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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: Laboratory Data Audit of Sandoz Agro, Inc. SAN-582H (Dimethanamid). Development of Common Moiety Analytical Method. MRID # 423368-01.

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THROUGH: Elizabeth T. Haeberer, Section Chief
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Background

SAN-582H (also known as dimethanamid or Frontier® Herbicide) is a preemergence/early postemergence herbicide to be used on corn and soybeans. Sandoz Agro, Inc. in PP0F3918 is petitioning for tolerances of 0.01 ppm for residues of parent in/on field corn grain, forage and fodder. The petition has not as yet been finalized.

The nature of the residue of SAN-582H in/on corn is adequately understood. SAN-582H is extensively metabolized in corn. The parent compound has not been identified in treated corn, and no individual metabolite has been found in concentrations greater than 10% of the total SAN-582H residue. All identified metabolites were found to have the thienyl ring of the parent unchanged.

Because parent or any individual metabolite is not expected to be present at detectable levels, the question of a suitable regulatory analytical method arises. In cases such as this, a registrant usually develops a "common moiety" analytical method, i.e., a method in which numerous metabolites -- present at very low concentrations -- are chemically converted to one or several discrete compounds which can be quantitated analytically. For example, in the case of the structurally similar herbicide alachlor, metabolites can be converted to either 2,6-diethylaniline or 2-(1-hydroxyethyl)-6-ethylaniline, and both these compounds are individually quantitated.

As part of PP#0F3918, Sandoz submitted a summary of its attempts to develop a common moiety method. All attempts were reportedly unsuccessful, i.e., when metabolite standards were subjected to various chemical transformations, different metabolites produced different compounds. In the absence of a suitable common moiety analytical method, CBTS would have no recourse other than to regulate parent SAN-582H itself, even though parent might be present in detectable quantities only in the event of gross misuse. Because of the importance of the common moiety method, CBTS asked to examine the raw data, which were only summarized in the Sandoz report. Therefore an audit was requested.

**Conclusions**

1. CBTS is satisfied from review of the data that a good faith effort was made to develop a common moiety analytical method for SAN-582H and its metabolites.

2. Although not affecting our previous conclusion, the analytical method for metalaxyl should have been carried out with metalaxyl as a positive control.

**Recommendation**

CBTS recommends no further action concerning this report, which can be considered a valid part of PP#0F3918.

**Detailed Considerations**

The following report was audited by CBTS:

"Common Moiety approaches for Development: a Residue Method for Analysis of SAN 582H and Its Metabolites," T.M. Bade, 5/26/92, Sandoz Agro ID No. 10582-10. (MRID # 423368-01)

The work was performed at Sandoz Agro Inc.'s laboratories in Des Plaines, IL, and was not a GLP study. As a part of OCM's general audit process, several GLP studies were reviewed

concurrently. In addition to this reviewer, EPA was represented by a chemist from OCM and three members from the Region V office.

CBTS' 7/28/92 memo for PP#0F3918, in which the Sandoz summary is reviewed, is given as Attachment 2 to this memo. The audit consisted of examination of all the supporting data that led to the Sandoz report. All laboratory notebooks were reviewed with the assistance of the various notebook authors: Saad Laban, Ken Smith, and Leo Formanski. A fourth author, Albrecht Glaenzel, was not present. Saad Laban assisted in reviewing Glaenzel's data. Not surprisingly, the notebooks were written with various degrees of clarity, depending on the author. Review without the assistance of the author would have been difficult, and at times impossible. There would typically be a description of an experiment using SAN-582 or one of the metabolites as one of the reactants along with the resulting GC/MS printout and identification of relevant product peaks, if possible. Percent recoveries were calculated when applicable.

The purpose of this particular audit was not to evaluate compliance with GLP regulations but to verify that Sandoz had indeed carried out a major effort to develop a common moiety method. From review of the available data, CBTS concludes that such an effort was made. However, occasional mislabelings of chromatograms were noted. Chromatograms were pasted into the notebook following the description of the experiment. While this procedure facilitated review, the question arises whether all relevant chromatograms were included. This issue was also raised in the GLP study audits. According to Sandoz, even if all chromatograms are not present in the notebooks, all data are on disk or tape and can therefore be retrieved if necessary.

Because many of Sandoz's experiments involved reaction of Raney Nickel with SAN-582H and its metabolites and because there are different types of Raney Nickel, we requested documentation for this test substance. Documentation was provided to our satisfaction. Raney Nickel was purchased from Sigma as a 50% suspension in $H_2O$ at pH 10.

CBTS' one criticism of the study concerned Sandoz's use of the metalaxyl residue analysis method to generate an amine common moiety from SAN-582H and its sulfonate conjugate. (Refer to Attachment 2, page 3.) Metalaxyl is structurally very similar to SAN-582H -- metalaxyl contains a benzene ring, SAN-582H contains a thienyl ring. Use of the metalaxyl method failed to produce a common moiety, but apparently no attempt was made to test the method on metalaxyl itself to demonstrate that the analytical method was being properly utilized. In particular, amines formed from base hydrolysis can be easily lost during steam distillation -- a common problem in this and related methods.

One very positive aspect of Sandoz's attempt is that the major reactions attempted -- hydrolysis, reaction with Raney Nickel -- were independently repeated by a synthetic organic chemist, Albrecht Glaenzel, visiting from the main laboratory in Basel, Switzerland. He too was unable to obtain any common moiety.

CBTS has no further questions concerning this study. At this time, the residue to be regulated remains SAN-582H only.

Attachment 1: Title page of Sandoz's summary report submitted in PP#0F3918.
Attachment 2: CBTS memo for PP#0F3918 dated 7/28/92.

cc (without Attachment 2): SF; Circu.; PP#0F3918; E. Haeberer; Mike Flood; D. Edwards; C.Giles-Parker/J.Stone, PM 22 (H7505C).

cc (with all attachments): Frances Liem (EN-342W), RF.

H7509C:CBTS:Reviewer(MTF):CM#2:Rm804P:703-305-7990:typist(mtf):2/9/93.
RDI:SectionHead:ETHaeberer:2/8/93:BranchSeniorScientist:RALorangèr: 2/9/93.