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PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

MEMORANDUM

Date: 5/21/2009

SUBJECT: **Florasulam:** Human Health Risk Assessment for proposed use on Turfgrass.

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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 the use of this active ingredient for selective control of a broad spectrum of annual broadleaf weeds in turfgrass, including residential lawns, golf courses, sports fields, sodfarms and commercial turfgrass areas. The proposed formulated end use product evaluated in this assessment is EF-1343 (liquid containing 4.84% ia). The proposed application rate for florasulam is low, 0.0013 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. Florasulam is currently registered for use on cereal grain crops (wheat, oats, rye, barley, and triticale) (D332983).

HUMAN HEALTH RISK ASSESSMENT:

Toxicology/Hazard

The florasulam toxicology database is essentially complete. Other than an immunotoxicity study, no additional studies are required. 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 endocrine related 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).

The FQPA Safety Factor is 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 (95^{th} 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.

Dietary Exposure (Food/Water)

The current proposed use on turfgrass is considered a non-food use; therefore, the dietary exposure assessment included risk estimates from the previously conducted food assessment and revised drinking water information. In this revised assessment, an unrefined chronic dietary exposure assessment was performed for florasulam using DEEM-FCID™. The chronic analysis utilized tolerance level residues, empirical processing factors, 100% CT, and incorporated estimated drinking water concentrations (EDWC). The 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. The residue of concern in food (wheat) for both tolerance expression and risk assessment is parent florasulam *per se* (D332983, K. Bailey, 5/31/2007).

The resulting DEEM-FCID™ food plus drinking water chronic exposure estimates were below HED's level of concern for the US Population and all population subgroups. All infants (<1 year) (0.000107 mg/kg/day, <1 % cPAD) was the most highly exposed population subgroup.

Residential Exposure and Risk

HED assumes residential handlers are short-term in nature due to the episodic uses associated with homeowner products. Consequently, no intermediate-term and chronic exposure assessments were completed for residential handler and postapplication exposure scenarios.

Residential Handler Risk

A short-term dermal point of departure was not identified for florasulam. Therefore, no dermal risks were assessed for residential handlers. For short-term inhalation residential exposure, the point of departure is 5 mg/kg/day. Since no inhalation absorption data are available, toxicity by the inhalation route is considered to be equivalent to the estimated toxicity by the oral route of exposure.

No chemical-specific handler exposure data were submitted in support of this registration so data from the Pesticide Handlers Exposure Database (PHED) Version 1.1 were used to assess handler exposures. In addition, data from the Outdoor Residential Exposure Task Force (ORETF) was used.

All residential handler inhalation risks do not exceed HED's level of concern. MOEs were all greater than 100.

Residential Postapplication Risk

HED determined there is a potential for exposure from entering florasulam-treated residential areas, such as lawns, sports fields, and golf courses that could lead to postapplication exposures to adults and children.

No short-term dermal point of departure was identified for florasulam. Therefore, no dermal risks were assessed for residential postapplication exposures.

HED assumes that inhalation exposures are minimal following outdoor applications of an active ingredient with low vapor pressure. Since the proposed use of florasulam include only outdoor applications and florasulam has a low vapor pressure, postapplication inhalation exposures and risks were not assessed.

Short-term incidental oral risks were assessed for toddlers after applications of florasulam to lawns. Short-term incidental to toddlers do not exceed HED's level of concern.

HED combines risk values resulting from separate postapplication exposure scenarios when it is likely they can occur simultaneously based on the use-pattern and the behavior associated with the exposed population. The combined risk assessment for incidental oral exposures to toddlers following home lawn applications was calculated. The combined risks do not exceed HED's level of concern.

Occupational Exposure and Risk

Agricultural Handler Risk

No chemical-specific handler exposure data were submitted in support of this registration thus PHED data were used to assess occupational handler exposures. In addition, data from the Outdoor Residential Exposure Task Force (ORETF) were used.

For the proposed use on turfgrass, the inhalation risks to handlers do not exceed HED's level of concern at baseline (no respirator) for any of the handler scenarios where baseline data are available.

The intermediate-term dermal and combined intermediate-term dermal plus intermediate-term inhalation risks to handlers do not exceed HED's level of concern with baseline attire (i.e., long-sleeve shirt, long pants, shoes, and socks) where baseline data are available. The only data available for applying with handgun equipment and mixing/loading/applying with handgun equipment is baseline attire plus chemical-resistant gloves. The dermal and combined intermediate-term dermal plus intermediate-term inhalation risks to handlers do not exceed HED's level of concern with the addition of gloves to baseline attire for these two scenarios.

