TRR.

Sandoz has now submitted TLC results from a different solvent system: chloroform/acetic acid/methanol 80:10:10. In this system, metabolite L15a separated into four components; L15b separated into two components and L15c separated into three components.

CBTS Comment

Although it is still uncertain whether all 9 components are different compounds, we can conclude from the Rf factors and the corresponding concentrations that no one compound will constitute as much as 10% of TRR. (L15a2, Rf 0.22 and 2.24% of TRR and L15b1, Rf 0.25 and 2.67% of TRR could conceivably be the same compound, but if so would still constitute < 5% of TRR.)

The nature of the residue in ruminants is now adequately understood. SAN-582H is extensively metabolized. A total of 18% of TRR is identified. The remaining unidentified metabolites do not individually comprise more than 10% of TRR.

Deficiency # 5b

Residue data for the sulfonate conjugate of SAN-582H and the sulfoxide of thiolactic acid conjugate of SAN-582H in corn grain, forage and fodder should be generated from field trials held in six states. Analyses should be supported by appropriate storage stability data. This requirement is made because of the absence of a suitable common moiety analytical method and is provisional, pending review by the HED Metabolism Committee.

If these metabolites (or common moiety) are non-detected in residue samples, the appropriate tolerance will be for parent only, pending concurrence by the HED Metabolism Committee.

Should it be necessary to regulate these metabolites, the analytical methods must undergo independent laboratory validation and EPA method validation.

Sandoz Response

Sandoz has submitted the following report:

"Analysis of Corn Samples for Residues of the Sulfonate Metabolite of SAN-582H;" K.L. Smith; 9/11/92; Sandoz Agro Inc. ID 414108-32. (MRID # 425160-03)

Samples from field trials held during 1990 in IL, IA, NY, NE

and OH and during 1991 in NC, CO, IN, OH, IL and IA were analyzed for the sulfonate metabolite. SAN-582H was applied preemergence, preplant incorporated and early postemergence at each site at an application rate of 1.5 lbs ai/A (1X). In addition, SAN-582H was applied preemergence at 7.5 lbs ai/A in OH for a processing study. All samples had been analyzed previously for SAN-582H.

Samples were analyzed by method AM-0868-09392-1, Sandoz's method for sulfonate. The method was reviewed in our 12/16/92 memo. The time interval between sampling and analysis of samples from the 1990 trials varied from 19 months to two years for forage, silage and fodder. Grain was analyzed slightly earlier. No detectable sulfonate residue is expected in grain because total radioactivity from the radiolabeled study was low to begin with (<0.03 ppm). As stated in our 12/16/92 memo, storage stability data will support residue analyses of the sulfonate metabolite for periods up to 16 months only. Therefore, until adequate storage stability data are received, we will not comment on these data. The time intervals between sampling and analysis of samples from the 1991 trials were always less than 13 months, so these residue data will be considered.

Percent recoveries are basically acceptable and were discussed in our 12/16/92 memo. Claimed limits of detection are 0.2 ppm for forage, 0.1 ppm for fodder and silage, and 0.05 ppm in grain and processed commodities. "This represents the method limit for excluding false positives, however in the majority of the samples, no Sulfonate or interference was detected at levels of 0.05 ppm or below." Our 12/16 memo noted occasional large differences between recoveries and "corrected recoveries", and we concluded that some samples probably had major interferences. The few chromatograms that were submitted as part of the method showed no interferences.

Chromatograms were submitted in a meeting held on 9/17/92 and subsequently by letter dated 10/28/92. Some of the residue data were from six trials held during 1992 in MN, WI, MI, IN, SD, and MO. Forage samples were collected 30-72 days after preplant, preemergence, or early postemergence treatment at 1.5 lbs ai/A. Samples were analyzed within 60 days of collection. The analyses were not relevant to the submission accompanying the letter -- analysis of goat excreta for the sulfonate metabolite -- so they are reviewed in this memo. At issue is whether CBTS can conclude from these chromatograms that the sulfonate is not present at 0.05 ppm -- even though it cannot be quantitated at that level. Sulfonate was not detected in forage at the quantitation limit of 0.2 ppm, but samples showed apparent sulfonate levels ranging from 0.007 ppm to 0.101 ppm. These are shown in the following table.

Table 1

Apparent Sulfonate Levels Found in
Treated Forage from Field Trials Held During 1992

Site	Treatment Type	Apparent Sulfonate (ppm)
IN	preplant	NR
	preemergence	NR
	early post	NR
MI	preplant	0.021
	preemergence	0.026
	early post	0.014
MN	preplant	0.007
	preemergence	0.007
	early post	0.009
MO	preplant	0.059
	preemergence	0.044
	early post	0.039
SD	preplant	0.027
	preemergence	0.094
	early post	0.101
WI	preplant	0.008
	preemergence	0.015
	early post	0.013

From examination of the chromatograms we are able to conclude that forage samples from trials held in MN, WI, and MI contained no sulfonate at a level of 0.05 ppm. Interpretation of the other chromatograms is more problematical. Chromatograms of extracts from forage samples taken from the IN trial showed no detectable sulfonate, but the only fortified sample present was fortified at 0.5 ppm. The recorded peak height is lower than those from other samples fortified at 0.2 ppm, suggesting different chromatograph settings. The problem is exemplified by results from the SD trial (Attachment). Here, preemergence treatment and early postemergence treatment resulted in levels exceeding 0.05 ppm. However, the reported check sample showed a

peak equivalent to 0.068 ppm sulfonate. Should this be subtracted from the treated sample results? Sandoz argues that levels of the sulfonate are <0.05 ppm because at room temperature the sulfonate metabolite is a rotamer -- the sulfonate standard produces two GC peaks -- and the peak with the lower retention time is not apparent in the chromatograms of treated samples. The second peak does appear as a shoulder in the chromatogram of the check sample fortified with 0.2 ppm sulfonate, but we question whether fortification with 0.05 ppm sulfonate would produce anything other than an ambiguous shoulder. Sandoz should obtain chromatograms of check and the two treated samples from the SD trial into which 0.05 ppm sulfonate has been spiked. If these chromatogams show no unambiguous side peak, we will have to evaluate the residue data assuming a level of 0.2 ppm sulfonate. The chromatograms from the MO field trial show similar ambiguities, but the SD results represent the worst case.

Attachment: Chromatograms from SD field trial samples.

cc: RF, SF(SAN-582H), Circu., PP#0G3892, PP#0F3918, Mike Flood, E. Haeberer.

H7509C:CBTS:Reviewer(MTF):CM#2:Rm804P:305-6362:typist(mtf):12/31/92.
RDI:SectionHead:ETHaeberer:12/30/92:BranchSeniorScientist:RALoranger: 12/31/92.

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