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WASHINGTON, D.C. 20460

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**EXPEDITE**

OFFICE OF  
PESTICIDES AND TOXIC  
SUBSTANCES

MEMORANDUM

SUBJECT: PP#0F3918 -- SAN-582H. Attempts to Develop "Common Moieity" Analytical Method. Submission dated 5/26/92.

DP Barcode: D179409 CBTS # 10051.  
MRID # 423368-01.

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This review is being expedited at the request of the Registration Division. The due date is 7/31/92.

Background

SAN-582H, 2-chloro-N-(2,4-dimethyl-3-thienyl)-N-(2-methoxy-1-methylethyl) acetamide, a preemergence or early postemergence herbicide, is extensively metabolized in corn and [REDACTED]. Although the nature of the residue is not as yet adequately understood -- see our concurrent memo for this petition -- it appears that no one component of the residue is present at greater than 10% of the total residue resulting from application of SAN-582H. For this reason, Sandoz Agro Inc. has been attempting to develop a "common moiety" analytical method, i.e., a method in which all or most of the metabolites are converted to a common species which can then be analyzed. The company has

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heretofore not been successful. The present submission summarizes Sandoz's attempts to date. A preliminary account of attempts to develop a common moiety analytical method appeared in the corn metabolism study of Sandoz's first submission (MRID # 415965-54)

### Detailed Considerations

Sandoz has submitted the following report:

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

Basic approaches investigated included the following: acid hydrolysis, base hydrolysis, reduction and desulfurization with Raney Nickel, oxidation, thiophene protection/stabilization followed by hydrolysis. Sandoz's criteria for a successful method were: 1) Generation of a SAN-582H fragment in consistent and preferably high yields, 2) Generation of this fragment from several different metabolites or from a radioactive mixture of all metabolites and 3) Generation of this common moiety from metabolite levels in the range 0.01 ppm to 0.5 ppm.

Acid Hydrolysis. Hydrolysis of SAN-582H with acid required strong acid and heat. Sulfuric acid (70%) produced a large range of products. Concentrated hydrochloric acid gave an 86% recovery of hydroxypropyl thiophene amine. (Structures are given in the attachment.) Hydrolysis of the cysteine conjugate of SAN-582H also produced the amine but at lower yield; hydrolysis of metabolite M3 -- SAN-582H with the Cl replaced by an H -- produced only trace amounts.

Attempted hydrolysis with 1N HCl at 95°C demonstrated that M3, M4, M11 and parent were recovered intact. When concentrated acid was used, recoveries were dependent on initial concentration. Hydroxypropyl thiophene amine recoveries of 54% and 36% could be obtained from milligram quantities of SAN-582 H and oxalamide, respectively; but at the microgram level no amine could be detected. Sandoz conducted a number of experiments, including use of dry HCl in methanol, 85% phosphoric acid, and a weak organic acid, with similar results.

Attempts to generate the hydroxypropyl amine from radioactive corn fodder extracts (presumably methanol extracts) using hydrolysis at 95°C for 3 hours with 1N, 6N, or 12N HCl produced no radioactivity in the ether extracts of the neutralized hydrolysates.

In an effort to stabilize the secondary amine during hydrolysis, Sandoz successfully acylated the amine using acetic anhydride but results could not be duplicated at expected residue

levels. Sandoz next attempted to block the thiophene ring from reaction by nitrating or acylating the 5-position, the only unfunctionalized position on the ring. Nitration (70% nitric acid in acetic anhydride) using 20 mg SAN-582H gave the nitrated product, but reaction with either 20% HCL or concentrated phosphoric acid at 95°C for 2 hrs. did not give any isolated amine products. Acylation using acetic anhydride and 1 mg. of sulfonate metabolite gave a small amount of acylated material but the experiment could not be repeated at the 10 µg level.

#### Base Hydrolysis

Synthetic base hydrolysis -- concentration unspecified -- of SAN-582H in various solvents resulted in products from displacement of the chloro group or recovery of the parent compound. Soil samples were fortified with 0.2 ppm M3, M4, M7, M9, M11, M12, PL1588, PL1688, and SAN-582H and subjected to 1N KOH at 90°C for one hour. M3, M4, M11 and M12 remained unchanged under conditions of hydrolysis, M7 was converted to M9 and SAN-582H was converted to M11. After 1N KOH hydrolysis of corn forage and subsequent methanol/water extraction, fortified cysteine conjugate was recovered intact.

The metalaxyl residue analysis method -- an acid hydrolysis followed by a base hydrolysis and steam distillation -- failed to generate a known product from SAN-582H or its sulfonate metabolite.

#### Reaction with Raney Nickel

It was hoped that reaction with Raney Nickel would remove sulfur containing segments of various conjugates and yield a common moiety. The cysteine conjugate reacted to form M3 and N-methyl-N-methoxypropyl-N-thiophene amine. The concentration of M3, the expected product, could be maximized relative to the thiophene amine by increasing the pH to 13-14; but recoveries of radioactivity from plant material fortified with <sup>14</sup>C-cysteine conjugate were less than 50%, and recoveries of M3 from fortified soybean hay extract ranged from 19 to 46%. M3 could be recovered from standards of M17 (mercapturic acid), the sulfoxide of the cysteine conjugate, and the thiolactic acid conjugate at levels of 40%, 32% and 53%, respectively. However, recovery of M3 from a radioactive soybean hay sample from the soybean metabolism study was only about 2%.

#### Oxidation

Attempts were made to generate a common moiety through oxidation using potassium permanganate or chromate. For example, oxidation of SAN-582H in acetone with 1M potassium permanganate and 6N HCl at 95°C for one hour gave at least two chlorinated high molecular weight materials and unreacted SAN-582H.

### Other Attempts

Reaction with  $\text{PCl}_5$  in toluene or reduction with lithium aluminum hydride di-(methoxyethoxy ether) did not produce any known compound. Mass spectrometric measurement of a common ion from all SAN-582H related materials demonstrated a large variation in the ionization potential and therefore response factors for various metabolites and SAN-582H. Capillary electrophoresis and counter current chromatography were found to lack the sensitivity necessary at residue levels.

### Conclusion

To date, the registrant has been unable to develop a common moiety method. As stated in our concurrent memo for PP#0F3918, in the absence of a common moiety method and pending review by the HED Metabolism Committee, residue samples must be analyzed for the sulfonate conjugate of SAN-582H and the sulfoxide of thiolactic acid conjugate of SAN-582H. These two metabolites were found at the highest concentrations in corn forage --  $\leq 10\%$  of the total radioactive residue. If no metabolite can be detected in residue samples, a tolerance in/on corn will have to be set for parent only.

Attachment: Structures of SAN-582H and metabolites.

cc: RF, SF, Reg.Std. File, Circu., PP#0F3918, Mike Flood, E. Haeberer.  
H7509C:CBTS:Reviewer(MTF):CM#2:Rm800A:305-6362:typist(mtf):7/27/92.  
RDI:BranchSeniorScientist:RALoranger:7/27/92.

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