Agricultural Postapplication Risk

HED assumes that inhalation exposures are minimal following outdoor applications of an active ingredient with low vapor pressure. Since the proposed use of florasulam include only outdoor applications and florasulam has a low vapor pressure, postapplication inhalation exposures and risks were not assessed. As previously stated a short-term dermal point of departure was not identified for florasulam; therefore, postapplication occupational risks were assessed using the intermediate-term dermal point of departure.

No chemical-specific dislodgeable foliar residue data are available for florasulam to assess postapplication dermal risks following applications to turfgrass or cereal grains. Using the default assumption that 20 percent of the application rate is retained on foliage on day 0, postapplication risks do not exceed HED's level of concern on Day 0 (12 hours following application).

Since systemic postapplication risks do not exceed HED's level of concern on day 0 (12 hours following application), the restricted entry interval (REI) is based on the acute toxicity of florasulam technical material. Florasulam is classified as Toxicity Category III for acute dermal and Category IV for skin irritation and eye irritation potential. 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.

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), the Outdoor Residential Exposure Task Force (ORETF), and the Agricultural Reentry Task Force (ARTF) have been determined to require a review of their ethical conduct, and have received that review.

ADDITIONAL DATA NEEDS/RECOMMENDATIONS

Regulatory Recommendations and Toxicological Deficiencies

- HED recommends that the product label establish a retreatment interval.
- An immunotoxicity study is now required under the revised CFR 158.

HED recommends registration for the proposed use on turf conditional upon fulfillment of these deficiencies.

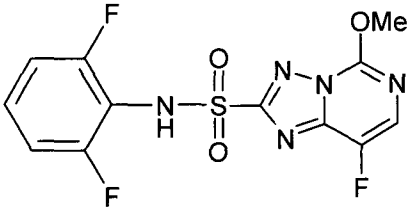
2.0 Ingredient Profile

Florasulam is a selective triazolopyrimidine sulfonanilide post-emergent herbicide. It is proposed for selective control of a broad spectrum of annual and perennial broadleaf weeds in established turfgrass, including residential lawns, sports fields, golf courses, and sodfarms. 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 Registered/Proposed Use Pattern for Florasulam						
Crop	**Product, Formulation**	**Treatment Type/Target of Application**	**Application Equipment**	**Maximum Application Rate (lb ai/A)**	**Treatment Interval**	**Preharvest Interval**
Turfgrass (proposed)	Liquid Concentrate EF-1343 (4.84% a.i.) Reg # 62719-560	Post-emergent broadcast or spot treatment use when weeds are actively growing	groundboom, handgun, low-pressure handwand, hose-end sprayer	0.013 lb ai/acre	Not provided	N/A
Cereal Grains (registered)	Liquid Concentrate EF-1343 (4.84% a.i.) Reg # 62719-560	Post-emergent broadcast use when weeds are actively growing	aerial, groundboom	0.00446 lb ai/acre	Not provided	60 days

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 water pH 5 pH 7 pH 9	Solubility (g/L) 0.121 0.084 6.36 94.2	
Solvent solubility	Solvent acetone acetonitrile ethyl acetate methanol dichloromethane xylene n-octanol n-heptane	Solubility (g/L) 123 72.1 15.9 9.81 3.75 0.227 0.184 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 4 7 10	Log K_{ow} 1.00 -1.22 -2.06	
UV/visible absorption spectrum	Form Acidic Basic Methanolic No absorbance above 300 nm.	λmax (nm) 259.8 203.8 262.4 209.7 204.1	

3.0 Hazard Characterization/Assessment for Florasulam

References:

Florasulam: Human Health Risk Assessment for Proposed Use on Cereal Grains (Wheat, Oats, Barley, Rye, and Triticale). K. Bailey, T. Morton, M Collantes. D332983.

