DATA EVALUATION RECORD - SUPPLEMENT

XDE-570 (FLORASULAM)

Study Type: OPPTS 870.7485 [' 85-1]; Metabolism Study in Rats

Work Assignment No. 4-1-128 S (MRID 46808301)

Prepared for
Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
2777 South Crystal Drive
Arlington, VA 22202

Prepared by
Pesticides Health Effects Group
Sciences Division
Dynamac Corporation
1910 Sedwick Road, Bldg 100, Ste B.
Durham, NC 27713

Primary Reviewer
Ronnie J. Bever, Jr., Ph.D.

Signature: _____
Date: _____

Secondary Reviewer
Michael E. Viana, Ph.D., D.A.B.T.

Signature: _____
Date: _____

Program Manager:
Michael E. Viana, Ph.D., D.A.B.T.

Signature: _____
Date: _____

Quality Assurance:
Mary L. Menetrez, Ph.D.

Signature: _____
Date: _____

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EPA Reviewer: Karlyn J. Bailey **Signature:** _____
Registration Action Branch 2, Health Effects Division (7509P) **Date:** _____
Work Assignment Manager: Myron Ottley, Ph.D. **Signature:** _____
Registration Action Branch 3, Health Effects Division (7509P) **Date:** _____

Template version 02/06

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See TXR # 0054348 for previous DER

This supplement contains:

- New cover page
- New executive summary

STUDY TYPE: Metabolism - Rat; OPPTS 870.7485 ('85-1); OECD 417.

PC CODE: 129108 **DP BARCODE:** D331116
TXR #: 0054348

TEST MATERIAL (RADIOCHEMICAL PURITY): XDE-570 (Florasulam; 99.3-99.5%)

SYNONYMS: *N*-(2,6-Difluorophenyl)-8-fluoro-5-methoxy(1,2,4)triazolo(1,5-*c*)pyrimidine-2-sulfonamide; XR-570; XRD-570; DE-570

CITATION: Dryzga, M. D., S. S. Hiroko, S. C. Hansen, and K. A. Brzak (1996) XR-570: tissue distribution and metabolism of ^{14}C-labeled XR-570 in Fischer 344 rats. The Toxicology Research Laboratory, Health and Environmental Sciences, The Dow Chemical Company, Midland, MI. Laboratory Project ID: HET DR 0312-6565-014, November 14, 1996. MRID 46808301. Unpublished.

SPONSOR: Dow AgroSciences Canada, Inc., 2100- 450 1 St. SW, Calgary, AB, Canada

EXECUTIVE SUMMARY: In a metabolism study (MRID 46808301), [^{14}C]-XDE-570 (Florasulam; 99.3-99.5% radiochemical purity; Lot Nos. B463-145 and B844-08A) in a suspension of 0.5% Methocel™ cellulose ethers was administered to 5 Fischer 344 rats/sex as a single gavage dose at 10 or 500 mg/kg bw. Additionally, 5 rats/sex were treated with 14 daily doses at 10 mg/kg bw/day of non-labeled XDE-570 followed by a single oral dose of [^{14}C]-XR-570 on Day 15. [^{14}C]-XDE-570 was uniformly labeled in the aniline ring for each of these test groups. In addition, 5 males were treated with a single gavage dose at 10 mg/kg bw with [^{14}C]-XR-570 (labeled at the 9 position in the triazolo-pyrimidine ring). All animals were killed 168 hours after the administration of the radiolabeled dose.

Absorption was rapid and extensive. Approximately 90-93% of the dose was absorbed in the 10 mg/kg rats, and 82-86% was absorbed in the 500 mg/kg rats (based on the sum of radioactivity detected in the urine, tissues/carcass, and cage rinse). Peak plasma concentrations (Cmax) were achieved within 0.5-1 hour following dose administration at 10 or 500 mg/kg. Cmax in the

plasma did not increase proportionally with dose, possibly indicating a saturation of the absorption and/or excretion mechanisms at the high dose. The apparent volume of distribution was increased at the high dose, possibly indicative of increased tissue binding.

Total recoveries at 168 hours post-dose were 95.9-100.2% of the administered dose. Elimination was rapid. The administered dose was mostly eliminated within 12 hours in the urine (>80% of the dose at 10 mg/kg and >60% of the dose at 500 mg/kg). Total radioactivity found in the urine was approximately 90-92% of the dose following single or repeated low-dose treatment, and 81-85% of the dose following treatment at 500 mg/kg. Radioactivity in the feces accounted for another 5-7% at 10 mg/kg and 14-17% at 500 mg/kg. Thus, compared to the low dose, excretion of the high dose was slightly slower, and more of the compound was excreted in the feces. At 24 hours, <0.5% of the dose was found in expired air. By 24 hours post-dose, plasma levels had declined to <0.1 µg eq/g plasma in both sexes at 10 mg/kg and <5.0 µg eq/g plasma in both sexes at 500 mg/kg. The highest residue levels were observed in the skin (single dose) and carcass (repeated dose), but the mean recovery of radioactivity in the tissues/carcass at sacrifice was <0.6% of the dose.

Identified compounds accounted for 87.6-91.6% of the administered dose in each group. In each group, the following compounds were isolated: parent accounted for 77.7-85.0% dose, OH-phenyl-XR-570 accounted for 3.1-9.0% dose, OH-phenyl-XR-570 sulfate conjugate accounted for 2.8-3.7% dose, and 2 unidentified metabolites accounted for <=0.32% dose. In the high dose, more of the parent was isolated in the feces and less in the urine compared to the low dose.

There were no sex-related differences in the metabolism or pharmacokinetics of the test compound. Similarly, the number of doses or the position of the radiolabel generally made no difference in the metabolism and pharmacokinetic profile.

This study is classified as **acceptable/guideline** and satisfies the guideline requirement for a metabolism study [OPPTS 870.7485, OECD 417] in rats.

COMPLIANCE: Signed and dated GLP Compliance, Quality Assurance, and Data Confidentiality statements were provided.