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

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

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MEMORANDUM

SUBJECT: Florasulam: Human Health Risk Assessment for Proposed Use on Cereal Grains (Wheat, Oats, Barley, Rye, and Triticale). PC Code: 129108, Petition No: 56F7061, DP Barcode: D332983

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1.0 Executive Summary

Florasulam is a selective triazolopyrimidine sulfonanilide post-emergent herbicide. The mode of action for florasulam is through inhibition of the plant enzyme acetolactate synthase (ALS). The inhibition of ALS results in retardation of plant growth processes leading to death of the plant. The registrant, Dow Agrosciences, is proposing this active ingredient for selective control of a broad spectrum of annual broadleaf weeds in cereal grain crops (wheat, oats, rye, barley, and triticale). The proposed application rate for florasulam is low, 0.00446 pounds (lbs) active ingredient (a.i.) per acre. Florasulam was first registered in Israel in 1998. It has also been registered in Canada (2001) and included in the European Annex Union Listing in 2002.

HUMAN HEALTH RISK ASSESSMENT:

Toxicology/Hazard

Florasulam has low or minimal acute toxicity via the oral (Category IV), dermal (Category III), and inhalation routes of exposure (Category IV). It is non- irritating to the eye and skin (Category IV); it is not a skin sensitizer.

Slight nephrotoxicity (increased kidney weights, hypertrophy, and histopathology) was observed in the kidneys of rats after subchronic ($\geq$ 500 mg/kg/day) and chronic exposure ($\geq$ 250 mg/kg/day) to florasulam. Liver toxicity was observed in dogs (90-days) in the form of increased liver weights and liver enzymes, hypertrophy, and histopathology; adverse histopathology was also observed in the adrenal glands (1-year). Other treatment-related effects noted were decreases in body weight and body weight gain in rats and dogs and general malaise in rats. There were no adverse treatment-related effects observed in mice.

There is no evidence of developmental or reproductive toxicity, neurotoxicity, mutagenicity, or carcinogenicity. In addition, there is no evidence of estrogen-, androgen-, or thyroid-mediated toxicity.

For chronic dietary exposure, the chronic toxicity study in dogs (NOAEL of 5 mg/kg/day and LOAEL of 100/50 mg/kg/day) was used to calculate the chronic reference dose (cRfD) of 0.05 mg/kg/day; endpoints for acute dietary risk assessments (general population and females age 13-49) were not selected. A 90-day oral toxicity study in dogs was used to select the dose and endpoint for occupational short-term inhalation exposure (NOAEL of 5 mg/kg/day and LOAEL of 50 mg/kg/day). A risk assessment was not conducted for occupational dermal exposures (short-term) due to the absence of adverse systemic effects in the dermal toxicity study (1000 mg/kg/day). There are no residential uses proposed for florasulam; therefore, incidental oral and residential dermal and inhalation risk assessments were not conducted.

HED recommends the FQPA SF be reduced to 1X because the toxicology database is complete; there is no evidence of increased susceptibility and no/low concerns and no residual uncertainties with regard to pre- and/or postnatal toxicity. Additionally, the dietary food exposure assessment is based on HED-recommended tolerance-level residues and assumes 100% crop treated for all commodities, which results in upper bound estimates of dietary exposure (95th percentile of

exposure). Furthermore, the drinking water assessment is based on values generated by model and associated modeling parameters which are designed to provide conservative, health protective upper bound estimates of water concentrations. Finally, there are no registered or proposed residential uses.

Dietary Exposure (Food/Water)

An acceptable wheat metabolism study using two radiolabels was submitted for florasulam. Total radioactive residue (TRR) level in grain was determined by combustion/LSC. The ^{14}C-residues were too low to elucidate the nature of the TRRs in mature wheat ears (up to 0.03 ppm) and grain (up to 0.008 ppm). Therefore, no further attempts to characterize/identify the ^{14}C-residues in grain were carried out. However, residues in immature whole wheat plants and mature wheat straw were present at levels permitting adequate identification. Metabolites detected in wheat matrices were 4-OH-(phenyl)-florasulam, the glucose conjugate of 4-OH-(phenyl)-florasulam, and 2-sulfonamide. The metabolism study was conducted at 10X the proposed label rate (5 g a.i./ha) and the 2-sulfonamide metabolite was detected only in winter wheat straw (0.059 ppm) and not in the grain. Based on the low level of residues observed in wheat grain (0.008 ppm) at the exaggerated application rate (10X the proposed application rate) in the wheat metabolism study, HED concludes the residue of concern (ROC) in plants is the parent compound, florasulam. This conclusion applies to cereal grains only. Additional plant metabolism studies will be needed for any future uses on other types of crops.

In confined rotational crops, the levels of TRRs were low (≤ 0.01 ppm) and no residues were identified. Therefore, a residue of concern does not need to be defined for rotational crops. Based on the results of the confined rotational crop study, field rotational crop studies are not needed, and a 30-day plant back interval (PBI) can be supported for all crops.

The metabolism of florasulam in the laying hen and lactating goat were similar. In both, the majority of the radioactivity was found in the excreta. Most of the parent compound in goat and hen was eliminated unchanged with minor unknown metabolites at unquantifiable levels. No significant cleavage of the sulfonanilide bridge was observed.

Residues of florasulam as the N-methyl florasulam derivative were determined by capillary gas chromatography with mass selective detection (GC/MSD). This method has been forwarded to BEAD/ACB for a petition method validation. The analytical methodology is acceptable as an enforcement method pending validation by ACB. The limit of detection (LOD) was calculated as three times the standard deviation (3s) which was 0.0012 ppm in grain, 0.005 ppm in forage and immature green plant, 0.0036 ppm in hay and immature dried plant and 0.0074 ppm in straw. The limit of quantitation (LOQ) for florasulam was established at 0.01 ppm for grain over the concentration range of 0.01-0.10 ppm, and at 0.05 ppm for forage, hay, straw, immature green plant and immature dried plant over the concentration range of 0.05-0.50 ppm. The method of analysis was independently validated at Enviro-Bio-Tech. Ltd. (Bernville, PA) using wheat grain, forage, hay and straw. This ILV study successfully validated the Dow AgroSciences method GRM 98.01 for the residues of the florasulam in wheat matrices, indicating good reproducibility.

The proposed use of florasulam on cereal grains is considered to fall under 40 CFR §180.6(a)3 (no expectation of finite residues in livestock commodities). Therefore, feeding studies and tolerances for meat, milk, poultry, and eggs are not needed for the purposes of this petition. HED also concludes that residue analytical methods and storage stability data for livestock commodities are not necessary.

There are adequate magnitude of the residue data for wheat, barley, oats, and rye. The supervised field trials indicated that residues of florasulam in grain, forage, hay, and straw of wheat, barley, rye, and oats were non quantifiable (<0.01 ppm for grain, <0.05 ppm for forage, hay, and straw), following a single foliar application at an exaggerated rate (2x proposed maximum seasonal application rate). Florasulam residues were greater than the proposed tolerances in one wheat forage field trial. However, HED concludes the proposed tolerance of 0.05 ppm for wheat forage would adequately cover residues in wheat forage since field trials were conducted at a 2x exaggerated rate.

Maximum residue levels (MRls) are established in Canada for residues of florasulam in barley, oats, and wheat grain at 0.01 ppm. There are no Codex MRLS and no harmonization issues exist since the same tolerance level is recommended for the use in the U.S.

The chronic analysis incorporated 100% crop treated and proposed tolerance values. The resulting DEEM-FCID™ food-only chronic exposure estimates were below HED's level of concern for the US Population and all population subgroups. Children 1-2 years of age (<1 % cPAD) were the most highly exposed population subgroup. When drinking water was included in the dietary exposure analysis, the resulting DEEM-FCID™ food-plus-water exposure estimates were below HED's level of concern for all population subgroups, with Children 1-2 years of age (<1 % cPAD) being the most highly exposed population.

For drinking water, estimated drinking water concentrations (EDWCs) in surface water were derived using the Environmental Fate and Effects Division (EFED) Tier I aquatic model FIRST (FQPA Index Reservoir Screening Tool, v.1.1.0; dated 12/12/2005). Estimated drinking water concentrations (EDWCs) in groundwater were derived using EFED's Tier I aquatic model SCI-GROW2 (Screening Concentration in Ground Water, v.2.3; dated 11/12/1997). The residues of concern in drinking water are the parent and 5-OH degradate.

Occupational Exposure/Risks

Margins of Exposure (MOE) equal to or less than 100 are of concern to HED. Since a dermal endpoint and dose were not selected a dermal exposure assessment was not conducted. Inhalation MOEs were significantly greater than 100 at baseline and are not of concern to HED.

Since a dermal endpoint and dose were not selected a postapplication dermal assessment was not conducted. As all scenarios are for outdoor agricultural uses postapplication inhalation exposure is expected to be negligible.

Restricted Entry Interval

Since systemic toxicity was not evaluated for the dermal route (i.e. not of concern), the restricted entry interval (REI) is based on the acute toxicity of the technical active ingredient. Florasulam is classified as Toxicity Category III for acute dermal and Category IV for acute oral, inhalation, and eye exposure. Acute toxicity Category III and IV chemicals require a 12 hour REI under the Worker Protection Standard (WPS).

The product label for EF-1343 proposes an REI of 4 hours. Based on review of the toxicological database for the active ingredient, florasulam, EF-1343 is a candidate for a reduced risk active ingredient. Therefore, florasulam is a candidate for a 4-hour REI. End-use products must meet the criteria of PR Notice 95-3 to qualify for an REI of 4-hours.

The product labels for GF-1727, GF-184, and EF-1383 propose various REIs ranging from 12 to 48 hours respectively. The REIs for these labels are based on a second active ingredient (e.g. MCPA, fluroxpyr, and 2-4-D). If products contain more than one active ingredient REI will be based on the active ingredient which requires the longest REI. **HED recommends that the Registration Division ensure that the proper REI be established for each of the proposed labels**.

ENVIRONMENTAL JUSTICE CONSIDERATIONS

Potential areas of environmental justice concerns, to the extent possible, were considered in this human health risk assessment, in accordance with U.S. Executive Order 12898, "Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations" http://www.eh.doe.gov/oepa/guidance/justice/eo12898.pdf).

As a part of every pesticide risk assessment, OPP considers a large variety of consumer subgroups according to well-established procedures. In line with OPP policy, HED estimates risks to population subgroups from pesticide exposures that are based on patterns of that subgroup's food and water consumption, and activities in and around the home that involve pesticide use in a residential setting. Extensive data on food consumption patterns are compiled by the USDA under the Continuing Survey of Food Intakes by Individuals (CSFII) and are used in pesticide risk assessments for all registered food uses of a pesticide. These data are analyzed and categorized by subgroups based on age, season of the year, ethnic group, and region of the country. Whenever appropriate, nondietary exposures based on home use of pesticide products and associated risks for adult applicators and for toddlers, youths, and adults entering or playing on treated areas postapplication are evaluated. Further considerations are currently in development as OPP has committed resources and expertise to the development of specialized software and models that consider exposure to bystanders and farm workers as well as lifestyle and traditional dietary patterns among specific subgroups.

Review of Human Research

This risk assessment relies in part on data from studies in which adult human subjects were intentionally exposed to a pesticide or other chemical. These studies, which comprise the Pesticide Handlers Exposure Database (PHED), have been determined to require a review of their ethical conduct, and have received that review.

ADDITIONAL DATA NEEDS/RECOMMENDATIONS

Regulatory Recommendations and Residue Chemistry Deficiencies

A revised Section F should be submitted with correct raw agricultural commodity definitions along with the correct spelling of the chemical name for florasulam.

Successful completion of a petition method validation by BEAD/ACB is needed. The method has been sent to BEAD/ACB for validation.

Analytical standards for florasulam are not currently available in the National Pesticide Standards Repository. Analytical reference standards for florasulam need to be supplied and supplies need to be replenished as requested by the Repository. The reference standards should be sent to the Analytical Chemistry Branch, which is located at Fort Meade, to the attention of either Theresa Cole, Dallas Wright, or Frederic Siegelman at the following address:
USEPA
National Pesticide Standards Repository/Analytical Chemistry Branch/OPP
701 Mapes Road
Fort George G. Meade, MD 20755-5350 (Note: mail will be returned if the extended zip code is not included).

The product labels for GF-1727, GF-184, and EF-1383 propose various REIs ranging from 12 to 48 hours respectively. The REIs for these labels are based on a second active ingredient (e.g. MCPA, fluroxpyr, and 2-4-D). If products contain more than one active ingredient, the REI will be based on the active ingredient which requires the longest REI. HED recommends that the Registration Division ensure that the proper REI is established for each of the proposed labels.

Provided the above issues are addressed, HED recommends for the establishment of the tolerances specified in Table C.1.

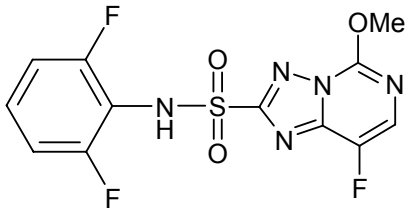
2.0 Ingredient Profile

Florasulam is a triazolopyrimidine sulfonanilide post-emergent herbicide. It is proposed for selective control of a broad spectrum of annual broadleaf weeds in cereal grain crops (wheat, barley, oats, rye, and triticale). The mode of action for florasulam is through inhibition of the plant enzyme acetolactate synthase (ALS). The inhibition of ALS results in a retardation of plant growth processes leading to death of the plant.

2.1 Summary of Registered/Proposed Uses

Table 2.1: Proposed Use Patterns for the End-Use Products Containing Florasulam				
Formulation and Product	**Method of Application**	**Use Sites**	**Application Rate**	**Timing of Application**
EF-1343 (4.84% a.i.) # 62719-LAN	Ground and Aerial equipment	Wheat, barley, oats, rye, and triticale	0.00446 lb ai/acre	Post-emergent use, apply when weeds are actively growing between 2 leaf and flag leaf emergence stage; do not apply more than 0.00446 lb ai/acre per growing season
EC-1383 (0.58% a.i.) # 62719-LL1				
GF-184 (0.25% a.i.) #62719-LA6				
GF-1727 (0.39% a.i.) 62719-LAE				

2.2 Structure and Nomenclature

Table 2.2. Test Compound Nomenclature	
Compound	Chemical Structure 
Common name	Florasulam
Company experimental name	DE-570 or EF-1343
IUPAC name	2', 6', 8-trifluoro-5-methoxy-*s*-triazolo [1,5-c]pyrimidine-2-sulfonanilide
CAS name	*N*-(2,6-difluorophenyl)-8-fluoro-5-methoxy(1, 2, 4)triazolo(1, 5-c)pyrimidine-2-sulfonamide
CAS #	145701-23-1
End-use product/EP	Florasulam Suspension Concentrate
Molecular Formula	$C_{12}H_8O_3N_5F_3S$
Molecular Mass	359.3

2.3 Physical and Chemical Properties

TABLE 2.3. Physicochemical Properties		
Parameter	**Value**	**Reference**
Physical State	Solid	PMRA Lab Services
Melting point/range	193.5-230.5 C	
Specific gravity	1.53 at 22 C	
Water solubility	Medium / Solubility (g/L) water 0.121 pH 5 0.084 pH 7 6.36 pH 9 94.2	
Solvent solubility	Solvent / Solubility (g/L) acetone 123 acetonitrile 72.1 ethyl acetate 15.9 methanol 9.81 dichloromethane 3.75 xylene 0.227 n-octanol 0.184 n-heptane 0.000019	
Vapor pressure	1 x 10^{-5} Pa at 25 C	
Dissociation constant (pK_a)	4.54	
Octanol/water partition coefficient (K_{ow}) at 22 C	pH / Log K_{ow} 4 1.00 7 -1.22 10 -2.06	
UV/visible absorption spectrum	Form / λmax (nm) Acidic 259.8, 203.8 Basic 262.4, 209.7 Methanolic 204.1 No absorbance above 300 nm.	

