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

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OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

Subject: SAN 582H (Dimethanamid/Frontiere®). Toxicology data.
MRID Nos. 425160-04, 425160-05, 425160-06, 416624-14
Barcode Nos. D181808, D185350, D185488
Submission Nos. S423987, S427885, S430836
ID Nos. OF03918, 055947-RUR
PC Code: 129051

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Thru: James N. Rowe, Ph.D., Head
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Marcia van Gemert 1/28/93

This review is being expedited at the 1/13/93 request of Lawrence E. Culleen, Acting Director, Registration Division. The due date is 1/28/93.

ACTION:

Expedited review of the following submissions has been requested:

1. Submission S423987

   - Toxicology of dimethanamid corn metabolites/Response to 6/8/92 meeting with Toxicology Branch. [No MRID Number].

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2. Submission S427885

- o SAN 582H: Determination of the Presence of Plant Metabolites in Rat. (Interim Report). [MRID 425160-04].
- o SAN 582 H: Addendum to determine Sulfoxide of Thioglycolic Acid Conjugate in Mouse Excreta. [MRID 425160-05].
- o Acute Oral Toxicity in Rats. [MRID 425160-06].

3. Submission S430836

- o Additional information required to upgrade the 21-Day dermal toxicity study with MRID 416624-14.

CONCLUSIONS

1. The Toxicology database for the herbicide SAN 582H (Frontier®, dimethanamide) is now complete for Food and Non-Food uses, except for the Dominant Lethal Study. In so far as the toxicology data requirements are concerned, a conditional registration could be granted pending the submission of a Dominant Lethal Study.

2. Although the Metabolism Committee, in its 11/3/92 meeting, concluded that the tolerance expression for SAN 582H in corn grain, forage, or fodder need only include the parent compound, that conclusion was based on preliminary information that the sulfonate conjugate was not present in corn raes at levels exceeding 0.05 ppm. More recently, in a 1/4/93 Memorandum (CBTS #10763, Attachment 1), Chemistry Branch I-Tolerance Support (CBTS) has recommended against the proposed tolerance pending a final conclusion on sulfonate conjugate levels from residue data from field trials.

3. Concerning the waiver of animal feeding studies, the Metabolism Committee (in its 11/3/92 meeting) concluded that tolerances are not necessary for residues on SAN 582H or its metabolites in animal commodities (See Attachment 2). Additionaly, CBTS in a Memorandum dated 1/4/93 (CBTS #9978, Attachment 3) stated that a residue transfer study with ruminants would not likely produce any useful information and is not required. However, future uses resulting in higher residue levels in crops could lead to reassessment.

DETAILED CONSIDERATIONS

1. Submission S423987

Toxicology of dimethanamid corn metabolites/Response to 6/8/92 meeting with Toxicology Branch. [No MRID Number].

This document contains the position of Sandoz Agro, Inc. (SAI) on: (a) the waiver of animal feeding studies and (b) parent-only permanent tolerances. In

addition, this submission contains summary data indicating that the sulfonate metabolite of SAN 582H, the principal metabolite of SAN 582H in corn, is present in urine and feces of mice dosed with SAN 582H.

Concerning issue (a), the Metabolism Committee (in its 11/3/92 meeting) concluded that tolerances are not necessary for residues on SAN 582H or its metabolites in animal commodities (See Attachment 2, for reasons). Additionaly, CBTS in a Memorandum dated 1/4/93 (CBTS #9978, Attachment 3) stated that a residue transfer study with ruminants would not likely produce any useful information and is not required. However, future uses resulting in higher residue levels in crops could lead to reassessment.

Concerning issue (b), the Metabolism Committee (also in its 11/3/92 meeting), concluded that only the parent compound should appear in the tolerance expression for corn grain, forage or fodder. This conclusion was based in part (See Attachment 2) on preliminary information that the sulfonate metabolite of SAN 582H was not present in corn race at levels exceeding 0.05 ppm. Because levels of sulfonate metabollite higher than 0.05 ppm could be present in samples from field trials, CBTS (Attachment 2) has recommended against the proposed tolerance pending a final conclusion on sulfonate metabolite levels from residue data from field trials.

Concerning the presence of the sulfonate metabolite in excreta of orally dosed mice, sulfonate metabolite was found in excreta at levels of 0.26-0.36% of the dose, as shown below:

| Oral Dose Level | Sulfonate metabolite as % of dose | | |
|---|---|---|---|
| (mg/kg) | Urine | Feces | Total |
| 1 | 0.06 | 0.3 | 0.36 |
| 100 | 0.06 | 0.2 | 0.26 |

2. Submission S427885

a. SAN 582H: Determination of the Presence of Plant Metabolites in Rat. (Interim Report). C.C. Yu, A.S. Guirguis, and D.A. Nietschmann. Performed at: Metabolism and Pharmacokinetics Section. Sandoz Agro, Inc. Des Plaines IL. Project No. 414105, Report No. 28; October 6, 1992. [MRID 425160-04].

Introduction

The sulfonate metabolite of SAN 582H (Dimethanamid) has been identified in corn, hen, goat, and mouse. The present report is an interim report of studies performed to determine the presence of the sulfonate metabolite in rats dosed orally with $^{14}$C-SAN 582H.