Pesticide Fact Sheet: Florasulam, Conditional Registration, September, 2007

Florasulam Toxicology Data Evaluation Records, May 31, 2007, DPBarcode: D331116 TXR#: 0054348
Karlyn J. Bailey, Toxicologist

3.1 Hazard and Dose-Response Characterization

3.1.1 Database Summary

3.1.1.1 Sufficiency of studies/data

No additional toxicity data were submitted in support of this proposed use on turfgrass. A detailed description of these data can be found in the last Human Health Risk Assessment for florasulam which was conducted on May 31, 2007 (Memo D332983). Based on the proposed use pattern, the toxicology database for florasulam is nearly complete and adequate for risk assessment. The only required study is an immunotoxicity study. There are acceptable studies available for endpoint selection that include subchronic oral toxicity studies in rats, mice, and dogs, chronic oral toxicity study in dogs and carcinogenicity studies in rats and mice, developmental and reproduction studies in rats and a developmental study in rabbits and a subchronic dermal toxicity study in rats. There is also a complete mutagenicity battery, acute battery, and neurotoxicity studies (acute and chronic), as well as a metabolism and dermal absorption 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.

There was 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 or greater than 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 developmental toxicity 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 gestation days 6-19, resulting in a 16% decrease in body weight gains during treatment (gestation days 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 post-natal day 4 pre-culling (F1 and F2 males) and post-natal day 7 (F1 females and F2 males and females); however, by post-natal day 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 endocrine related 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 because for the Acute Dietary (General Population, including Infants and Children), the effects observed in the only applicable study, an acute neurotoxicity study, were seen at an extremely high dose (2000 mg/kg/day) which is considered not applicable to human exposure. For the Acute Dietary (Females 13-49 years of age), no appropriate endpoint identified in the submitted studies. 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.

3.1.4 FQPA

The FQPA SF is 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 nearly 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 $\leq$ 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 ≥ 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.

3.5 Hazard Identification and Toxicity Endpoint Selection

A summary of the toxicological endpoints and doses chosen for the relevant exposure scenarios for human risk assessment is found in Tables 3.5a and 3.5b. For background information on the endpoints selected for risk assessment, please refer to the May 7, 2007 Human Health Risk Assessment.

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**

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 (All populations)	N/A	N/A	N/A	**No appropriate endpoint identified.**
Incidental Oral Short-Term (1-30 days) and Intermediate-Term (1-6 months)	NOAEL = 5 mg/kg/day	UF_A = 10X UF_H = 10X FQPA SF = 1X	Residential LOC for MOE = 100	**Subchronic toxicity – dogs** LOAEL = 50 mg/kg/day based on hepatotoxicity (increases in alkaline phosphatase activity and hepatic vacuolation) observed in both sexes
Dermal Short-Term (1-30 days)	NA			**28-day dermal toxicity – rats** LOAEL = not determined, no systemic effect up to the limit dose of 1000 mg/kg/day.
Dermal Intermediate-Term (1-6 months)	NOAEL = 5 mg/kg/day DAF = 0.39%	UF_A = 10X UF_H = 10X FQPA SF = 1X	Residential LOC for MOE = 100	**Subchronic toxicity – dogs** LOAEL = 50 mg/kg/day based on hepatotoxicity (increases in alkaline phosphatase activity and hepatic vacuolation) observed in both sexes
Inhalation Short-Term (1-30 days) and Intermediate-Term (1- 6 months)	NOAEL = 5 mg/kg/day IAF=100%	UF_A = 10X UF_H = 10X FQPA SF = 1X	Residential LOC for MOE = 100	**Subchronic toxicity – dogs** LOAEL = 50 mg/kg/day based on hepatotoxicity (increases in alkaline phosphatase activity and hepatic vacuolation) observed in both sexes
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	28-day dermal toxicity study – rats LOAEL = not determined, no systemic effect up to the limit dose of 1000 mg/kg/day.

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 Intermediate-Term (1-6 months)	NOAEL = 5mg/kg/day DAF = 0.39%	UF_A = 10X UF_H = 10X FQPA SF = 1X	Occupational 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.
Inhalation Short-term (1-30 days and Intermediate-Term (1-6 months)	NOAEL = 5mg/kg/day IAF=100%	UF_A = 10X UF_H = 10X FQPA SF = 1X	Occupational 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" No increase in tumors were noted in 2 studies submitted			

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.

3.5.1 Level of Concern for Margin of Exposure

Table 3.5.10 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

3.5.2 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. A short-term aggregate risk assessment was conducted for florasulam using average dietary exposures from food and drinking water sources, inhalation and oral (children only) residential exposures. A short-term dermal endpoint was not selected and therefore, was not included in the aggregate risk estimates

3.5.3 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."