3.0 Hazard Characterization/Assessment for Florasulam

3.1 Hazard and Dose-Response Characterization

3.1.1 Database Summary

3.1.1.1 Sufficiency of studies/data

Based on the proposed use pattern, the toxicology database for florasulam is complete and adequate for risk assessment. There are acceptable studies available for endpoint selection that include: 1) subchronic oral toxicity studies in rats, mice, and dogs; 2) a chronic oral toxicity

study in dogs and carcinogenicity studies in rats and mice; 3) developmental and reproduction studies in rats and a developmental study in rabbits; and 4) a subchronic dermal toxicity study in rats. There is also a complete mutagenicity battery, acute LD50, and neurotoxicity studies (acute and chronic), as well as a metabolism study in the rat.

3.1.1.2 Mode of action, metabolism, toxicokinetic data

Florasulam is a selective triazolopyrimidine sulfonanilide post-emergent herbicide. The pesticidal mode of action (MOA) is through inhibition of acetolactate synthase (ALS) in plants. ALS is found in the chloroplast where it catalyses branch chained amino acid biosynthesis. Inhibition of ALS results in inhibition of plant cell division, decreased plant growth, and ultimately, plant death.

3.1.2 Toxicological effects

Florasulam has low or minimal acute toxicity via the oral (Category IV), dermal (Category III), and inhalation routes of exposure (Category IV). It is non-irritating to the eye and skin (Category IV); it is not a skin sensitizer.

Slight nephrotoxicity (increased kidney weights, hypertrophy, and degeneration/regeneration and inflammation of the descending portion of proximal tubules) was observed in the kidneys of rats (both sexes) after subchronic exposure to florasulam (90 days) at ≥ 500 mg/kg/day. Chronic exposure in rats led to slight nephrotoxicity (increased kidney weights, hypertrophy, and slight multi-focal mineralization of the papilla) at 250 and 500 mg/kg/day in males only. Additionally at 500 mg/kg/day, papillary necrosis and hyperplasia of the transitional epithelium (papilla) were observed in the kidney (males). Decreases in body weight and body weight gain were also observed in females after subchronic (500 mg/kg/day) and chronic exposure (250 mg/kg/day). Liver toxicity was observed in dogs (both sexes) in the form of increased alkaline phosphatase activity (59-127%), increased liver weights, hypertrophy, and hepatic vacuolation at 50 mg/kg/day after 90 days. After 1 year, there were increases in alkaline phosphatase (233-783%) in dogs (both sexes) but no changes in liver weights or gross or microscopic pathology at 50 mg/kg/day. Additionally, there were decreases in body weight, body weight gain and food consumption, as well as vacuolation of the zona reticularis and zona fasciculate in the adrenal gland (consistent with fatty change) in both sexes. There were no adverse effects noted after subchronic/chronic exposure to florasulam in mice up to the limit dose of 1000 mg/kg/day.

There was no evidence of teratogenicity or indications of neonatal sensitivity in the developmental and reproduction toxicity studies (rats and rabbits). In the rat developmental toxicity study (750 mg/kg/day) body weights were decreased by 4-6% during GD 6-19, resulting in a 16% decrease in body weight gains during treatment (GD 6-16); food consumption was also decreased (not statistically analyzed) by 6-13% during the treatment period. Additionally at this dose, absolute and relative (to body weight) kidney weights were increased ($p<=0.05$) by 8 and 12%, respectively. At 250 and 750 mg/kg/day, slight decreases (3-4%) were observed in fetal body weight. Additionally, there were delays in ossification observed in fetuses at 750 mg/kg/day. However, the minor differences were not considered adverse since there was no clear dose-response and the values (both findings) fell within historical control values.

Furthermore, the findings were attributed to the associated decreases in maternal body weights. There were no treatment-related effects observed in dams or offspring in the developmental toxicity study in rabbits. In the reproduction toxicity study in rats, there were decreased body weights, body weight gains, and food consumption, as well as increased kidney weights and hypertrophy in both sexes at 500 mg/kg/day. Additionally at 500 mg/kg/day, transient decreases in pup body weights were observed on PND 4 pre-culling (F1 and F2 males) and PND 7 (F1 females and F2 males and females); however, by PND 21, all treated groups were similar to controls. The decreases observed were associated with decreased maternal body weight and food consumption and were transient in nature; thus, they were not considered adverse.

Dermal exposure to florasulam did not result in systemic toxicity up to the limit dose of 1000 mg/kg/day.

There is no evidence of neurotoxicity, mutagenicity, or carcinogenicity after exposure to florasulam. In addition, there is no evidence of estrogen-, androgen-, and/or thyroid-mediated toxicity.

3.1.3 Dose-response

For chronic dietary exposure, the chronic study in dogs was used to calculate the chronic reference dose (cRfD) of 0.05 mg/kg/day. The NOAEL of 5 mg/kg/day and the LOAEL of 50 mg/kg/day were based on changes in body weight, body weight gain and food consumption in females, and adverse liver alterations, as well as slight vacuolation of the zona reticularis and zona fasciculata in the adrenal gland (consistent with fatty change) in both sexes; endpoints for acute dietary risk assessments (general population and females age 13-49) were not selected. A 90-day toxicity study in dogs was used to select the dose and endpoint for occupational short- and intermediate-term inhalation exposure. The NOAEL of 5 mg/kg/day and the LOAEL of 50 mg/kg/day were based on adverse liver alterations (increased liver weights and alkaline phosphatase activity, hypertrophy, and histopathology) in both sexes. A risk assessment was not conducted for occupational dermal exposures (short-term) due to the absence of adverse systemic effects in the dermal toxicity study. There are no residential uses proposed for florasulam; therefore, incidental oral and residential dermal and inhalation risk assessments were not conducted.

3.1.4 FQPA

HED recommends the FQPA SF be reduced to 1X because there is no evidence of increased susceptibility, there are no/low concerns and no residual uncertainties with regard to pre- and/or postnatal toxicity. Additionally, the toxicological database is complete (see Section 3.4).

3.2. Absorption, Distribution, Metabolism, Excretion (ADME)

In a metabolism study, [^{14}C]-Florasulam in a suspension of 0.5% Methocel™ cellulose ethers was administered to Fischer 344 rats as a single gavage dose at 10 or 500 mg/kg. Additional rats were treated with 14 daily doses at 10 mg/kg/day of non-labeled Florasulam followed by a single oral dose of [^{14}C]-Florasulam on Day 15. To examine biliary excretion, male rats were fitted

with indwelling bile-duct cannulas prior to dosing. Bile was periodically sampled, and urine and feces were collected for a 24 h interval. 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 (C_{max}) were achieved within 0.5-1 h following dose administration. C_{max} 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 h post-dose were 95.9-100.2% of the administered dose. Elimination was rapid. The administered dose was mostly eliminated within 12 h 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 h, <0.5% of the dose was found in expired air. By 24 h 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. Total recovery was 98.7% in the bile duct cannulated group. The highest concentration of radioactivity was found in the kidney (570 µg-eq/g). On a percentage-of-the dose basis, excluding the carcass and GIT/ingesta, the blood, kidneys, liver, and skin had relatively high amounts of radioactivity; however, the radioactivity isolated in the skin may have been due to urinary contamination. Excluding the skin, the amount (% dose) isolated was generally highest in the blood, but all amounts were low (0.5-5.0% dose), regardless of dose, time point, or sex. Parent accounted for >91% of the radioactivity in the kidney, liver, and blood for each dose, time point, and sex. At 24 h postdose, biliary excretion accounted for only 1.0% of the administered dose, while urinary excretion (81.0% dose) accounted for the majority of the dose in this test group. The remaining administered radioactivity in the bile duct cannulated test group was isolated in the feces (3.9% dose), tissues, GIT/ingesta, and carcass (8.3% dose), and final cage wash (4.6% dose). There were no sex-related differences in the metabolism or pharmacokinetics of the test compound. 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 (exact position of hydroxyl group not determined) 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. Similarly, the number of doses or the position of the radiolabel generally made no difference in the metabolism and pharmacokinetic profile.

3.3 FQPA Considerations

3.3.1 Adequacy of the Toxicity Database

The database is adequate to characterize potential pre- and/or post-natal risk for infants and children. Acceptable/guideline studies for developmental toxicity studies in rats and rabbits, a

reproduction study in rats, and acute and subchronic neurotoxicity studies in rats were available for FQPA assessment.

3.3.2 Evidence of Neurotoxicity

There was no evidence of neurotoxicity observed in the toxicology database. In the acute neurotoxicity study, there was a slight transient decrease in motor activity, increased incidence of minimal activity (open-field), and decreased reactivity to sharp noise (Day 1) at 2000 mg/kg/day. However, the differences from control values did not exceed the historical controls and complete recovery occurred by the next test session (Day 8). When the FOB and motor activity findings were combined they were considered to be a treatment-related high dose effect. As there were no corroborative gross or neurological pathology, this pattern of decreased activity was considered to be likely due to general malaise. In the chronic neurotoxicity study, there were no compound-related effects on mortality, clinical signs, food consumption, FOB parameters, motor activity, or gross or neurological pathology observed at any dose. Organ weights were not provided; however, in the concurrently performed 2-year dietary chronic toxicity/carcinogenicity study, brain weight was unaffected after 12 and 24 months of treatment. There were no other potential signs of neurotoxicity noted in the toxicology database.

3.3.3 Developmental Toxicity Studies

There were no treatment-related effects observed in dams or offspring in the developmental toxicity study in rabbits. In the rat developmental toxicity study, at 750 mg/kg/day, body weights were decreased by 4-6% during GD 6-19, resulting in a 16% decrease in body weight gains during treatment (GD 6-16); food consumption was also decreased (not statistically analyzed) by 6-13% during the treatment period. Additionally at this dose, absolute and relative (to body weight) kidney weights were increased ($p<=0.05$) by 8 and 12%, respectively. At $\geq$ 250 mg/kg/day, slight decreases (3-4%) were observed in fetal body weight, accompanied by delayed ossification (not significant) of the skull, ribs, and sternebrae at 750mg/kg/day. However, both findings were within the historical control range and attributed to the decreased maternal body weights also seen in this dose group.

3.3.4 Reproductive Toxicity Study

In the 2-generation reproduction study, at 500 mg/kg/day, there were decreases in pre-mating body weights and food consumption (Weeks 3-10), resulting in decreased overall body weight gains (Weeks 0-10) in the F1 males and in the P and F1 females. During gestation, body weights and food consumption were decreased during gestation days (GD) 0-21, resulting in decreased overall (GD 0-21) body weight gains in the P and F1 females. During lactation, body weights were decreased during lactation days (LD) 1-14; however, food consumption and overall (LD 1-21) body weight gains were not adversely affected. Additionally at 500 mg/kg/day, there were increases in kidney weights and hypertrophy. In the offspring, there were no adverse treatment-related effects observed on birth index, live birth index, viability indices, clinical signs, developmental landmarks, kidney weights, or gross pathology. Transient decreases in pup body weights (500 mg/kg/day) were observed on PND 4 pre-culling (F1 and F2 males) and PND 7 (F1 females and F2 males and females); however, by PND 21, all treated groups were similar to

controls. The decreases observed were associated with decreased maternal body weight and food consumption and were transient in nature; thus, they were not considered adverse. There were no other treatment-related effects noted.

3.3.5 Additional Information from Literature Sources

A literature search did not reveal information that would impact the risk assessment.

3.3.6 Pre-and/or Postnatal Toxicity

3.3.6.1 Determination of Susceptibility

There is no concern for increased quantitative and/or qualitative susceptibility after *in utero* or postnatal exposure to florasulam in developmental toxicity studies in rats and rabbits, or a reproduction study in rats.

3.3.6.2 Degree of Concern Analysis and Residual Uncertainties for Pre- and/or Postnatal Susceptibility

The purposes of the Degree of Concern analysis are: (1) to determine the level of concern for the effects observed when considered in the context of all available toxicity data; and (2) to identify any residual uncertainties after establishing toxicity endpoints and traditional uncertainty factors to be used in the risk assessment. If residual uncertainties are identified, then HED determines whether these residual uncertainties can be addressed by a FQPA safety factor and, if so, the size of the factor needed.

There is no evidence (quantitative or qualitative) of increased susceptibility and no residual uncertainties with regard to pre- and/or postnatal toxicity following *in utero* exposure to rats or rabbits and pre and/or post-natal exposures to rats. Therefore, it is recommended that the FQPA safety factor be reduced to 1X and no additional safety factors are needed (section 3.4).

3.3.7 Recommendation for a Developmental Neurotoxicity Study

There was no evidence of neurotoxicity observed following acute, subchronic, or chronic exposure to florasulam, and no clinical signs of neurotoxicity were observed following pre-natal or postnatal exposure; therefore, a developmental neurotoxicity study is not warranted at this time.

3.4 Safety Factor for Infants and Children

HED recommends the FQPA SF be reduced to 1x because there is no evidence of increased susceptibility; there are no residual uncertainties with regard to pre- and/or postnatal toxicity; and the toxicological database for florasulam is complete. After evaluating the toxicological and exposure data, the florasulam risk assessment team recommends that the FQPA SF be reduced to 1x based on the following:

The toxicity data showed no increase in susceptibility in fetuses and pups with *in utero* and post-natal exposure.

The dietary food exposure assessment is based on HED-recommended tolerance- level residues and assumes 100% crop treated for all commodities, which results in upper bound estimates of dietary exposure.

The dietary drinking water assessment is based on values generated by model and associated modeling parameters which are designed to provide conservative, health protective, upper bound estimates of water concentrations.

There are no registered or proposed residential uses.

3.5 Hazard Identification and Toxicity Endpoint Selection

3.5.1 Acute Reference Dose (aRfD) – General Population

In an acute neurotoxicity study, there was a slight transient decrease in motor activity, an increased incidence of minimal activity (open-field), and decreased reactivity to sharp noise (Day 1) at 2000 mg/kg/day. However, the differences observed did not exceed the historical controls and complete recovery occurred by the next test session (Day 8). As there were no corroborative gross or neurological pathology to suggest a neurotoxic effect, this pattern of decreased activity was considered to be likely due to general malaise (treatment-related) and not frank neurotoxicity. Since the effects were observed at a very high dose considered non-applicable to human exposure, a risk assessment for acute dietary exposure (general population) was not conducted. There were no other studies with effects resulting from single dose exposure.