Experimental

Young CD rats of both sexes (Charles River Co., 5 rats/sex/dose level) received single oral doses of $^{14}$C-SAN 582H at levels of 1 or 100 mg/kg. The radiochemical was 3-$^{14}$C-thienyl labeled and the protocol indicated a radiopurity of 98%.

Urine and feces were collected separately daily for 3 days. All samples were kept frozen until analysis. Pre-coated silica gel chromatoplates were used to separate the sulfonate from other metabolites by thin layer chromatography TLC. Organic extracts of urine and feces were purified by TLC by sequential application of 5 solvent systems (A,I,C,D, and E for urine and A,B,C,E and D for feces). The presence of the putative isolated sulfonate metabolite was confirmed by 2-dimensional TLC and HPLC against synthetic standards. Liquid secondary ion mass spectrometry (LSIMS) showed parent ions consistent with the structure of the sulfonate metabolite.

Results

Sulfonate metabolite was found in rat urine and feces at levels of 0.04-0.05% of the dose, as shown below:

| Dose Level | Sulfonate metabolite as % of dose | | |
|---|---|---|---|
| (mg/kg) | Urine | Feces | Total |
| 1 | 0.025 | 0.016 | 0.041 |
| 100 | 0.030 | 0.020 | 0.050 |

Conclusion

Evidence has been presented for the formation of the sulfonate metabolite in rats dosed with SAN 582H.

b. SAN 582 H: Addendum to determine Sulfoxide of Thioglycolic Acid Conjugate in Mouse Excreta. M.L. Ekdawi and C.C. Yu. Performed at: Metabolism and Pharmacokinetics Section. Sandoz Agro, Inc. Des Plaines IL. Project No. 414105, Report No. 26; September 22, 1992. [MRID 425160-05].

Introduction

The SAN 582H sulfoxide of thioglycolic acid has been identified as a terminal residue in corn and in hen. The current study was done to determine the presence of the sulfoxide of thioglycolic acid in mice dosed orally with $^{14}$C-SAN 582H. This study is an addendum to the following study: Ekdawi, M.L. and Yu, C.C. 1992. SAN 582 H: Determination of the Presence of Sulfonate Metabolite in Mice. Sandoz Agro, Inc. Project No. 414105, Report No. 25, TDS DP300931. June 11, 1992.

Experimental

The Addendum subject of this review does not contain information on the dosing of the mice. For information on dosing the authors refer to the above main study by Ekdawi, M.L. and Yu, C.C. (1992). From summary data and information submitted by the Registrant [Submission S423987, no MRID], mice [strain unspecified] of both sexes received single oral doses of $^{14}$C-SAN 582H at levels of 1 or 100 mg/kg. The radiochemical was 3-$^{14}$C-thienyl labeled with a radiopurity of 98.6%. Urine and feces were collected separately for 4 days and stored frozen until analyzed.

Pre-coated silica gel chromatoplates were used to separate the sulfoxide of thioglycolic acid from other metabolites by thin layer chromatography (TLC).

After initial purification by solvent partition, the organic extracts of urine and feces were purified using TLC by sequential application of 3 solvent systems (A,B, and C). The presence of the putative isolated sulfonate metabolite was confirmed by 2-dimensional TLC and HPLC against synthetic standards. No mass spectrometry data were available.

Results

Sulfoxide of thioglycolic acid was found in mouse urine and feces at levels of of 0.5-0.64% of the dose, as shown below:

| Dose Level (mg/kg) | Sulfoxide of thioglycolic acid as % of dose | | |
|---|---|---|---|
| | Urine | Feces | Total |
| 1 | 0.25 | 0.25 | 0.50 |
| 100 | 0.24 | 0.40 | 0.64 |

Conclusion
Evidence was presented to indicate that the sulfoxide of thioglycolic acid is present in excreta of mice orally dosed with SAN 582H.

c. Acute Oral Toxicity in Rats . D. L. Blaszczak. Bio/dynamics, Inc. East Millstone, NJ. Study Number 92-62-91. [MRID 425160-06].

The single-dose acute oral $LD_{50}$ of the sulfonate metabolite of SAN 582H was found to be > 5000 mg/kg in Sprague-Dawley rats of both sexes. The reported value places the sulfonate metabolite of SAN 582H in Category IV, as far as acute oral toxicity is concerned. The DER for this study is attached (Attachment 4).

3. Submission S430836

Additional information required to upgrade the 21-Day Dermal Toxicity Study in rabbits with MRID 416624-14.

Background
The Registrant Sandoz Agro, Inc. has submitted the additional information on the dose volumes which the Agency requested on the 21-Day Dermal Study in Rabbits (MRID No. 416624-14). In the original DER reviewed by T. McMahon on March 11, 1991, the actual dose applied to the skin could not be verified and the study was classified supplementary.

Conclusion
The dose volume information submitted by Sandoz indicates that the appropriate dosages were administered in the 21-Day study. Therefore, the 21-Day Dermal Study in rabbits (MRID No. 416624-14) will be upgraded from Core Supplementary to Core Minimum.