DATA EVALUATION RECORD - SUPPLEMENT

XDE-570 (FLORASULAM)

OPPTS 870.4300 [' 83-5]; Combined Chronic Toxicity/Carcinogenicity Study in Rats

Work Assignment No. 4-1-128 N (MRID 46808236)

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: _____

Disclaimer

This Data Evaluation Record my have been altered by the Health Effects Division subsequent to signing by Dynamac Corporation personnel

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

DATA EVALUATION RECORD – SUPPLEMENT

See TXR # 0054348 for previous DER

This supplement contains:

- New cover page
- New executive summary

STUDY TYPE: Combined chronic toxicity/carcinogenicity, dietary study in rats; OPPTS 870.4300 [' 83-5]; OECD 453.

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

TEST MATERIAL (PURITY): XDE-570 (Florasulam; 99.3% a.i.)

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: Johnson, K. H., K. T. Haut, and K. E. Stebbins (1997) XDE-570: Two year chronic toxicity/oncogenicity study in Fischer 344 rats. The Toxicology Research Laboratory, Health and Environmental Sciences, The Dow Chemical Company, Midland, MI. Laboratory Project ID: 960004, November 24, 1997. MRID 46808236. Unpublished.

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

EXECUTIVE SUMMARY: In a combined chronic toxicity/carcinogenicity study (MRID 46808236), XDE-570 (Florasulam; 99.3% a.i.; Lot No. 940714) was administered in the diet for 104 weeks to 50 Fischer 344 rats/sex/dose at dose levels of 0/0, 10/10, 250/125, or 500/250 mg/kg bw/day nominally in males/females (actual intake was 0/0, 10/10, 254/127, and 506/254 mg/kg bw/day in males/females). An additional 10 rats/sex/dose were treated in a similar manner and killed after 52 weeks. A concurrent neuropathology group (5 rats/sex/dose) were treated similarly and killed at 52 weeks; however, only body weights and body weight gains were reported in this study.

No adverse treatment-related effects were observed on mortality, clinical signs, food consumption, food efficiency, hematology, clinical chemistry, or gross pathology.

In the 250 mg/kg/day females, body weight was decreased (p<=0.05) by approximately 3-8% after Week 52. Only a minor decrease of 6% was observed in body weight gain for Weeks 0-52, but overall body weight gain decreased by 14%. In the 500 mg/kg/day males, body weight was decreased (p<=0.05) by approximately 13-18% after Week 13. Body weight gain was similar to controls at Weeks 0-13, but was decreased at Weeks 0-52 by 27% and overall (Weeks 0-104) by 23%.

Slight nephrotoxicity was observed in males. At 250 and 500 mg/kg/day, increased (p<=0.05) incidences of very slight to moderate renal collecting duct hypertrophy (82-98% treated vs 0% controls) and very slight to slight multi-focal mineralization in the papilla (28-78% treated vs 4% controls) were observed. Renal collecting duct hypertrophy was also observed at 12 months at 250 and 500 mg/kg/day (50-100% treated vs 0% controls). At 250 mg/kg/day, due to the severity and the type of lesion found, the condition of the kidney was considered equivocally adverse. Additionally, at 500 mg/kg/day, increased (p<=0.05) relative to body kidney weights were observed at 12 and 24 months (↑22-25%), and the incidence of focal/multi-focal transitional cell hyperplasia in the papilla was increased (22% treated vs 0% controls) at 24 months.

It was not clear if the following findings were adverse and treatment-related. In the 250 mg/kg/day females, the incidence of cloudy cornea was increased (57% treated vs 20% controls); however histological examination did not corroborate an adverse effect. Urinary pH was decreased in the 500 mg/kg/day males (5.3-6.1 treated vs 7.0-8.1 controls).

The LOAEL is 250 mg/kg/day, based on decreased body weights and body weight gains in the females. The NOAEL is 125 mg/kg/day.

At the doses tested, there was not a treatment related increase in tumor incidence when compared to controls. Dosing was considered adequate based on decreased body weights and body weight gains in both sexes and slight nephrotoxicity in males.

This study is classified as **acceptable/guideline** and satisfies the guideline requirements (OPPTS 870.4200b; OECD 451) for a carcinogenicity study in mice.

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

To the EPA reviewer: A dose-dependent effect on mortality was not observed in the males at Weeks 0-104 or in the females at Weeks 0-96. There was a dose-related increase of 10% at Weeks 0-104 in females; however, the DER writer did not state that it was statistically different. As this effect was minor and no treatment-related effect was observed for Weeks 0-96, there was no adverse effect on mortality observed in this study.

Minor decreases were observed in food consumption. At the high dose at Weeks 79, 99, and 103, decreases of 7-11% were noted in males and decreases of 2-4% in females. This effect was not considered adverse and may reflect the reduced size (weight of the rats).

The writers of the previous DER selected 125 mg/kg/day as the LOAEL, based on "equivocal urinary acidification, marginal to slight increase in kidney weight, and hypertrophy of the epithelial cells of the collecting ducts in females." In the 125 mg/kg/day females, the pH of the urine and the relative to body and absolute kidney weights were within the standard deviation of the control; thus, these effects were not considered adverse. A significant ($p \leq 0.05$) difference in kidney weights was not found at 125 mg/kg/day. In short, the values in the treated group were similar to controls. An increased ($p \leq 0.05$) incidence of very slight hypertrophy of the collecting ducts was noted in the 125 mg/kg/day females (28/50 treated vs 0/50 controls). Due to the minimal severity of this lesion and the absence of corroborating evidence of toxicity, this effect is not considered adverse.