3.5.2 Acute Reference Dose (aRfD) - Females age 13-49

No appropriate endpoint identified for this population.

3.5.3 Chronic Reference Dose (cRfD)

Study Selected: Chronic Toxicity-Dog
MRID No: 46808229
Dose and Endpoint for Risk Assessment: NOAEL= 5 mg/kg/day
Uncertainty Factor: 100x (10x interspecies extrapolation, 10x intraspecies variability)

$$\textbf{Chronic RfD} = \frac{5\ mg\ /\ kg\ /\ day}{100\ (UF\ )} = \textbf{0.05 mg/kg/day}$$

Comments about Study/Endpoint/Uncertainty Factors:
A chronic toxicity study in dogs was used to select the dose and endpoint for establishing the cRfD of 0.05 mg/kg/day. This study is the appropriate route and duration to establish

a chronic dietary endpoint. The NOAEL of 5 mg/kg/day and the LOAEL of 50 mg/kg/day were based on decreased body weights, body weight gains, and food consumption in females, adverse liver alterations, and slight vacuolation of the zona reticularis and zona fasciculata in the adrenal gland (consistent with fatty change) in both sexes. Uncertainty factors (100x) include: 10x interspecies extrapolation, 10x intraspecies variability.

3.5.4 Incidental Oral Exposure

There are no residential uses proposed; therefore, a risk assessment was not conducted for incidental oral exposure.

3.5.5 Dermal Absorption

In a dermal absorption study in rats, recovery of the applied dose (mass balance) was 100-103%. The majority of the dose was recovered in the skin swab (71-90% of the applied dose). Dermal absorption (based on the sum of residues in urine, feces, cage wash, tissues, residual carcass, and untreated skin) was only 0.13-0.45% of the applied dose and only 10-22% of the applied dose remained in the skin at the application site (considered potentially absorbable). Increasing the dose 200-fold resulted in only approximately 2-fold increase in absorption. Absorption increased 44% at 48 h and 61% at 72 h compared to 24 h in the low dose groups; however, a time-dependent increase in absorption was not evident in the high dose groups. The absorbed dose was almost completely excreted in the urine at the low dose, but was found primarily in the urine, cage wash, and untreated skin at the high dose. The amount of radioactivity at the treatment site increased at 48 hours in the low dose, but did not decrease within 72 hours at either dose, suggesting that the compound in the skin was not readily absorbable. This study is supported by a 28-day repeated dose dermal toxicity study, in which no compound-related effects in mortality, clinical signs, body weight, body weight gain, food consumption, hematology, clinical chemistry, urinalysis, organ weights, and gross or microscopic pathology parameters were observed in either sex up to the limit dose (1000 mg/kg/day). At 1000 mg/kg/day, very slight (grade 1) edema and erythema at the treatment site were noted in 4/5 males beginning on Day 23. Dermal irritation was resolved by Day 28.

3.5.6 Occupational Dermal Exposure (Short-Term)

There were no systemic effects observed up to the limit dose of 1000 mg/kg/day in a 28-day dermal toxicity study in rats; therefore, a quantitative dermal assessment was not conducted.

3.5.7 Occupational Inhalation Exposure (Short-Term)

Study Selected: 90-Day Dog
MRID No: 46808223
Dose and Endpoint for Risk Assessment: NOAEL= 5 mg/kg/day

Uncertainty Factor: 100x (10x interspecies extrapolation, 10x intraspecies variability)

Comments about Study/Endpoint/Uncertainty Factors: A 90-day oral toxicity study in dogs was used to select the dose and endpoint for short-term inhalation exposure. The study is the appropriate duration for selecting short-term endpoints. The NOAEL of 5 mg/kg/day and the LOAEL of 50 mg/kg/day were based on increased liver weights and alkaline phosphatase activity, hypertrophy, and histopathology. Inhalation studies were not available; thus, inhalation absorption was assumed to be 100% (default value). Uncertainty factors (100x) include: 10x interspecies extrapolation, and 10x intraspecies variability.

3.5.8 Level of Concern for Margin of Exposure

Table 3.5.8 Summary of Levels of Concern for Risk Assessment.

Route	Short-Term (1 - 30 Days)	Intermediate-Term (1 - 6 Months)	Long-Term (> 6 Months)
Occupational (Worker) Exposure			
Dermal	N/A	N/A	N/A
Inhalation	100	N/A	N/A

3.5.9 Recommendation for Aggregate Exposure Risk Assessments

As per FQPA, 1996, when there are potential residential exposures to a pesticide, aggregate risk assessment must consider exposures from three major routes: oral, dermal, and inhalation exposures. However, an aggregate risk assessment across the three routes of exposure was not conducted for florasulam since there are no registered or proposed residential uses.

3.5.10 Classification of Carcinogenic Potential

There were no treatment-related increases in tumors in rat and mouse carcinogenicity studies after exposure to florasulam. Additionally, there was no evidence of mutagenicity noted. Therefore, according to *EPA's Final Guidelines for Carcinogen Risk Assessment* (March, 2005), florasulam is classified as "Not Likely to be Carcinogenic to Humans."

Summary of Toxicological Doses and Endpoints for Florasulam for Use in Human Risk Assessments.

Table 3.5a Toxicological Doses and Endpoints for Florasulam for Use in Dietary and Non-Occupational Human Health Risk Assessments				
Exposure/ Scenario	**Point of Departure**	**Uncertainty/ FQPA Safety Factors**	**RfD, PAD, Level of Concern for Risk Assessment**	**Study and Toxicological Effects**
Acute Dietary (General Population, including Infants and Children)	N/A	N/A	N/A	**The risk assessment was not conducted**. The effects observed in an acute neurotoxicity study were seen at a very high dose (2000 mg/kg/day) that is considered not applicable to human exposure.
Acute Dietary (Females 13-49 years of age)	N/A	N/A	N/A	**No appropriate endpoint identified.**
Chronic Dietary (All Populations)	NOAEL = 5 mg/kg/day	UF_A = 10X UF_H = 10X FQPA SF = 1X	Chronic RfD = 0.05 mg/kg/day cPAD = 0.05 mg/kg/day	**Chronic toxicity – dogs** LOAEL = 50 mg/kg/day, based on decreased body weights (17%), body weight gains (68%), and food consumption in the females; adverse liver alterations; slight vacuolation of the zona reticularis and zona fasciculata in the adrenal gland (fatty change) in both sexes.
Cancer (oral, dermal, inhalation)	"Not Likely to be Carcinogenic to Humans"			

NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. UF = uncertainty factor. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). FQPA SF = FQPA Safety Factor. PAD = population adjusted dose (a = acute, c = chronic). RfD = reference dose. N/A = not applicable.

Table 3.5b Summary of Toxicological Doses and Endpoints for Florasulam for Use in Occupational Human Health Risk Assessments				
Exposure/ Scenario	**Point of Departure**	**Uncertainty Factors**	**Level of Concern for Risk Assessment**	**Study and Toxicological Effects**
Dermal Short-term (1-30 days)	N/A	N/A	N/A	**The risk assessment was not conducted** 28-day dermal toxicity study – rats LOAEL = not determined, no systemic effect up to the limit dose of 1000 mg/kg/day.
Inhalation Short-term(1-30 days	NOAEL = 5mg/kg/day IAF=100%	UF_A = 10X UF_H = 10X FQPA SF = 1X	Residential LOC for MOE = 100	**90-day oral toxicity – dogs** LOAEL = 50 mg/kg/day, based on increased alkaline phosphatase activity and increased incidence/severity of hepatic vacuolation in both sexes.
Cancer (oral, dermal, inhalation)	"Not Likely to be Carcinogenic to Humans"			

NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. UF = uncertainty factor. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human

population (intraspecies). MOE = margin of exposure. LOC = level of concern. N/A = not applicable. IAF=inhalation absorption factor.

3.6 Endocrine Disruption

EPA is required under the FFDCA, as amended by FQPA, to develop a screening program to determine whether certain substances (including all pesticide active and other ingredients) "may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." Following recommendations of its Endocrine Disruptor and Screening and Testing Advisory Committee (EDSTAC), EPA determined that there was a scientific basis for including, as part of the program, the androgen and thyroid hormone systems, in addition to the estrogen hormone system. EPA also adopted EDSTAC's recommendation that the Program include evaluations of potential effects in wildlife. For pesticide chemicals, EPA will use FIFRA and, to the extent that effects in wildlife may help determine whether a substance may have an effect in humans, FFDCA authority to require the wildlife evaluations. As the science develops and resources allow, screening of additional hormone systems may be added to the Endocrine Disruptor Screening Program (EDSP).

When additional appropriate screening and/or testing protocols being considered under the Agency's EDSP have been developed, florasulam may be subjected to further screening and/or testing to better characterize effects related to endocrine disruption.

4.0 Public Health and Pesticide Epidemiology Data

No public health/epidemiology data were used in developing this risk assessment.

5.0 Dietary Exposure/Risk Characterization

5.1 Pesticide Metabolism and Environmental Degradation

5.1.1 Metabolism in Primary Crops

In the metabolism study, [^{14}C]-DE-570 (>98%) formulated with EF 1343 blank formulation, radiolabeled as [^{14}C]-phenyl-XDE-570 and [^{14}C]-TP-XDE-570 was applied to winter wheat at crop growth stages of BBCH30 (stem elongation-early application) and BBCH49 (postflag leaf emergence/first awns visible-late application) at 50 g a.i./ha. The rate used was equivalent to 10x the proposed label rate of 5 g a.i./ha.

Total radioactive residue (TRR) level in grain was determined by combustion/LSC. The ^{14}C-residues were too low to elucidate the nature of the TRRs in mature wheat ears (up to 0.03 ppm) and grain (up to 0.008 ppm). Therefore, no further attempts to characterize/identify the ^{14}C-residues in grain were carried out. However, residues in immature whole wheat plants and mature wheat straw were present at levels permitting adequate identification.

The metabolism of florasulam in wheat proceeded via hydroxylation in the 4-position of the phenyl ring with subsequent glucose conjugation. Additional degradation was followed by

tentative cleavage of the sulfonamide bridge. The metabolites detected in wheat matrices were 4-OH-(phenyl)-florasulam, the glucose conjugate of 4-OH-(phenyl)-florasulam, and 2-sulfonamide. The metabolism study was conducted at 10X the proposed label rate (5 g a.i./ha) and the 2-sulfonamide metabolite was detected only in winter wheat straw (0.059 ppm) and not in the grain.

Based on the low level of residues observed in wheat grain (0.008 ppm) at the exaggerated application rate (10X the proposed application rate) in the wheat metabolism study, HED concludes the residue of concern (ROC) in plants is the parent compound, florasulam. This conclusion applies to cereal grains only. Additional plant metabolism studies will be needed for any future uses on other types of crops.

5.1.2 Metabolism in Rotational Crops

In the confined rotational crop study, XDE-570 (florasulam), > 97% a.i., E-1343 Suspension Concentrate labeled either as the [UL-phenyl-^{14}C]XDE-570 or the [9-triazolopyrimidine-^{14}C]XDE-570, was applied to sandy loam soil at an application rate of 7.5 g a.i./ha (1.5X the maximum proposed postemergent application rate). Spring wheat, sunflower, cabbage and carrots were planted at 30 days after treatment (DAT) of soil.

Spring wheat, sunflowers, cabbage and carrots were harvested at maturity, 168 DAT (spring wheat and sunflowers), 195 DAT (cabbage), and 156 DAT (carrots). Each crop was separated into fractions as spring wheat (ears and straw), sunflower (heads and stems), cabbage (shoots) and carrot (leaves and roots). The samples were subjected to three sequential surface washes (an aqueous wash, a dichloromethane wash and a methanol wash). Each wash was analyzed to determine total ^{14}C-residues (TRRs) using combustion/liquid scintillation counting. In addition, tissue samples were combusted and TRRs determined. None of the fractions from rotational crops had TRRs greater than 0.01 ppm. Therefore, no further attempt was made to profile TRRs.

Because levels of TRRs in the rotational crops were low (≤ 0.01 ppm), no residues were identified. Therefore, the confined rotational crop study supports the definition of ROC as parent only as defined in the plant and livestock metabolism studies.

Based on the results of the confined rotational crop study, field rotational crop studies are not required, and a 30-day plant back interval (PBI) can be supported for all crops. The label has a plant back interval of greater than 30 days for barley, canola, forage grasses, oats, peas, rye and wheat.

5.1.3 Metabolism in Livestock

In the lactating goat metabolism study, XDE-570, radiolabeled as either [UL-aniline-^{14}C]XDE-570, or [triazolopyrimidine-9- ^{14}C]XDE-570 was administered to two lactating goats (one per treatment) at a dose level of approximately 0.48 mg/kg bw/day. The dose was administered orally once daily in the morning for five consecutive days using a bolus gun and was equivalent to approximately 11 ppm (~100X the XDE-570 dietary burden) at an average feed consumption of 2 kg/day.

The results indicated that the total radioactive residues (TRRs) were almost comparable between two labeling positions for urine, feces, muscle and fat. But a slight difference in TRR was noted for kidney, liver and milk. Recoveries of the administered dose in goat were 89% of the aniline label (A-label) and 83% for the triazolopyrimidine label (TP-label). The majority of the radioactivity was excreted in the urine and feces, accounting for a total of 99.8% of the recovered radioactivity. Total residues in tissues were very low. These residues in the tissues, milk and blood samples were below 0.1% of the administered dose. The highest concentration of residues in tissues was found in the kidneys, 0.069 ppm and 0.039 ppm from the A-label and TP-label experiments, respectively. Total radioactive residue in liver was 0.033 ppm and 0.023 ppm from the A-label and TP-label experiments, respectively. Total radioactive residue in muscle was 0.0016 ppm and 0.0009 ppm from the A-label and TP-label experiments, respectively. Total radioactive residue in fat was 0.0016 ppm and 0.0017 ppm from the A-label and TP-label experiments, respectively. Total radioactive residue in milk was 0.016 ppm and 0.033 ppm from the A-label and TP-label experiments, respectively. The predominant radioactive component extracted from urine, milk, liver and kidney samples was parent. One minor metabolite representing up to 1.5% of TRR was tentatively identified as 5-OH-florasulam in urine, liver and kidney samples.

In the laying hen metabolism study, XDE-570, radiolabeled as either [UL-aniline-^{14}C]XDE-570, or [triazolopyrimidine-9- ^{14}C]XDE-570 was administered to two groups of 10 laying hens at a dose level of 0.76 ± 0.01 mg/kg bw/day. The dose was equivalent to 11 ppm (~1300X the XDE-570 dietary burden) at an average feed consumption of 0.13 kg/day. Samples of eggs and excreta were collected throughout the study. The test hens were sacrificed approximately 24 hours after the final dose. The tissue samples of fat, composite muscle (light and dark), skin, and liver were collected for analysis.

