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DATA EVALUATION RECORD – SUPPLEMENT

XDE-570 (FLORASULAM)

Study Type: OPPTS 870.3100 [§82-1a]; Subchronic (90-day) Oral Toxicity Study in Rats

Work Assignment No. 4-1-128 B (MRID 46808219)

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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: 90-Day Oral Toxicity [feeding]-[rat]; OPPTS 870.3100 [' 82-1a] (rodent); OECD 408.

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

TEST MATERIAL (PURITY): XDE-570 (Florasulam; 99.2% 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: Redmond, J. M., and K. A. Johnson (1996) XDE-570: 13-week dietary toxicity and 4-week recovery in F344 rats. The Toxicology Research Laboratory, Health and Environmental Sciences, The Dow Chemical Company, Midland, MI. Laboratory Project Study ID: DR-0312-6565-011, January 31, 1996. MRID 46808219. Unpublished.

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

EXECUTIVE SUMMARY: In a subchronic oral toxicity study (MRID 46808219), XDE-570 (Florasulam; 99.2% a.i.; Lot No. 930910) was administered in the diet to ten Fischer 344 rats/sex/dose at dose levels of 0, 20, 100, 500, or 1000/800 (males/females) mg/kg/day (time-weighted intake was 0/0, 22/21, 112/106, 550/528, and 1111/843 mg/kg/day [males/females]) for 13 weeks. An additional ten rats/sex/dose were fed test diets containing 0 or 1000/800 (males/females) mg/kg/day for 13 weeks, followed by a 4-week recovery period, during which time all rats were fed control diet.

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

At 500 mg/kg/day, body weights were decreased (p<=0.05) in the females by 5-8% during Weeks 6-13, contributing to a 21% decrease (p<=0.05) in overall (Weeks 0-13) body weight gains. At 1000 mg/kg/day, body weights were decreased (p<=0.05) in both sexes by 7-17% throughout treatment, resulting in decreased (p<=0.05) overall body weights gains (decr. 23-30%). Body weights and body weight gains remained decreased (p<=0.05) in the 1000 mg/kg/day males following recovery (decr. 11% and 17% at Week 17, respectively).

Slight nephrotoxicity was observed at 500 mg/kg/day and above. Absolute and relative (to body weight) kidney weights were increased (p<=0.05) by 9-37% in both sexes. Urinary pH was decreased in both the males (5.90-6.85 vs. 7.55 in controls) and females (6.65-7.10 vs. 8.20 in controls). Very slight to slight hypertrophy of the epithelial cells of the collecting ducts were observed in the males (10/10 at each dose vs. 0/10 controls) and females (8-9/10 vs. 0/10 controls); and degeneration/regeneration and inflammation (with or without necrosis) of the descending portion of the proximal tubules was noted in the females (3/10 at each dose vs. 0/10 controls). Additionally, the specific gravity of the urine was decreased (p<=0.05) in the 1000 mg/kg/day males (1.035 vs. 1.051 in controls), and very slight multifocal mineralization of the kidney papilla was observed in the 800 mg/kg/day females (9/10 vs. 0/10 controls). Following recovery, both very slight mineralization of the tubules of the papilla (9/10 vs. 0/10 controls) and very slight degeneration/regeneration of the cortical tubules (5/10 vs. 0.10 controls) were noted in the kidney of the 800 mg/kg/day females.

The LOAEL is 500 mg/kg/day, based on decreased body weights and body weight gains in the females, and evidence of slight nephrotoxicity (described above) in both sexes. The NOAEL is 100 mg/kg/day.

This study is classified as **acceptable/guideline** and satisfies the guideline requirements (OPPTS 870.3100; OECD 408) for a subchronic oral toxicity study in the rat.