The results indicated that the TRRs were comparable between two labeling positions for excreta, muscle, fat, liver, and egg. TRR in muscle, fat and liver were less than limit of quantification (< LOQ). TRR in skin and eggs were very low (0.013%, < 0.007 ppm). Almost 100% of the recovered radioactivity that was administered to hen was found in excreta. The highest concentration of residues in tissues was found in the skin, 0.0066 ppm and 0.005 ppm in A-label and TP-label, respectively. The concentrations of residues in egg were about 0.004 ppm for both the A-label and TP-label, respectively. Total radioactive residue in liver was 0.0014 ppm and 0.001 ppm from the A-label and TP-label experiments, respectively. Total radioactive residue in composite muscle was 0.0005 ppm and 0.0008 ppm from the A-label and TP-label experiments, respectively. Total radioactive residue in composite fat was 0.0004 ppm and 0.0006 ppm from the A-label and TP-label experiments, respectively.

The metabolism of florasulam in the laying hen and lactating goat were similar. In both, the majority of the radioactivity was found in the excreta. Most of the parent compound in goat and hen was eliminated unchanged with minor unknown metabolites at unquantifiable levels. No significant cleavage of the sulfonanilide bridge was observed.

5.1.4 Analytical Methodology

Residues of florasulam were extracted from wheat, barley and oat matrix with acidified acetone. An aliquot of the extract was purified by filtration through a graphitized carbon solid-phase extraction (SPE) column. The extract was concentrated to remove acetone, diluted with 0.01 N hydrochloric acid and partitioned onto an octadecyl (C_{18}) SPE column. The florasulam was eluted with a 30% acetonitrile in 0.01 N hydrochloride acid solution. Florasulam is partitioned, after salting, into methyl *t*-butyl ether (MTBE). The MTBE was concentrated to dryness. Residues of florasulam were dissolved in acetone and derivatized at room temperature with iodomethane and triethylamine. The acetone solution was concentrated to dryness and *N*-methyl florasulam residues were dissolved in a 5% sodium thiosulfate solution and partitioned into toluene containing the internal standard *N*-propyl florasulam. Residues of florasulam as the N-methyl florasulam derivative were determined by capillary gas chromatography with mass selective detection (GC/MSD). This is a specific method that identifies/quantifies florasulam, the parent compound only.

The limit of detection (LOD) was calculated as three times the standard deviation (3s) which was 0.0012 ppm in grain, 0.005 ppm in forage and immature green plant, 0.0036 ppm in hay and immature dried plant and 0.0074 ppm in straw. The limit of quantitation (LOQ) for florasulam was established at 0.01 ppm for grain over the concentration range of 0.01-0.10 ppm, and at 0.05 ppm for forage, hay, straw, immature green plant and immature dried plant over the concentration range of 0.05-0.50 ppm.

Representative chromatograms of control matrices of wheat, barley and oat showed no interferences from crop components or from reagents, solvents and glassware. The chromatographic peaks were sharp and free of interferences in the retention areas of internal standard or *N*-methyl florasulam derivative. The registrant stated no radiovalidation of the analytical method was performed since residue levels were below LOQ.

The method of analysis was independently validated at Enviro-Bio-Tech. Ltd. (Bernville, PA) using wheat grain, forage, hay and straw. This ILV study successfully validated the Dow AgroSciences method GRM 98.01 for the residues of the florasulam in wheat matrices, indicating good reproducibility.

The GC/MSD method will be forwarded to BEAD/ACB for a petition method validation. The analytical methodology is acceptable as an enforcement method pending validation by ACB.

5.1.5 Environmental Degradation

Florasulam does not hydrolyze at acidic or neutral pHs, but hydrolyzes slowly (half-life of 99 days) at pH 9. The major hydrolysis degradates at pH 9 are 5-OH-XDE-570 and a second hydrolysis product for which the structure was not confirmed. In water, florasulam photodegrades slowly (adjusted half-life of 46 days), the only major degradate is triazolopyrimidine sulphonic acid of florasulam (TSPA). Florasulam is stable to photodegradation on soil. Abiotic degradation (by hydrolysis or photolysis) is not expected to be a significant route of dissipation in the environment.

Florasulam is not persistent in aerobic soil, degrading rapidly with half-lives of 0.7-8.3 days. The major degradates are N-(2,6-difluorphenyl)-8-fluoro-5-hydroxy (1,2,4)triazolo (1,5c) pyrimidine-2-sulphonamide (5-OH-XDE-570; N-(2,6-difluorophenyl)-5-aminosulphonyl-1H-1,2,4-triazole-3-carboxylic acid (DFP-ASTCA), 5-(aminosulphonyl)-1H-1,2,4-triazole-3-carboxylic acid (ASTCA), and 1H-1,2,4-triazole-3-sulphonamide (TSA). Based on the study results and the chemical structures, florasulam appears to biotransform rapidly to 5-OH-XDE-570, which is then further biotransformed to DFP-ASTCA, DFP-TSA, and polar compounds, eventually forming CO2 and bound residues. The major degradate 5-OH-XDE-570 degrades more slowly than the parent in aerobic soil, with half-lives ranging from 10 to 56 days in 11 soils, and is labile to moderately persistent. Biotransformation of florasulam is a significant route of dissipation in aerobic soils. Data for anaerobic soils were not submitted.

In aquatic systems, florasulam degrades with half-lives of 3-18 days in aerobic systems and half-lives of 2-13 days in anaerobic systems. In aerobic aquatic systems, florasulam is biotransformed to 5-OH-XDE-570, which is then further biotransformed to DFP-ASTCA and STCA (tentative identification). However, 5-OH-XDE-570 degrades much more slowly than the parent, degrading with a half-life of 169 days in one aerobic system and remaining stable in another aerobic system. In anaerobic aquatic systems, 5-OH-XDE-570 is stable. Thus, 5-OH-XDE-570 is expected to be persistent in both aerobic and anaerobic aquatic systems.

Based on the results from the laboratory batch equilibrium studies and column leaching studies, as supported by the results of multiple terrestrial field dissipation studies in which leaching was observed, both florasulam and 5-OH-XDE-570 are very mobile in soil and, thus, have the potential to leach. All measured Kds are less than 1. For the parent compound, the potential to leach will be somewhat reduced by the fairly rapid biotransformation of the parent in aerobic soil. For 5-OH-XDE-570, the potential to leach is enhanced (relative to the parent) by slower biotransformation in aerobic soil and by a much higher solubility in water. For either compound, both of which partition mainly to the water phase, the potential to leach will be greater when there is excessive rainfall or irrigation.

Based on bioconcentration in fish (BCF) values of 0.9-2.0X, florasulam is not expected to bioaccumulate in aquatic organisms.

5.1.6 Comparative Metabolic Profile

Data depicting the metabolism of florasulam in plants and animals, as well as data on environmental degradates, have been submitted to the Agency. The nature of the residue for the use in/on cereal grains is adequately understood based on acceptable metabolism studies in wheat, rotational crops (spring wheat, sunflower, cabbage, and carrot), ruminants (goat), and poultry (hen). Major metabolites (> 10%) observed include: parent (all matrices), 5-OH florasulam (rotational crops), 4-OH-(phenyl)-florasulam (wheat), the glucose conjugate of 4-OH-(phenyl)-florasulam (wheat), and 2-sulfonamide (wheat).

The metabolism of florasulam in wheat proceeded via hydroxylation in the 4-position of the phenyl ring with subsequent glucose conjugation. Additional degradation was followed by tentative cleavage of the sulfonamide bridge.

In rats, metabolism is limited to hydroxylation of the phenyl ring without affecting the sulfonamide bond. The parent compound accounted for 80% of the administered dose. The major metabolite observed was OH-phenyl-florasulam (exact position of hydroxyl group not determined) at 3-10%; 2-4% of a sulfate conjugate of OH-phenyl-florasulam was also seen.

For the purposes of this petition, the ROC in plant and livestock commodities for risk assessment and tolerance expression is the parent compound. A metabolite summary table (Table B.1.2) is located in Appendix B.

5.1.7 Toxicity Profile of Major Metabolites and Degradates of Concern

Per correspondence with Alberto Protzel (Toxicology Branch, HED, 5/1/07), the major florasulam metabolites (4-OH phenyl florasulam, glucose conjugate of 4-OH phenyl florasulam, 5-OH florasulam, TPSA, ASTCA, and DFP-ASTCA) observed in the rat and primary crops, and as environmental degradates in drinking water, are unlikely to be more toxic than the parent compound.

5.1.8 Pesticide Metabolites and Degradates of Concern

Since residues in grain were too low to identify, the decision for the residue of concern in cereal grains is based on the results for the whole wheat plants (30 days after application) and wheat straw. The wheat metabolism study was conducted at a 10x rate (50 g ai/ha; 0.045 lb ai/A). Parent was identified in all but one of these samples at levels of 0.02-0.12 ppm (7-32% TRR). The only metabolites consistently observed were the 4-OH phenyl florasulam and its glucose conjugate. The conjugate was present at 0.0018-0.088 ppm (2.5-41.5% TRR) and the free 4-OH metabolite at 0.0012-0.06 ppm (5.5-15% TRR). In the absence of toxicology data for the OH metabolite and its conjugate, HED is not able to consider these residues to be significantly less toxic than parent florasulam. Since these residues are present at comparable or higher levels than the parent, one would normally include them as residues of concern. However, in this case due to the very low application rate, residues of both the parent and metabolites are likely to be below the LOQ of an analytical method from the proposed use. Based on the 10x rate metabolism study, the parent or the metabolite with its conjugate could serve as a marker of serious misuse for tolerance enforcement purposes. Considering that total radioactivity in wheat grain from the 10x rate was only 0.008 ppm, use of the parent compound LOQ of 0.01 ppm is a conservative measure of exposure for dietary risk purposes. Taking into account all of these factors, HED concludes that the residue of concern in cereal grains is the parent compound florasulam.

The 5-OH degradate formed by demethylation of florasulam is by far the predominant environmental residue reaching maximum levels of 70% of applied material in the hydrolysis and metabolism (soil, aquatic) studies. As with the 4-OH metabolite in plants, it is assumed to be of comparable toxicity to the parent. Although several other degradates do occur at levels >10% applied, they do so in only one or two studies and their maximum levels do not approach those of the 5-OH degradate. On this basis, the residues of concern in drinking water are the

parent and 5-OH degradate. EFED has supplied separate estimate drinking water concentrations for these two compounds.

Table 5.1.8 Summary of Metabolites and Degradates to be included in the Risk Assessment and Tolerance Expression			
Matrix		Residues included in Risk Assessment	Residues included in Tolerance Expression
Plants	Primary Crop	Parent Florasulam	Parent Florasulam
	Rotational Crop	N/A	N/A
Livestock	Ruminant	N/A	N/A
	Poultry	N/A	N/A
Drinking Water		Parent Florasulam & 5-OH florasulam	Not Applicable

5.1.9 Drinking Water Residue Profile

Estimated drinking water concentrations (EDWCs) in surface water were derived using the Environmental Fate and Effects Division (EFED) Tier I aquatic model FIRST (FQPA Index Reservoir Screening Tool, v.1.1.0; dated 12/12/2005). Estimated drinking water concentrations (EDWCs) in groundwater were derived using EFED's Tier I aquatic model SCI-GROW2 (Screening Concentration in Ground Water, v.2.3; dated 11/12/1997).

Table 5.1.9a. Maximum Tier I Estimated Drinking Water Concentrations (EDWCs) of parent florasulam for drinking water risk assessment based on aerial and ground applications of florasulam. Results are reported in parts per trillion.			
Drinking Water Source (Model Used)	**Use/Rate Modeled (lb ai/A)**	**Maximum Estimated Drinking Water Concentration (EDWC; ppTr)**	
Groundwater (SCI-GROW)	0.0045	Acute and Chronic	1.35×10^{-2}
Surface Water (FIRST)	Aerial spray/0.0045	Chronic	**16.8**
Surface Water (FIRST)	Ground spray/0.0045	Chronic	16.7

Table 5.1.9 b Maximum Tier I Estimated Drinking Water Concentrations (EDWCs) of 5-OH-XDE-570 for drinking water risk assessment based on aerial and ground applications of florasulam. Results are reported in parts per trillion.			
Drinking Water Source (Model Used)	**Use/Rate Modeled (lb ai/A)**	**Maximum Estimated Drinking Water Concentration (EDWC; ppTr)**	
Groundwater (SCI-GROW)	0.0045	Acute and Chronic	7.44
Surface Water (FIRST)	Aerial spray/0.0045	Chronic	217.3
Surface Water (FIRST)	Ground spray/0.0045	Chronic	**217.5**

5.1.10 Food Residue Profile

There are adequate storage stability data for wheat forage, hay, straw, and grain. These data indicate residues of florasulam were relatively stable at -20 ^{o}C for 524, 410, 313 and 459 days in spiked forage, grain, straw and hay, respectively.

The proposed use of florasulam on cereal grains is considered to fall under 40 CFR §180.6(a)(3) (no expectation of finite residues in livestock commodities). Therefore, feeding studies and tolerances for meat, milk, poultry, and eggs are not necessary for the purposes of this petition. HED also concludes that residue analytical methods and storage stability data for livestock commodities are not needed. This determination is based on the results of the wheat, barley, oats, and rye field trials treated at a 2x application rate. The decision is also based on the low florasulam dietary burdens for dairy and beef cattle (0.1 ppm), poultry (0.008 ppm), and swine (0.007 ppm), and the low transfer of residues to tissues, milk, and eggs seen in the metabolism studies. HED reserves the right to require these waived studies if the petitioner seeks to register additional feed crops in the future.

There are adequate magnitude of the residue data for wheat, barley, oats, and rye. The supervised field trials indicated that residues of florasulam in grain, forage, hay, and straw of wheat, barley, rye, and oats were non quantifiable (<0.01 ppm for grain, <0.05 ppm for forage, hay, and straw), following a single foliar application at an exaggerated rate (2x proposed maximum seasonal application rate). Florasulam residues were greater than the proposed tolerances in one wheat forage field trial. However, HED concludes the proposed tolerance of 0.05 ppm for wheat forage would adequately cover residues in wheat forage since field trials were conducted at a 2x exaggerated rate. No processing studies on wheat were submitted; however, the metabolism studies in wheat treated with ^{14}C-DE-570 at the exaggerated rate of 50 g a.i./ha (10x the proposed maximum season rate) indicated very low radioactive residue levels in grain (maximum of 0.002 ppm). HED concludes that it is unlikely that residues of florasulam in processed food/feed items will concentrate to quantifiable levels when treated according to the proposed use pattern. A wheat processing study is also not needed to support the proposed use.

For the proposed use on cereal grains, field rotational crop studies and tolerances on rotational crops are not needed. Based on the results of the confined rotational crop studies, it is permissible to rotate to any crop after 30 days.

5.1.11 International Residue Limits

Maximum residue levels (MRLs) are established in Canada for residues of florasulam in barley, oats, and wheat grain at 0.01 ppm. There are no Codex MRLS. No harmonization issues exist since the same tolerance level is recommended for the use in the U.S.

5.2 Dietary Exposure and Risk

The chronic dietary risk assessment was conducted using the Dietary Exposure Evaluation Model (DEEM-FCID, Version 2.03), which uses food consumption data from the USDA's Continuing Survey of Food Intakes by Individuals (CSFII) from 1994-1996 and 1998. The

drinking water residues used in the dietary risk assessment were provided by EFED (see Table 5.1.9a and b). Water residues were incorporated in the DEEM-FCID into the food categories "water, direct, all sources" and "water, indirect, all sources." To arrive at the total EDWC, the maximum surface water value for the parent was added to the maximum surface water value for the major degradate. For the parent, the chronic aerial spray value (16.8 ppTr) was higher than the ground spray value. For the degradate, the ground spray value was the higher of the two (217.5 ppTr). Adding the 2 values (16.8 + 217.5) results in the total EDWC of 234 ppTr, or 0.00023 ppm.

5.2.1 Acute Dietary Exposure/Risk

No acute dietary endpoint was identified; therefore, an acute dietary risk assessment was not conducted.

5.2.2 Chronic Dietary Exposure/Risk

The chronic analyses assumed tolerance level residues, 100% crop treated, and DEEM™ (ver. 7.81) default processing factors for proposed commodities. For those processed commodities in the DEEM-FCID™ residue list which were not in DEEM™ (ver 7.81) e.g. (flour, bran, etc.), a processing factor of 1 was assumed.

Table 5.2.3.1. Results of Chronic Dietary Exposure Analysis (Food Only)

Population Subgroup	cPAD (mg/kg/day)	Exposure (mg/kg/day)	% cPAD
General U.S. Population	0.05	0.000019	<1
All Infants (< 1 year old)	0.05	0.000013	<1
Children 1-2 years old	0.05	0.000047	<1
Children 3-5 years old	0.05	0.000046	<1
Children 6-12 years old	0.05	0.000031	<1
Youth 13-19 years old	0.05	0.000018	<1
Adults 20-49 years old	0.05	0.000016	<1
Females 13-49 years old	0.05	0.000014	<1
Adults 50+ years old	0.05	0.000013	<1

Table 5.2.3.2. Results of Chronic Dietary Exposure Analysis (Food Plus Water)

Population Subgroup	cPAD (mg/kg/day)	Exposure (mg/kg/day)	% cPAD
General U.S. Population	0.05	0.000024	<1
All Infants (< 1 year old)	0.05	0.000029	<1
Children 1-2 years old	0.05	0.000054	<1
Children 3-5 years old	0.05	0.000053	<1

Table 5.2.3.2. Results of Chronic Dietary Exposure Analysis (Food Plus Water)			
Population Subgroup	**cPAD (mg/kg/day)**	**Exposure (mg/kg/day)**	**% cPAD**
Children 6-12 years old	0.05	0.000036	<1
Youth 13-19 years old	0.05	0.000022	<1
Adults 20-49 years old	0.05	0.000020	<1
Females 13-49 years old	0.05	0.000019	<1
Adults 50+ years old	0.05	0.000018	<1

5.2.3 Cancer Dietary Risk

There were no treatment-related tumors observed in carcinogenicity studies in rats and mice. As a result, a cancer assessment was not conducted.

5.3 Anticipated Residue and Percent Crop Treated (%CT) Information

The chronic analyses assumed tolerance level residues, 100% crop treated, and DEEM™ (ver. 7.81) default processing factors for all registered and proposed commodities. For those processed commodities in the DEEM-FCID™ residue list which were not in DEEM™ (ver 7.81) e.g. (flour, bran, etc.), a processing factor of 1 was assumed.

6.0 Residential (Non-Occupational) Exposure/Risk Characterization

Currently, there are no registered or proposed residential uses for florasulam; thus, there is no exposure via this pathway and an assessment was not conducted.

7.0 Aggregate Risk Assessments and Risk Characterization

7.1 Acute Aggregate Risk

No acute dietary endpoint was identified; therefore, an acute aggregate risk assessment was not conducted.

7.2 Short-Term Aggregate Risk

As there are no residential uses for florasulam, short-term aggregate risk assessments were not conducted.

7.3 Intermediate-Term Aggregate Risk

As there are no residential uses for florasulam, intermediate-term aggregate risk assessments were not conducted.

7.4 Long-Term Aggregate Risk

The chronic dietary exposure analysis included both food and drinking water. As a result, the chronic aggregate risk assessment is equivalent to the chronic dietary risk assessment. Refer to Section 5.2.2 for a discussion of the dietary exposure analysis. The general U.S. population and all population subgroups have risk estimates that are below HED's level of concern. The most highly exposed population subgroup is Children (1-2 years) which utilizes < 1% of the cPAD. The general U.S. population utilizes <1% of the cPAD.

7.5 Cancer Risk

Exposure to florasulam did not result in a treatment-related increase in tumor formation in rats or mice; therefore, a cancer risk assessment was not conducted.

8.0 Cumulative Risk Characterization/Assessment

Section 408(b)(2)(D)(v) of the FFDCA requires that, when considering whether to establish, modify, or revoke a tolerance, the Agency consider "available information concerning the cumulative effects" of a particular pesticide's residues and "other substances that have a common mechanism of toxicity."

Unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, EPA has not made a common mechanism of toxicity finding as to florasulam and any other substances, and florasulam does not appear to produce a toxic metabolite produced by other substances. For the purposes of this tolerance action, EPA has not assumed that florasulam has a common mechanism of toxicity with other substances. For information regarding EPA's efforts to determine which chemicals have a common mechanism of toxicity and to evaluate the cumulative effects of such chemicals, see the policy statements released by EPA's Office of Pesticide Programs concerning common mechanism determinations and procedures for cumulating effects from substances found to have a common mechanism on EPA's website at http://www.epa.gov/pesticides/cumulative/.

9.0 Occupational Exposure/Risk Pathway

9.1 Short-Term Handler Risk

The following agricultural products have been assessed for occupational exposure: EF1343, EF1383, GF-184 and GF-1727. The end-use products are formulated as a liquid with the following respective concentrations of the a.i.: 4.84% a.i., 0.58% a.i., 0.25% a.i., and 0.39% a.i. It may be applied by either ground or aerial equipment, at an application rate of 0.00446 pounds a.i. per acre. Based on the number of seasonal applications indicated on the product labels, handler exposures are expected to be short-term in duration.

A quantitative risk assessment for the dermal exposure route was not conducted. There were no adverse systemic or dermal effects seen up to the limit dose tested (1,000 mg/kg/day) in the 28-

day dermal toxicity study. The quantitative exposure/risk assessment developed for handlers is based on the following exposure scenarios:

Mixing/loading liquid for groundboom
Applying liquid for groundboom to wheat, barley, rye, oats, and triticale
Mixing/loading liquid for aerial application
Applying liquid for aerial application to wheat, barley, rye, oats, and triticale
Flagger

9.1.1 Data and Assumptions for Handler Exposure Scenarios

The following assumptions, parameters, and factors were used in the exposure and risk assessment:

Unit Exposures:

Chemical-specific data for assessing exposure during pesticide handling activities were not submitted to the Agency in support of this Section 3 application. It is HED policy to use data from the Pesticide Handlers Exposure Database (PHED) Version 1.1 to assess handler exposures for regulatory actions when chemical-specific data are not available (HED Science Advisory Council for Exposure, SOP Number .007, January 1999).

Area Treated:
(HED Exposure Science Advisory Committee SOP Number 9.1)

200 acres of wheat, barley, rye, oats, and triticale were treated per day with groundboom sprayer
1200 acres of wheat, barley, rye, oats, and triticale were treated per day with aerial spray equipment
350 acres assessed for flaggers

Application Rate:

The maximum application rate is 0.00446 lb ai/acre

Body Weight:

The average adult body weight of 70 kg was used for estimating both inhalation exposure and risk.

Dermal Absorption Factor:

Since a dermal endpoint was not selected, there was no need to use a dermal absorption factor to determine dermal exposure and risk.

9.1.2 Handlers Exposure and Risk

Since a dermal endpoint and dose were not selected, a dermal exposure assessment was not conducted. Inhalation MOEs were significantly greater than 100 at baseline and are not of concern to HED (MOEs of equal to or less then 100 are of concern to HED).

Table 5.1.2: Handler Inhalation Exposure and Risk

Scenario	Mitigation	Inhalation Unit Exposure (mg/lb ai)	Application Rate (lb ai/A)	Acres Treated (A/Day)	Daily Dose [a] (mg/kg/day)	Inhalation MOE [b]
Mixer/Loader						
Groundboom	Baseline	0.0012	0.00446	200	0.00001529	330,000
Aerial				1200	0.0000917	54,000
Applicator						
Groundboom	Baseline	0.00074	0.00446	200	0.0000094	530,000
Aerial	Eng. Cont. [c]	0.000068		1200	0.0000052	960,000
Flagger						
Aerial	Baseline	0.011	0.00446	350	0.000245	20,000

a. Inhalation Dose (mg/kg/day) =[Rate (lb ai/A) x UE (mg /lb ai) x Acres Treated (A/day)] / BW (70 kg)
b. Inhalation MOE = [Inhalation NOAEL (5 mg/kg/day)] / Inhalation Dose (mg/kg/day)

9.2 Short-Term Postapplication Risk

A dermal non-cancer agricultural postapplication exposure assessment was not conducted due to the absence of systemic toxicity in the dermal toxicity study. Postapplication inhalation exposures are expected to be minimal and less than the application exposures. As all scenarios are for outdoor agricultural uses, inhalation postapplication exposure is expected to be negligible.

Restricted Entry Interval

The restricted entry interval (REI) is based on the acute toxicity of the technical active ingredient. Florasulam is classified as Toxicity Category III for acute dermal and Category IV for acute oral, inhalation, and eye exposure. Acute toxicity Category III and IV chemicals require a 12 hour REI.

The proposed label for EF-1343 proposes an REI of 4 hours. Based on review of the toxicological database for florasulam, EF-1343 is a candidate for a reduced risk active ingredient; therefore, HED does not object to the proposed 4-hour REI.

The product labels for GF-1727, GF-184, and EF-1383 propose various REIs ranging from 12 to 48 hours respectively. The REIs for these labels are based on a second active ingredient (e.g. MCPA, fluroxpyr, and 2-4-D). If products contain more than one active ingredient, the REI will be based on the active ingredient which requires the longest REI. **HED recommends that the Registration Division ensure that the proper REI is established for each of the proposed labels**.

10.0 Data Needs and Label Recommendations

10.1 Toxicology

There are no toxicology data gaps.

10.2 Residue Chemistry

Regulatory Recommendations and Residue Chemistry Deficiencies

A revised Section F should be submitted with correct raw agricultural commodity definitions along with the correct spelling of the chemical name for florasulam.

Successful completion of a petition method validation by BEAD/ACB. The method has been sent to BEAD/ACB for validation.

Analytical standards for florasulam are not currently available in the National Pesticide Standards Repository. Analytical reference standards of florasulam need to be supplied and supplies need to be replenished as requested by the Repository. The reference standards should be sent to the Analytical Chemistry Branch, which is located at Fort Meade, to the attention of either Theresa Cole, Dallas Wright, or Frederic Siegelman at the following address:

USEPA
National Pesticide Standards Repository/Analytical Chemistry Branch/OPP
701 Mapes Road
Fort George G. Meade, MD 20755-5350
(Note that the mail will be returned if the extended zip code is not used.)

10.3 Occupational and Residential Exposure

The product labels for GF-1727, GF-184, and EF-1383 propose various REIs ranging from 12 to 48 hours respectively. The REI for these labels are based on a second active ingredient (e.g. MCPA, fluroxpyr, and 2-4-D). If products contain more than one active ingredient, the REI will be based on the active ingredient which requires the longest REI. **HED recommends that the Registration Division ensure that the proper REI is established for each of the proposed labels**.

References:

Florasulam: Occupational and Residential Exposure Assessment for Section 3 Registration for use of Florasulam on Weeds in Wheat, Barley, Oats, Rye and Triticale. M. Collantes. D333360.

Florasulam: First Food Use Petition for the Establishment of Tolerances on the Raw Agricultural Commodities of Barley, Oats, Rye, Triticale, and Wheat. Summary of Analytical Chemistry and Residue Data. T. Morton. D333759.

Florasulam: Chronic Aggregate Dietary and Drinking Water Exposure and Risk Assessment for the New Active Ingredient. T. Morton. D366694.

Tier I Drinking Water Assessment for the Florasulam Proposed Section 3 Registration for Use on Wheat (Including Durum), Barley, Oats, Rye and Triticale. C. Sutton. D332069

Appendix A: Toxicology Assessment

A.1 Toxicology Data Requirements

The requirements (40 CFR 158.340) for a food use for florasulam are in Table 1. Use of the new guideline numbers does not imply that the new (1998) guideline protocols were used.

Test		Technical	
		Required	**Satisfied**
870.1100	Acute Oral Toxicity	yes	yes
870.1200	Acute Dermal Toxicity	yes	yes
870.1300	Acute Inhalation Toxicity	yes	yes
870.2400	Primary Eye Irritation	yes	yes
870.2500	Primary Dermal Irritation	yes	yes
870.2600	Dermal Sensitization	yes	yes
870.3100	Oral Subchronic (rodent)	yes	yes
870.3150	Oral Subchronic (nonrodent)	yes	yes
870.3200	21/28-Day Dermal	yes	yes
870.3250	90-Day Dermal	no	---
870.3465	90-Day Inhalation	no	---
870.3700a	Developmental Toxicity (rodent)	yes	yes
870.3700b	Developmental Toxicity (nonrodent)	yes	yes
870.3800	Reproduction	yes	yes
870.4100a	Chronic Toxicity (rodent)	yes	yes
870.4100b	Chronic Toxicity (nonrodent)	yes	yes
870.4200a	Oncogenicity (rat)	yes	yes
870.4200b	Oncogenicity (mouse)	yes	yes
870.4300	Chronic/Oncogenicity	yes	yes
870.5100	Mutagenicity—Gene Mutation - bacterial	yes	yes
870.5300	Mutagenicity—Gene Mutation - mammalian	yes	yes
870.5375	Mutagenicity—Structural Chromosomal Aberrations	yes	yes
870.5395	Mutagenicity—Other Genotoxic Effects	yes	yes
870.6100a	Acute Delayed Neurotox. (hen)	no	---
870.6100b	90-Day Neurotoxicity (hen)	no	---
870.6200a	Acute Neurotox. Screening Battery (rat)	no	yes
870.6200b	Chronic Neurotox. Screening Battery (rat)	no	yes
870.6300	Develop. Neuro	no	---
870.7485	General Metabolism	yes	yes
870.7600	Dermal Penetration	no	yes

A.2 Toxicity Profiles

Table A.2.1 Acute Toxicity Profile – Florasulam				
Guideline No.	**Study Type**	**MRID(s)**	**Results**	**Toxicity Category**
870.1100	Acute oral – rat	46808209	LD_{50} >= 5000 mg/kg	IV
870.1100	Acute oral – mouse	46827915	LD_{50} >= 5000 mg/kg	IV
870.1200	Acute dermal – rabbit	46808211	LD_{50} >= 2000 mg/kg	III
870.1300	Acute inhalation – rat	46808212	LC_{50} >= 5.0 mg/L	IV
870.2400	Acute eye irritation – rabbit	46808213	Non- irritating	IV
870.2500	Acute dermal irritation – rabbit	46808214	Non- irritating	IV
870.2600	Skin sensitization – guinea pig	46808215 46808216	No sensitization	

Table A.2.2 Subchronic, Chronic, and Other Toxicity Profile for Florasulam Technical		
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 (5-8%) and body weight gains (21%) in females, and evidence of slight nephrotoxicity (increased kidney weights, hypertrophy, and degeneration/regeneration and inflammation of the descending portion of proximal tubules) 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** **LOAEL = Not determined**
870.3150 90-Day oral toxicity (dog)	46808223 (1995) Acceptable/guideline 0, 5, 50, 100 mg/kg/day	**NOAEL = 5 mg/kg/day** **LOAEL = 50 mg/kg/day,** based on increased alkaline phosphatase (59-127%) activity, increased liver weights, hypertrophy and increased incidence/severity of hepatic vacuolation in both sexes.
870.3200 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	**Systemic NOAEL = 1000 mg/kg/day** **Systemic LOAEL = Not determined** **Dermal NOAEL = 500 mg/kg/day** **Dermal LOAEL = 1000 mg/kg/day**, based on edema and erythema in males (4/5)
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 (4-6%, GD 6-16), body weight gains (16%, GD 6-16%), food consumption (6-13%), and increased kidney weights. **Developmental NOAEL = 750 mg/kg/day** **Developmental LOAEL = Not determined**
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** **Maternal LOAEL = Not determined** **Developmental NOAEL = 500 mg/kg/day** **Developmental LOAEL = Not determined** Note: Study acceptable due to findings of preliminary developmental toxicity study at 600 mg/kg/day (mortality and decreased body weight gains and food consumption).
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** **Parental/Systemic LOAEL = 500 mg/kg/day**, based on decreased body weights, body weight gains, and food consumption, as well as kidney alterations.