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

Table A.2.2 Subchronic, Chronic, and Other Toxicity Profile		
Guideline No./Study Type	**MRID No. (year) Classification/Doses**	**Results**
870.3100 90-Day oral toxicity (rat)	46808219 (1996) Acceptable/guideline 0, 20, 100, 500, 1000/800 mg/kg/day	NOAEL = 100 mg/kg/day LOAEL = 500 mg/kg/day based on decreased body weights and body weight gains in the females and evidence of slight nephrotoxicity in both sexes
870.3100 90-Day oral toxicity (mouse)	46808222 (1996) Acceptable/guideline 0, 20, 100, 500, 1000 mg/kg/day	NOAEL = 1000 mg/kg/day (limit dose) LOAEL = Not observed
870.3150 90-Day oral toxicity (dog)	46808223 (1995) Acceptable/guideline 0, 5, 50, 100 mg/kg/day	NOAEL = 50 mg/kg/day LOAEL = 100 mg/kg/day based on increased alkaline phosphatase activity and absolute and relative (to body) liver weights, and increased incidence/severity of hepatic vacuolation in both sexes
870.3200 21/28-Day dermal toxicity (rat)	46808225 (1997) Acceptable/guideline 0, 100, 500, 1000 mg/kg/day, 6 h/day, 7 days/week for 28 days	NOAEL = 1000 mg/kg/day (limit dose) LOAEL = Not observed
870.3250 90-Day dermal toxicity (species)		
870.3465 90-Day inhalation toxicity (species)		
870.3700a Prenatal developmental toxicity (rat)	46808234 (1997) 46808231 (1996) Acceptable/guideline 0, 50, 250, 750 mg/kg/day (GD 6-15)	**Maternal** NOAEL = 250 mg/kg/day LOAEL = 750 mg/kg/day based on decreased body weights, body weight gains, and food consumption, and increased kidney weights **Developmental** NOAEL = 750 mg/kg/day LOAEL = Not observed
870.3700b Prenatal developmental toxicity (rabbit)	46808233 (1997) 46808232 (1997) Acceptable/guideline 0, 50, 250, 500 mg/kg/day (GD 7-19)	**Maternal** NOAEL = 500 mg/kg/day LOAEL = Not observed **Developmental** NOAEL = 500 mg/kg/day LOAEL = Not observed Study was found acceptable due to findings of preliminary developmental toxicity study at 600 mg/kg/day
870.3800 Reproduction and fertility effects (rat)	46808235 (1997) Acceptable/guideline 0, 10, 100, 500 mg/kg/day	**Parental/Systemic** NOAEL = 100 mg/kg/day LOAEL = 500 mg/kg/day based on decreased body weights, body weight gains, and food consumption, increased relative kidney weights, and increased incidence of multi-focal hypertrophy of the collecting duct in both sexes **Offspring** NOAEL = 500 mg/kg/day LOAEL = Not observed **Reproductive** NOAEL = 500 mg/kg/day LOAEL = Not observed
870.4100a Chronic toxicity (species)		

870.4100b Chronic toxicity (dog)	46808229 (1997) Acceptable/guideline 0, 0.5, 5, 100/50 mg/kg/day	NOAEL = 5 mg/kg/day LOAEL = 100/50 mg/kg/day based on decreased body weights, body weight gains, and food consumption in the females
870.4200 Carcinogenicity (mouse)	46808230 (1997) Acceptable/guideline 0, 50, 500, 1000 mg/kg/day	NOAEL = 1000 mg/kg/day (limit dose) LOAEL = Not observed **No evidence of carcinogenicity**
870.4300 Combined chronic toxicity/carcinogenicity (rat)	46808236 (1997) Acceptable/guideline M: 0, 10, 250, 500 mg/kg/day F: 0, 10, 125, 250 mg/kg/day	NOAEL = 125 mg/kg/day LOAEL = 250 mg/kg/day based on decreased body weights and body weight gains in the females **No evidence of carcinogenicity**
870.5100 Bacterial gene mutation/mammalian activation gene mutation assay	46808240 (1995) Acceptable/guideline 0, 0.333, 1, 3.33, 10, 33.3, 100 µg/plate (*S. typhimurium*) 0, 10, 33.3, 100, 333, 1000, 3330 g/plate (*E. coli*)	No evidence of induced mutant colonies over background in the presence or absence of S9-induced activation
870.5300 Gene mutation at the HGPRT locus in Chinese hamster ovary cells	46808238 (1995) Acceptable/guideline 0, 187.5, 375, 750, 1500, 3000 µg/mL	No evidence of induced mutant colonies over background in the presence or absence of S9-activation
870.5375 Chromosomal aberration assay in rat lymphocytes	46808237 (1995) Acceptable/guideline 0, 3, 10, 30, 100, 300, 1000, 3000 µg/mL	No evidence of chromosome aberrations induced over background in the presence or absence of S9-activation
870.5395 Mouse bone marrow micronucleus assay	46808239 (1995) Acceptable/guideline 0, 1250, 2500, 5000 mg/kg	No significant increase in the frequency of micronucleated polychromatic erythrocytes in bone marrow
870.6200a Acute neurotoxicity screening battery	46808217 (1997) Acceptable/guideline 0, 200, 1000, 2000 mg/kg	**Systemic** NOAEL = 1000 mg/kg LOAEL = 2000 mg/kg based on decreased body weight gains in the males **Neurotoxicity** NOAEL = 2000 mg/kg LOAEL = Not observed
870.6200b Subchronic neurotoxicity screening battery	46808228 (1996) Acceptable/guideline 0, 10, 125 (female only), 250, 500 (male only) mg/kg/day	**Systemic** NOAEL = 250 mg/kg/day LOAEL = 500 mg/kg/day based on decreased body weights and body weight gains in the males **Neurotoxicity** NOAEL = 250 mg/kg (highest dose tested in females) LOAEL = Not observed
870.6300 Developmental neurotoxicity		

870.7485 Metabolism and pharmacokinetics (rat)	46808301 (1996) 46808303 (1997) Acceptable/guideline 10 and 500 mg/kg	Absorption was rapid and extensive (≈90-93% at 10 mg/kg; ≈82-86% at 500 mg/kg rats). Peak plasma concentrations (Cmax) were achieved within 0.5-1 hour. 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%. Elimination was rapid. The administered dose was mostly eliminated within 12 hours in the urine (>80% at 10 mg/kg; >60% at 500 mg/kg). Total radioactivity found in the urine was approximately 90-92% following single or repeated low-dose treatment, and 81-85% 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.
870.7600 Dermal penetration (species)		
Special studies		