Table A.2.2 Subchronic, Chronic, and Other Toxicity Profile for Florasulam Technical		
Guideline No./Study Type	**MRID No. (year) Classification/Doses**	**Results**
		Offspring NOAEL = 500 mg/kg/day **Offspring LOAEL = Not determined** **Reproductive NOAEL = 500 mg/kg/day** **Reproductive LOAEL = Not determined**
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 (17%), body weight gains (68%), and food consumption in females; increased liver enzymes (alanine aminotransferase and alkaline phosphatase) and slight vacuolation of the zona reticularis and zona fasciculata in the adrenal gland (consistent with fatty change) in both sexes.
870.4200 Carcinogenicity (mouse)	46808230 (1997) Acceptable/guideline 0, 50, 500, 1000 mg/kg/day	**NOAEL = 1000 mg/kg/day.** **LOAEL = Not determined** **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 = 10 mg/kg/day-males; 125 mg/kg/day-females** **LOAEL = 250 mg/kg/day (males)**, based on slight nephrotoxicity (increased kidney weights, hypertrophy, and slight multi-focal mineralization in the papilla); **250 mg/kg/day (females)**, based on decreased body weights (3-8%) and body weight gains (14%). **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*)	**Negative**-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	**Negative**-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	**Negative**-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	**Negative**-No significant increase in the frequency of micronucleated polychromatic erythrocytes in bone marrow
870.6200a Acute neurotoxicity screening battery (rat)	46808217 (1997) Acceptable/guideline 0, 200, 1000, 2000 mg/kg	**Systemic NOAEL = 1000 mg/kg** **Systemic LOAEL = 2000 mg/kg**, based on decreased body weight gain (21%) and general malaise (slight transient decrease in motor activity, minimal activity in open field, and reactivity) in males. **Neurotoxicity NOAEL = 2000 mg/kg** **Neurotoxicity LOAEL = Not determined**

Table A.2.2 Subchronic, Chronic, and Other Toxicity Profile for Florasulam Technical		
Guideline No./Study Type	**MRID No. (year) Classification/Doses**	**Results**
870.6200b Chronic neurotoxicity screening battery (rat)	46808228 (1996) Acceptable/guideline 0, 10, 125 (female only), 250, 500 (male only) mg/kg/day	**Systemic NOAEL = 250 mg/kg/day** **Systemic LOAEL = 500 mg/kg/day**, based on decreased body weight (9-15% at 6, 9, and 12 months) and body weight gain in males (61-67% at 3-12 months; 27% at 0-12 months) **Neurotoxicity NOAEL = 250 mg/kg** (highest dose tested in females). **Neurotoxicity LOAEL= Not determined.**
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 (rat)	46808304 (1997) Acceptable/guideline 0.001 or 0.5 mg/cm^2	In a dermal absorption study in rats, recovery of the applied dose (mass balance) was 100-103%. The majority of the dose was recovered in the skin swab (71-90% of the applied dose). Dermal absorption (based on the sum of residues in urine, feces, cage wash, tissues, residual carcass, and untreated skin) was only 0.13-0.45% of the applied dose and only 10-22% of the applied dose remained in the skin at the application site (considered potentially absorbable). Increasing the dose 200-fold resulted in only approximately 2-fold increase in

Table A.2.2 Subchronic, Chronic, and Other Toxicity Profile for Florasulam Technical		
Guideline No./Study Type	**MRID No. (year) Classification/Doses**	**Results**
		absorption. Absorption increased 44% at 48 h and 61% at 72 h compared to 24 h in the low dose groups; however, a time-dependent increase in absorption was not evident in the high dose groups. The absorbed dose was almost completely excreted in the urine at the low dose, but was found primarily in the urine, cage wash, and untreated skin at the high dose. The amount of radioactivity at the treatment site increased at 48 hours in the low dose, but did not decrease within 72 hours at either dose, suggesting that the compound in the skin was not readily absorbable.

A.3 Executive Summaries

A.3.1 Subchronic Toxicity

870.3100 90-Day Oral Toxicity – Rat

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 (5-8%) and body weight gains (21%) in the females, and evidence of slight nephrotoxicity (increased kidney weights, hypertrophy, and degeneration/regeneration and inflammation of the descending portion of proximal tubules) 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.

870.3100 90-Day Oral Toxicity – Mouse

EXECUTIVE SUMMARY: In a subchronic oral toxicity study (MRID 46808222), XDE-570 (Florasulam; 99.2% a.i.; Lot No. 930910) was administered in the diet to ten B6C3F1 mice/sex/dose at dose levels of 0, 20, 100, 500, or 1000 mg/kg/day (time-weighted intake was 0/0, 22/20, 110/101, 549/503, and 1125/1007 mg/kg/day [males/females]) for 13 weeks.

No adverse treatment-related effects were observed on mortality, clinical signs, body weights, body weight gains, food consumption, food efficiency, ophthalmoscopic examination, hematology, clinical chemistry, organ weights, or gross or microscopic pathology. Very slight multi-focal bilateral hypertrophy was observed in the collecting ducts of the kidney in 10/10 males at 500 and 1000 mg/kg/day and in 8/10 females at 1000 mg/kg/day. There were no significant clinical chemistry or histopathological findings to corroborate the observed kidney effects.

The LOAEL is not determined and the NOAEL is 1000 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 mice.

870.3150 90-Day Oral Toxicity – Dog

EXECUTIVE SUMMARY - In a 90-day oral toxicity study (MRID 46808223), XDE-570 (Florasulam; 99.3% a.i.; Lot # 940714) was administered to 4 Beagle dogs/sex/dose *ad libitum* in the diet at dose levels of 0, 5, 50, or 100 mg/kg/day (time-weighted average test substance intake was 0/0, 6/6, 56/55, and 104/94 mg/kg/day [M/F]) for 13 weeks.

There were no compound-related effects on mortality, clinical signs, body weight, body weight gain, food consumption, ophthalmoscopy, hematology, urinalysis, or gross pathology observed at any dose.

The target organ appeared to be the liver. At 50 mg/kg, alkaline phosphatase activity was increased ($p<0.05$) by 59-112% in the males and 91-127% in the females on Days 45 and 91, and there was a slight increase in the incidence of hepatic vacuolation (3/4 treated [very slight to

slight severity] vs. 1/4 control [moderate severity] females). At 100 mg/kg, the following liver effects were noted: (i) alkaline phosphatase activity was increased ($p<0.05$) by 213-451% in both sexes on Days 45 and 91; (ii) increased incidence of very slight to slight hepatic vacuolation (4/4 treated vs. 3/4 control males and 3/4 treated vs. 1/4 control females); and (iii) increased ($p<0.05$) absolute (incr. 22-29%) and relative (to body; incr. 26-27%) liver weight in both sexes.

The LOAEL is 50 mg/kg/day, based on increased alkaline phosphatase (59-127%) activity and increased incidence/severity of hepatic vacuolation in both sexes. The NOAEL is 5 mg/kg/day.

This study is classified as **acceptable/guideline** and satisfies the guideline requirement for Test Guideline OPPTS 870.3150; OECD 409 for a 90-day oral toxicity study in the dog.

870.3200 21/28-Day Dermal Toxicity – Rat

EXECUTIVE SUMMARY - In a repeated-dose dermal toxicity study (MRID 46808225), XDE-570 (Florasulam; 99.3% a.i.; Lot # 940714) in aqueous 0.5% Methocel was applied to the shaved skin of 5 Fischer 344 rats/sex/dose at dose levels of 0, 100, 500, or 1000 mg/kg/day, 6 hours/day for 7 days/week during a 28-day period.

No compound related effects in mortality, clinical signs, body weight, body weight gain, food consumption, hematology, clinical chemistry, urinalysis, organ weights, and gross or microscopic pathology parameters were observed in either sex.

At 1000 mg/kg/day, very slight (grade 1) edema and erythema at the treatment site were noted in 4/5 males beginning on Day 23. Dermal irritation was resolved by Day 28
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The systemic LOAEL is not determined and the systemic NOAEL is 1000 mg/kg/day.

The dermal LOAEL is 1000 mg/kg/day, based on edema and erythema observed at the treatment site in males (4/5). The dermal NOAEL is 500 mg/kg/day.

This study is classified as **acceptable/guideline** and satisfies the guideline requirement for Test Guideline OPPTS 870.3200; OECD 410 for a 28-day dermal toxicity study in rats.

870.3465 90-Day Inhalation – Rat

There are no inhalation studies available.

A.3.2 Prenatal Developmental Toxicity

870.3700a Prenatal Developmental Toxicity Study – Rat

EXECUTIVE SUMMARY: In a developmental toxicity study (MRID 46808234), XDE-570 (Florasulam; 99.3% a.i.; Lot No. 940714) in aqueous 0.5% methylcellulose was administered daily via oral gavage to 25-27 time-mated CD (Sprague Dawley) rats/group at a dose volume of

4 mL/kg at dose levels of 0, 50, 250, or 750 mg/kg/day from gestation day (GD) 6-15. On GD 21, all surviving dams were killed and a limited necropsy was performed. The kidneys and uterus were removed and weighed, and the fetuses were delivered by cesarean section.

No adverse treatment-related effects were observed on mortality, clinical signs, or gross pathology.

Four 750 mg/kg/day dams died on study. One female was found dead on GD 9; one female was killed for humane reasons on GD 10; and two females were found dead on GD 13. These animals did not display clinical signs of toxicity prior to death. In three of the dams, necropsy revealed dark or firm lungs, with gavage error noted as the probable cause of death.

At 750 mg/kg/day, body weights were decreased ($p<=0.05$) by 4-6% during GD 6-19, resulting in decreased ($p<=0.05$) body weight gains during treatment (GD 6-16; decr. 16%). Food consumption was also decreased (not statistically analyzed) by 6-13% during the treatment period. Additionally at this dose, absolute and relative (to body weight) kidney weights were increased ($p<=0.05$) by 8 and 12%, respectively. The kidney findings were considered treatment-related since adverse kidney effects (increased kidney weights, hypertrophy, and histopathology) were observed in several rat studies at ≥ 250 mg/kg/day.

The maternal LOAEL is 750 mg/kg/day, based on decreased body weights (4-6%), body weight gains (16%), food consumption (6-13%), and increased kidney weights. The maternal NOAEL is 250 mg/kg/day.

There were no effects of treatment on the numbers of implantations, live or dead fetuses, litters, or resorptions, or post-implantation loss.

There were no treatment-related external, visceral, or skeletal malformations.

At 750 mg/kg/day, a slight decrease ($p<=0.05$) in fetal body weight (4%) was observed; however, this finding was attributed to the decrease in maternal body weight observed in this dose group. The delayed ossification (not significant) of the skull, ribs, and sternebrae, also seen at 750 mg/kg/day, was within normal range of the historical control data.

The developmental LOAEL is not determined and the developmental NOAEL is 750 mg/kg/day.

This study is classified **acceptable/ guideline** and satisfies the guideline requirements (OPPTS 870.3700a; OECD 414) for a developmental toxicity study in rats.

EXECUTIVE SUMMARY: In a preliminary developmental toxicity study (MRID 46808231), XDE-570 (Florasulam; 99.3% a.i.; Lot No. 940714) in aqueous 0.5% methylcellulose was administered daily via oral gavage to ten time-mated CD rats/group at a dose volume of 4 mL/kg at dose levels of 0, 100, 500, or 1000 mg/kg/day from gestation day (GD) 6-15. Excessive maternal toxicity was observed in the 1000 mg/kg/day group, so two additional groups of ten rats were administered the test compound as previously described at dose levels of 0 or 750

mg/kg/day in order to more accurately determine the maximum tolerated dose. On GD 16, all surviving does were killed and a detailed necropsy was performed. The kidneys were removed and weighed, and the uterus and ovaries were removed and examined grossly for numbers of implantations, resorptions, and corpora lutea. Fetuses were not examined. Prior to death, two of these dams were observed with excessive chromorhinorrhea; and one also displayed decreased activity. Additionally at this dose, body weights were decreased ($p<=0.05$) by 7-8% on GD 9-12, resulting in a body weight loss on GD 6-9 (-3.8 g vs. 13.9 g in controls; $p<=0.05$) and decreased ($p<=0.05$) body weight gains on GD 9-12 (decr. 36%). Food consumption was also decreased (not significant [NS]) by 27% on GD 6-12. For these reasons, the surviving animals in this dose group were killed on GD 13 for humane reasons. No further data were collected or reported for this dose group.

In the remaining groups, no treatment-related effects were observed on mortality, clinical signs, or body weights. Gross pathology results were not provided for the 750 mg/kg/day group.

One 750 mg/kg/day dam was found dead on GD 15. This animal had no prior clinical signs of toxicity. At necropsy, this animal presented with decreased amounts of body fat, perineal soiling, hemolyzed blood in the digestive tract, erosions and/or ulcers in the stomach, and an enlarged spleen. The cause of death was attributed to a probable lymphoreticular tumor and uterine hemorrhage and was not considered treatment-related.

At 750 mg/kg/day, overall (GD 6-16) body weight gains were decreased (NS) by 14%, and food consumption was decreased by 5-10% during the treatment period. Additionally, absolute and relative (to body weight) kidney weights were increased ($p<=0.05$) by 12 and 16%, respectively.

The maternal LOAEL is 750 mg/kg/day, based on decreased body weight gains and food consumption, and increased kidney weights. The maternal NOAEL is 500 mg/kg/day.

There were no effects of treatment on the numbers of implantations, litters, or resorptions, or post-implantation losses. Fetal evaluations were not conducted.

The developmental LOAEL and NOAEL are not determined.

870.3700b Prenatal Developmental Toxicity Study – Rabbit

EXECUTIVE SUMMARY: In a developmental toxicity study (MRID 46808233), XDE-570 (Florasulam; 99.3% a.i.; Lot No. 940714) in aqueous 0.5% methylcellulose was administered daily via oral gavage to 20 naturally mated New Zealand White rabbits/group at a dose volume of 4 mL/kg at dose levels of 0, 50, 250, or 500 mg/kg/day from gestation day (GD) 7-19. On GD 28, all surviving does were killed and a limited necropsy was performed. The liver, kidneys, and gravid uterus were removed and weighed, and the fetuses were delivered by cesarean section and examined.

One 250 mg/kg/day doe aborted on GD 22, and one 500 mg/kg/day doe aborted on GD 17. Prior to aborting, both animals displayed decreased fecal output, body weight loss, and markedly lower food consumption. At necropsy, the 500 mg/kg/day doe was found to have findings

indicative of pneumonia, which was most likely due to deposition of the test substance in the lungs. One 500 mg/kg/day doe was found dead on GD 19; the cause of death was attributed to a ruptured esophagus with atelactic lungs, with thoracic adhesions and hydrothorax present.
No treatment-related effects were observed on mortality, clinical signs, body weights, body weight gains, food consumption, organ weights, or gross pathologic examinations in the animals that survived to scheduled termination.

The maternal LOAEL is not determined and the maternal NOAEL is 500 mg/kg/day.

There were no premature deliveries or complete litter resorptions, and no effects of treatment on the numbers of litters, live fetuses, dead fetuses, or resorptions (early), or on gestation index, fetal body weights, sex ratio, post-implantation loss, or gravid uterine weights. There were no treatment-related external, visceral, or skeletal findings.

The developmental LOAEL is not determined and the developmental NOAEL is 500 mg/kg/day.

This study is classified **acceptable/guideline (OPPTS 870.3700b)** and satisfies the guideline requirements for a developmental toxicity study in the rabbit. Although the animals were not dosed to the limit dose, a preliminary developmental toxicity study in rabbits (MRID 46808232) was performed and indicated that a dose of 600 mg/kg/day probably would have exceeded the maximum tolerated dose and resulted in excessive maternal death. Therefore, selection of the high dose (500 mg/kg/day) used in this study was considered reasonable. Additionally, while this study did not dose the animals for the recommended interval (implantation through the day prior to cesarean section), it must be noted that this study was performed prior to the adoption of the current guidelines (OPPTS 870.3700, August, 1998).

EXECUTIVE SUMMARY: In a preliminary developmental toxicity study (MRID 46808232), XDE-570 (Florasulam; 99.3% a.i.; Lot No. 940714) in aqueous 0.5% methylcellulose was administered daily via oral gavage to seven naturally mated New Zealand White rabbits/group at a dose volume of 4 mL/kg at dose levels of 0, 100, 300, 600, or 1000 mg/kg/day from gestation day (GD) 7-19. On GD 20, all surviving does were killed and necropsied. The liver and kidneys were removed and weighed, and a detailed examination of the uterus and ovaries was performed.

One 600 mg/kg/day doe died on GD 19, and one 1000 mg/kg/day doe died on each of GDs 10, 13, 17. These animals all exhibited decreased fecal output, body weight loss, and markedly lower food consumption. At necropsy, findings of congested, edematous lungs, decreased ingesta in the digestive tract, a gastric hairball, slight hemorrhage in the vaginal wall, and a distended bladder were noted. Due to increased mortality (43%), the remaining does from the 1000 mg/kg/day group were killed for humane reasons on GD 17, and no further data were collected from this group.
No treatment-related effects were observed on organ weights or gross pathological examinations of animals that survived to scheduled termination.

At 600 mg/kg/day, body weight gains were decreased (not significantly [NS]) during treatment (GD 7-19) by 16%, due to body weight loss during GD 7-10 (-33.1 g vs. 53.1g in controls) and

decreased (NS) body weight gains during GD 13-16 (decr. 56%). Food consumption was decreased (NS) during GD 10-19 (decr. 7-36%).

The maternal LOAEL is 600 mg/kg/day, based on mortality and decreased body weight gains and food consumption. The maternal NOAEL is 300 mg/kg/day.

No treatment-related effects were observed on the numbers of implantations or resorptions, or litter size at up to 600 mg/kg/day. Cesarean section data were not reported for the 1000 mg/kg/day group. Fetuses were not examined in any dose group.

The developmental LOAEL and NOAEL are not determined.

This study is classified as an **acceptable/non-guideline** range-finding developmental toxicity study in rabbits.

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A.3.3 Reproductive Toxicity

870.3800 Reproduction and Fertility Effects – Rat

EXECUTIVE SUMMARY: In a two-generation reproduction toxicity study (MRID 46808235), XDE-570 (Florasulam; 99.3% a.i.; Lot No. 940714) was administered in the diet to 30 CD (Sprague Dawley) rats/group at dose levels of 0, 10, 100, or 500 mg/kg/day. The P generation parents were dosed for at least 70 days before they were mated to produce the F1 litters. From the F1 weanlings, 30 rats/sex/dose were selected to be parents and were fed the same test diet concentrations as their parents for 70 days prior to mating to produce the F2 litters.

No adverse treatment-related effects were observed on mortality, clinical signs, or gross pathology.

Systemic toxicity was observed at 500 mg/kg. During pre-mating, body weights ($p<=0.05$) and food consumption (not significant [NS]) generally were decreased during Weeks 3-10, resulting in decreased (NS) overall (Weeks 0-10) body weight gains in the F1 males and in the P and F1 females. During gestation, body weights ($p<=0.05$) and food consumption (NS) were decreased during gestation days (GD) 0-21, resulting in decreased ($p<=0.05$) overall (GD 0-21) body weight gains in the P and F1 females. During lactation, body weights were decreased ($p<=0.05$) during lactation days (LD) 1-14; however, food consumption and overall (LD 1-21) body weight gains were not adversely affected.

Additionally at 500 mg/kg/day, relative (to body weight) kidney weights were increased ($p<=0.05$) in the F1 males (incr. 19%) and in the P and F1 females (incr. 18-19%), and very slight multi-focal hypertrophy of the collecting ducts was observed in both sexes in both generations (70-83% treated vs. 0 controls). Although the kidney findings were not associated with histopathological findings in this study (urinalysis and clinical chemistry not measured) adverse kidney effects (increased kidney weights, hypertrophy, and histopathology) were observed in subchronic and chronic rat studies at ≥ 250 mg/kg/day. Therefore, these findings are considered adverse.

The LOAEL for parental toxicity is 500 mg/kg/day, based on decreased body weights, body weight gains, and food consumption, as well as increased relative kidney weights, and hypertrophy in both sexes. The NOAEL is 100 mg/kg/day.

No adverse treatment-related effects were observed on birth index, live birth index, or viability indices, clinical signs, developmental landmarks, kidney weights, or gross pathology.

Transient decreases ($p<=0.05$) in the 500 mg/kg/day pup body weights were observed on PND 4 pre-culling (F1 males) and PND 7 (F1 females and F2 males and females); however, by PND 21, all treated groups were similar to controls. These transient decreases were not considered adverse.

The LOAEL for offspring toxicity is not determined and the NOAEL is 500 mg/kg/day.

There were no effects of treatment on any reproductive parameter in either generation, including: estrous cycle length and periodicity; mating, fertility, and gestation indices; and pre-coital and gestation durations.

The LOAEL for reproductive toxicity is not determined and the NOAEL is 500 mg/kg/day.

This study is classified as **acceptable/guideline** and satisfies the guideline requirements (OPPTS 870.3800; OECD 416) for a two-generation reproduction study in the rat.

A.3.4 Chronic Toxicity

870.4100b Chronic Toxicity – Dog

EXECUTIVE SUMMARY: In a chronic toxicity study (MRID 46808229), XDE-570 (Florasulam; 99.3% a.i.; Lot No. 940714) was administered in the diet to four purebred beagle dogs/sex/dose at dose levels of 0, 0.5, 5, or 100 mg/kg/day for 52 weeks. Severe body weight loss and reduced food consumption were observed in both sexes at 100 mg/kg/day during the first three months of the study; therefore, the high dose was reduced to 50 mg/kg/day in both sexes beginning on Study Day 105 (Week 15).

No adverse treatment-related effects were observed on mortality, clinical signs, food efficiency, ophthalmoscopic examinations, hematology, urinalysis, organ weights, or gross or microscopic pathology.

At 100 mg/kg/day, both sexes exhibited loss of body weight accompanied by reduced food consumption. Following reduction of the high dose to 50 mg/kg/day, the females continued to exhibit both decreased (not significant [NS]) body weights (decr. 17% at Week 52) and food consumption, resulting in decreased (NS) overall (Week 0-52) body weight gains (decr. 68%). Male body weights and food consumption at Week 52, and overall body weight gains were similar to controls.

Additionally at 100 mg/kg/day, males and females had increased (p<=0.05) alkaline phosphatase (incr. 233-783%) and alanine aminotransferase (incr. 268-390%) after 3 months of dosing. Alkaline phosphatase continued to be elevated (p<=0.05) in both sexes through 12 months of dosing (incr. 141-354%). Slight vacuolation of the zona reticularis and zona fasciculata was also observed in the adrenal gland of both sexes; the findings were consistent with fatty change.

The LOAEL is 100/50 mg/kg/day, based on decreased body weights (17%), body weight gains (68%), and food consumption in the females; increased liver enzymes (alanine aminotransferase and alkaline phosphatase), and slight vacuolation of the zona reticularis and zona fasciculata in the adrenal gland (consistent with fatty change) of both sexes. The NOAEL is 5 mg/kg/day.

This study is classified as **acceptable/guideline** and satisfies the guideline requirements (OPPTS 870.4100b, OECD 452) for a chronic toxicity study in the dog.

A.3.5 Carcinogenicity

870.4200a Combined Chronic/Carcinogenicity Study – rat

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 absolute and relative kidney weights (5 and 3%, 8-9 and 22-24%, respectively), increased 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). Additionally, at 500 mg/kg/day, 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 (3-8%) and body weight gains (14%) in the females; slight nephrotoxicity (increased kidney weights, hypertrophy, and histopathology) in males. The NOAEL is 10 mg/kg/day in males; 125 mg/kg/day in females.

At the doses tested, there were no treatment-related increases 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.

870.4200b Carcinogenicity (feeding) – Mouse

EXECUTIVE SUMMARY: In a carcinogenicity study (MRID 46808230), XDE-570 (Florasulam; 99.3% a.i.; Lot No. 940714) was administered in the diet to 50 B6C3F1 mice/sex/dose at dose levels of 0, 50, 500, or 1000 mg/kg bw/day nominally (actual intake was 0/0, 50/51, 505/497, and 1009/1019 mg/kg bw/day in males/females) for 104 weeks. An additional 10 mice/sex/dose were treated in a similar manner and sacrificed after 52 weeks.

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

At 500 and 1000 mg/kg/day, mortality was increased in the females (42% each dose vs 26% controls) at Week 106; however, a dose-related effect was not observed at Week 96, and a statistically significant difference was not found at either time point. Therefore, the effect on mortality was considered equivocal. Increased ($p<=0.05$) incidences of very slight to slight renal collecting duct hypertrophy (82-96% treated vs 0% controls) and decreased slight to moderate vacuolization in the renal cortex tubule (94-96% treated vs 48% controls) were noted at 24 months in males, and similar findings were also noted at 12 months. The toxicological significance of these findings in the kidney was considered equivocal.

The LOAEL is not determined and the NOAEL is 1000 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 because the limit dose was tested.

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

A.3.6 Mutagenicity

870.5100 Bacterial Reverse Mutation Test

EXECUTIVE SUMMARY – In two independent trials of a reverse gene mutation assay in bacteria (MRID 46808240), *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537, and *Escherichia coli* strain WP2*uvr*A were exposed to XDE-570 (Florasulam; 99.2% a.i.; Lot # 930910) in dimethylsulfoxide (DMSO) at concentrations of 0, 0.333, 1, 3.33, 10, 33.3, or 100 µg/plate (*S. typhimurium*) and 0, 10, 33.3, 100, 333, 1000, or 3330 µg/plate (*E. coli*) both in the presence and absence of S9-activation. The S9 fraction was derived from the livers of male Sprague-Dawley rats induced with Aroclor 1254. The pre-incubation method was used in both the initial and confirmatory assays. Standard strain-specific mutagens served as positive controls.

XDE-570 was tested up to cytotoxic concentrations, as indicated by the reduced numbers of revertants at 33.3 µg/plate and above in the *S. typhimurium* strains and at 3333 µg/plate in the *E. coli* strain. There were no marked increases in the mean number of revertants/plate in any strain. The positive controls induced the appropriate response in all strains in the presence and absence of S9-activation. **There was no evidence of induced mutant colonies over background.**

The study is classified as **acceptable/guideline** and satisfies the guideline requirement for Test Guideline OPPTS 870.5100; OECD 471 for *in vitro* mutagenicity (bacterial reverse gene mutation) data.

870.5300 *In Vitro* Mammalian Cell Gene Mutation Test

EXECUTIVE SUMMARY - In two independent trials of a mammalian cell gene mutation assay at the HGPRT locus (MRID 46808238), Chinese hamster ovary (CHO) cells cultured *in vitro* were exposed to XDE-570 (Florasulam; 99.2% a.i.; Lot # 930910) in dimethylsulfoxide (DMSO) at concentrations of 0, 187.5, 375, 750, 1500, or 3000 µg/mL (+/-S9) for 4 hours. The S9 fraction was derived from the livers of male Sprague-Dawley rats induced with Aroclor 1254. The positive controls were ethyl methanesulfonate (-S9) and 20-methylcholanthracene (+S9).

XDE-570 was tested up to the limit of solubility (3000 µg/mL). No evidence of cytotoxicity was observed at any concentration in either trial in the presence or absence of S9-activation. No marked increase in mutant frequency was observed in any trial in the presence or absence of S9-activation. The positive controls induced the appropriate response in both trials (+/-S9). **There was no evidence of induced mutant colonies over background in the presence or absence of S9-activation.**

This study is classified as **acceptable/guideline** and satisfies the guideline requirement for Test Guideline OPPTS 870.5300; OECD 476 for *in vitro* mutagenicity (mammalian forward gene mutation) data.

870.5375 *In Vitro* Mammalian Chromosome Aberration Test

EXECUTIVE SUMMARY - In two independent trials of a mammalian cell cytogenetics assay (chromosome aberration; MRID 46808237), primary rat lymphocyte cultures were exposed to XDE-570 (Florasulam; 99.2% a.i.; Lot # 930910) in dimethylsulfoxide (DMSO) for 4 hours in the presence of S9 and 24 hours in the absence of S9 at concentrations of 0, 3, 10, 30, 100, 300, 1000, or 3000 µg/mL (Trial 1, +/-S9); 0, 30, 100, or 300 µg/mL (Trial 2, –S9); and 0, 300, 1000, or 3000 µg/mL (Trial 2, +S9). Cells were harvested at 24 hours after initiation of treatment in Trial 1 and at 24 and 48 hours after initiation of treatment in Trial 2. The S9 fraction was derived from the livers of male Sprague-Dawley rats induced with Aroclor 1254. The positive controls were mitomycin C (-S9) and cyclophosphamide (+S9).

It was stated that XDE-570 was tested up to the limit of solubility (3000 µg/mL). Based on the observed cytotoxicity (as indicated by reduced mitotic index), cultures at concentrations of 30, 100, and 300 µg/mL (-S9, both trials, 24 hours); 300, 1000, and 3000 µg/mL (+S9, both trials, 24 hours); 300 µg/mL (-S9, Trial 2; 48 hours); and 3000 µg/mL (+S9, Trial 2, 48 hours) were selected for evaluation of chromosomal aberrations. No relevant increases in the number of metaphases with aberrations (excluding gaps) were observed at any concentration at the 24 or 48 hour harvest time in either the presence or absence of S9. The positive controls induced the appropriate response in the presence and absence of S9. **There was no evidence of chromosome aberrations induced over background in the presence or absence of S9-activation.**

This study is classified as **acceptable/guideline** and satisfies the guideline requirement for Test Guideline OPPTS 870.5375; OECD 473 for *in vitro* mutagenicity (chromosome aberration) data.

870.5395 Bacterial Mutation Assay

EXECUTIVE SUMMARY - In a bone marrow micronucleus assay (MRID 46808239), young adult CD-1 mice (5/sex/dose/harvest time) were treated once via gavage (20 mL/kg) with XDE-570 (Florasulam; 99.2% a.i.; Lot # 930910) in corn oil at doses of 0, 1250, 2500, or 5000 mg/kg. Bone marrow cells were harvested at 24, 48, and 72 hours after dosing. Cyclophosphamide (120 mg/kg) served as the positive control.

No treatment-related clinical signs of toxicity were observed during the study. At 5000 mg/kg, two females died on Day 2; however, the cause of death and association with the test substance was not established. Both the MPCE frequency and the PCE:NCE ratio were comparable between vehicle controls and all treated groups at all sampling times in both sexes. Although there were no clinical signs and no apparent effect on marrow toxicity, dosing was considered to be adequate as XDE-570 was tested up to more than twice the limit dose of 2000 mg/kg. The positive control induced the appropriate response. **There was no significant increase in the frequency of micronucleated polychromatic erythrocytes in bone marrow after any treatment time.**

This study is classified as **acceptable/guideline** and satisfies the guideline requirement for Test Guideline OPPTS 870.5395; OECD 474 for *in vivo* cytogenetic mutagenicity data.

A.3.7 Neurotoxicity

870.6200a Acute Neurotoxicity Screening Battery

EXECUTIVE SUMMARY - In an acute neurotoxicity study (MRID 46808217), groups of 10 fasted young adult Fischer 344 rats/sex/dose were given a single oral gavage dose of XDE-570 (Florasulam; 99.3% a.i.; Lot # 940714) in aqueous methylcellulose at dose levels of 0, 200, 1000, or 2000 mg/kg (limit dose) and were observed for 15 days. Neurobehavioral assessment (functional observational battery [FOB] and motor activity testing) was performed in all rats at one week prior to dosing and on Days 1 (approximately 6-7 hours post-dosing), 8, and 15. At study termination, 5 rats/sex/dose were euthanized and perfused *in situ* for neuropathological examination. The brain and peripheral nervous system tissues collected from the perfused animals in the control and 2000 mg/kg groups were subjected to histopathological evaluation. Positive control data were provided.

There were no compound-related effects on mortality, clinical signs, body weight, and gross or neuropathology observed at any dose.

In the 2000 mg/kg males, overall (Days 0-15) body weight gain was decreased by 21%, although body weight at termination was comparable to controls. This was attributed to a lower body weight gain (decr. 33%) in these animals during Week 1. Additionally in these animals, there was a slight transient decrease in motor activity, increased incidence of minimal activity in the open-field, and decreased reactivity to sharp noise on Day 1. However, the differences from control values did not exceed the historical controls and complete recovery occurred by the next test session (Day 8). When the FOB and motor activity findings were combined they were considered to be a treatment-related effect. As there were no corroborative gross or neuropathological findings to suggest a neurotoxic effect, this pattern of decreased activity was considered to be likely due to general malaise.

No treatment-related effects were observed in the females at any dose and the males at 1000 mg/kg or below.

No evidence of neurotoxicity was observed at any dose in either sex.

The systemic LOAEL is 2000 mg/kg (limit dose), based on decreased body weight gain (21%) and general malaise (slight transient decrease in motor activity, minimal activity in open field, and reactivity) in the males. The systemic NOAEL is 1000 mg/kg.

The neurotoxicity LOAEL is not determined. The neurotoxicity NOAEL is 2000 mg/kg (limit dose).

This study is classified as **acceptable/guideline** and satisfies the guideline requirement for Test Guideline OPPTS 870.6200a; OECD 424 for an acute neurotoxicity study in the rat.

870.6200b Chronic Neurotoxicity Screening Battery

EXECUTIVE SUMMARY - In a chronic neurotoxicity study (MRID 46808228), XDE-570 (Florasulam; 99.3% a.i.; Lot # 940714) was administered to 10 young adult Fischer 344 rats/sex/dose in the diet at dose levels of 0, 10, 125 (females only), 250, or 500 (males only) mg/kg/day (time-weighted average test substance intake was 0, 8.6, 216, and 460 mg/kg/day in males and 0, 9, 113, and 266 mg/kg/day in females) for 12 months. Neurobehavioral assessment (functional observational battery [FOB] and motor activity testing) was performed in all rats at pre-dosing and at 3, 6, 9, and 12 month post-dosing. At study termination, auditory function (auditory brainstem response) was evaluated in 5 rats/sex/dose from the control and high-dose animals (500 mg/kg/day males and 250 mg/kg/day females). After completion of the auditory function examination, a neuropathological examination of perfusion-fixed central and peripheral nervous system tissues was conducted using these control and high-dose animals. All animals were subjected to a gross necropsy at termination. Positive control data were provided.

There were no compound-related effects on mortality, clinical signs, food consumption, FOB parameters, motor activity, and gross or neuropathology observed at any dose. Organ weights were not provided; however, in the concurrently performed 2-year dietary chronic toxicity/ oncogenicity study (MRID 46808236), brain weight was unaffected after 12 and 24 months of treatment.

At 500 mg/kg/day, body weights were decreased ($p<0.05$) by 9-15% in the males at 6, 9, and 12 months. Additionally, body weight gains were decreased by 61-67% at 3-12 months and overall (0-12 months) gains were decreased by 27% compared to controls. Food consumption was similar to controls in these animals.
No treatment-related effects were observed at 250 mg/kg/day and below in either sex.

No evidence of neurotoxicity was observed at any dose in either sex.

The systemic LOAEL is 500 mg/kg/day, based on decreased body weight (9-15%) and body weight gain in males (61-67%). The systemic NOAEL is 250 mg/kg/day.

The neurotoxicity LOAEL is not determined. The neurotoxicity NOAEL is 250 mg/kg/day, the highest dose tested in females.

This study is classified as **acceptable/guideline** and satisfies the guideline requirement for Test Guideline OPPTS 870.6200 for a chronic neurotoxicity feeding study in the rat

A.3.8 Metabolism

870.7485 Metabolism – Rat

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 (exact position of hydroxyl group not determined) 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.

870.7600 Dermal Absorption – Rat

EXECUTIVE SUMMARY: In a dermal penetration study (MRID 46808304), [^{14}C]-XDE-570 (Florasulam; 98-99% radiochemical purity as applied; Batch Nos. B463-145 and C237-7B) was applied to the skin (12 cm^2) of Fischer 344 rats (4 males for each time point at each dose level).

Nominal doses were 0.001 or 0.5 mg/cm^2 skin. The high dose (EF-1343 commercial formulation) was included to assess exposure to mixer/loaders. The low dose (spray dilution, using an EF-1343 blank as a vehicle) represented a dose that was 2.39-fold more concentrated than the highest anticipated spray concentration for use on field crops, which was necessary in order to provide sufficient analytical sensitivity. The exposure duration was 24 hours, after which one group of 4 males for each dose level was sacrificed. The remaining 2 groups/dose were sacrificed at 48 or 72 hours post-application.

Recovery of the applied dose (mass balance) was 100-103%. The majority of the dose was recovered in the skin swab (71-90% of the applied dose). Dermal absorption (based on the sum of residues in urine, feces, cage wash, tissues, residual carcass, and untreated skin) was only 0.13-0.45% of the applied dose and only 10-22% of the applied dose remained in the skin at the application site (considered potentially absorbable). Increasing the dose 200-fold resulted in only approximately 2-fold increase in absorption. Absorption increased 44% at 48 h and 61% at 72 h compared to 24 h in the low dose groups; however, a time-dependent increase in absorption was not evident in the high dose groups. The absorbed dose was almost completely excreted in the urine at the low dose, but was found primarily in the urine, cage wash, and untreated skin at the high dose. The amount of radioactivity at the treatment site increased at 48 hours in the low dose, but did not decrease within 72 hours at either dose, suggesting that the compound in the skin was not readily absorbable.

The compound isolated in the treated skin after 72 hours (including the 24 hour exposure period) would be absorbed in negligible amounts. The highest dermal absorption noted was 0.45% of the applied dose. This value is considered appropriate for use in risk assessment, with the appropriate uncertainty factors applied.

This study is classified as **acceptable/guideline** and satisfies the guideline requirements (OPPTS 870.7600; OECD none) for a dermal penetration study in rats.

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Appendix B: Metabolism Assessment

B.1. Metabolism Guidance and Considerations

Table B1.2 Tabular Summary of Metabolites

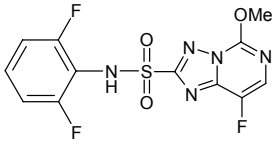
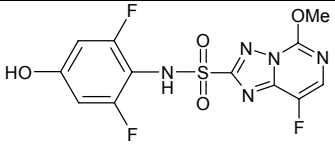
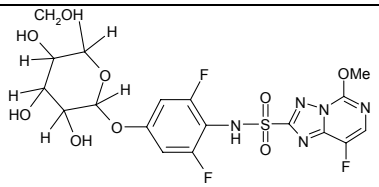
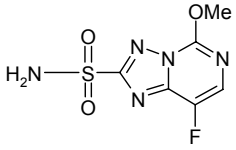
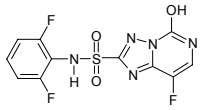
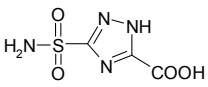
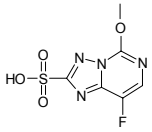
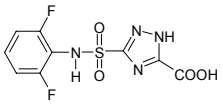
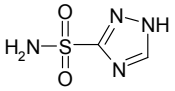
Chemical Name (other names in parenthesis)	Matrix	Percent TRR (PPM) [1]	
		Matrices - Major Residue (>10%TRR)	**Structure**
Florasulam	Wheat straw	≤14 % TRR	
	Wheat forage	≤32 % TRR	
	Ruminant	≤98 % TRR	
	Poultry	≤95 % TRR	
	Rotational crops	≤92 % TRR	
4-OH-phenyl florasulam	Wheat straw	≤14 % TRR	
	Wheat forage	≤15 % TRR	
Glucose conjugate of 4-OH-phenyl florasulam	Wheat straw	≤22 % TRR	
	Wheat forage	≤42 % TRR	
2-sulfonamide	Wheat straw	≤18 % TRR	

Table B.1.3 Summary of Major Florasulam Degradation Products.							
Study Type	**Degradate and Maximum Concentration (% of applied, day)**						**Source/ Comments**
	5-OH-XDE-570	**ASTCA**	**TPSA**	**DFP-ASTCA**	**STCA**	**TSA**	
					–		
Hydrolysis (pH 9 only)	78% (7 d, 50 °C); 32% (90 d, 25°C)	–	–	–	–	–	MRIDs 46808130, 46827909
Aqueous Photolysis	–	–	17% (32 d)	–	–	–	MRID 46808132
Soil Photolysis	–	–	–	–	–	–	MRID 46808134 (there were no photoproducts)
Aerobic Soil Metabolism	41-72% (3-7 d); 69-74% (3-7 d); 54-70% (7-30 d); 44-50% (14-29 d)	20% (100 d); 25-40% (59 d); minor deg. in other soils	–	17-18% (59 d); minor deg. in other soils		10% (14 d); 16% (100 d)	MRIDs 46808135 46808136 46808137 46808138
Aerobic Aquatic Metabolism	90-99% (60-100 d); 77% (10 d)	–	–	14.6% (100 d); 30% (1 yr)	16-21% (1 yr)	–	MRIDs 46827910, 4680,8143, 46287911
Anaerobic Aquatic Metabolism	83-87% (97 d)	–	–	–	–	–	MRID 46808140

5-OH-XDE-570 = N-(2,6-difluorphenyl)-8fluoro-5-hydroxy (1,2,4)triazolo (1,5c) pyrimidine 2-sulphonamide; TPSA = (triazolopyrimidine sulphonic acid) of florasulam; DFP-ASTCA = N-(2,6-difluorophenyl)-5-aminosulphonyl-1H-1,2,4triazole-3-carboxylic acid; ASTCA = 5-(aminosulphonyl)-1H-1,2,4-triazole-3-carboxylic acid; TSA = 1H-1,2,4-triazole-3-sulphonamide;

Appendix C: Tolerance Reassessment Summary and Table

Table C.1. Tolerance Summary for Florasulam			
Commodity	**Proposed Tolerance (ppm)**	**Recommended Tolerance (ppm)**	**Comments (correct commodity definition)**
Barley grain	0.01	0.01	Barley, grain
Barley forage	0.05	None	Not a RAC per Table 1, OPPTS 860 Guidelines.
Barley hay	0.05	0.05	Barley, hay
Barley straw	0.05	0.05	Barley, straw
Oats grain	0.01	0.01	Oat, grain
Oats forage	0.05	0.05	Oat, forage
Oats hay	0.05	0.05	Oat, hay
Oats straw	0.05	0.05	Oat, straw
Rye grain	0.01	0.01	Rye, grain
Rye forage	0.05	0.05	Rye, forage
Rye hay	0.05	None	Not a RAC per Table 1, OPPTS 860 Guidelines.
Rye straw	0.05	0.05	Rye, straw
Triticale grain	0.01	None	Triticale is covered by wheat per 40CFR 180.1(g)
Triticale forage	0.05	None	
Triticale hay	0.05	None	
Triticale straw	0.05	0.05	
Wheat grain	0.01	0.01	Wheat, grain
Wheat forage	0.05	0.05	Wheat, forage
Wheat hay	0.05	0.05	Wheat, hay
Wheat straw	0.05	0.05	Wheat, straw