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 the recommendations of its Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC), EPA determined that there were scientific bases for including, as part of the program, 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. When the appropriate screening and/or testing protocols being considered under the Agency's Endocrine Disrupter Screening Program (EDSP) have been developed and vetted, florasulam may be subjected to additional 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

References:

Florasulam. Chronic Aggregate Dietary (Food and Drinking Water) Exposure and Risk Assessment for the Section 3 Registration Action on Turfgrass. D. Wilbur. D364543.

Florasulam. Chronic Aggregate Dietary and Drinking Water Exposure and Risk Assessment for the New Active Ingredient. T. Morton. D338497.

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.

Revised Tier I Drinking Water Assessment for the Florasulam Proposed Section 3 New Use Registration for Use on Turfgrass. C. Sutton. D356624.

5.1 Pesticide Metabolism and Environmental Degradation

5.1.1 Drinking Water Residue Profile

The Environmental Fate and Effects Division (EFED) conducted a Tier I drinking water assessment that uses modeling to estimate the groundwater and surface water concentrations of pesticides in drinking water source water (pre-treatment) resulting from pesticide use on sites that are vulnerable. This initial tier screens out chemicals with low potential risk and provides estimated exposure concentrations for the human health dietary risk assessment. Estimated drinking water concentrations (EDWCs) in surface water were derived using the 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 for drinking water exposure were determined to be the parent compound and the major degradate 5-OH-XDE-570.

Florasulam was assessed using the proposed maximum application rate for a single application rate of 0.013 lb ai/A, with a maximum "annual growing season" rate of 0.039 lb ai/A, applied at 28-day application intervals by aerial spray or ground spray application to foliage (amended label dated 07-08-08). This rate is approximately 9X higher than the previously assessed rate of 0.0045 lb ai/A (for wheat, barley, oats, rye and triticale not underseeded with legumes; DP Barcode D332069).

The drinking water residues used in the dietary risk assessment were incorporated directly into the dietary assessment. Water residues were incorporated in the DEEM-FCID into the food categories "water, direct, all sources" and "water, indirect, all sources." Table 5.1.1a and 5.1.1b below summarize the results of the EFED assessment.

To arrive at the total EDWC (estimated drinking water concentrations), the maximum surface water value for the parent was added to the maximum surface water value for the major degradate. Surface water estimates were used as they exceeded groundwater estimates for the chronic scenarios. For the parent, the chronic aerial spray value (0.06 ppb) was used. For the degradate, the chronic aerial spray value was also used (1.3 ppb). Adding the 2 values (0.06 + 1.3) results in the total EDWC of 1.36 ppb, or 0.00136 ppm.

Table 5.1.1a. Maximum Tier 1 Estimated Drinking Water Concentrations of parent florasulam in groundwater and surface water based on florasulam use on turfgrass at 0.013 lb ai/A x 3 applic. (total of 0.039 lb ai/A//season) by aerial spray application.

Drinking Water Source (Model Used)	Use/Rate Modeled (lb ai/A)	Maximum Estimated Drinking Water Concentration (EDWC; ppb)	
Groundwater (SCI-GROW2)	0.013 x 3 applic. for total of 0.039	Acute and Chronic	1.2×10^{-4}
Surface Water (FIRST2)	Aerial spray/0.013 x 3 applic. for total of 0.039	Acute	1.04
	Aerial spray/0.013 x 3 applic. for total of 0.039	**Chronic**	**0.06**

Table 5.1.1b. Maximum Tier 1 Estimated Drinking Water Concentrations of the florasulam degradate 5-OH-XDE-570 in groundwater and surface water based on florasulam use on turfgrass at 0.0123 lb ai/A x 3 applic. (total of 0.0369 lb ai/A//season) by aerial spray application.

Drinking Water Source (Model Used)	Use/Rate Modeled (lb ai/A)	Maximum Estimated Drinking Water Concentration (EDWC; ppb)	
Groundwater (SCI-GROW2)	0.0123 x 3 applic. for total of 0.0369	Acute and Chronic	6.1×10^{-2}

Surface Water (FIRST2)	Aerial spray/0.0123 x 3 applic. for total of 0.0369	Acute	2.4
	Aerial spray/0.0123 x 3 applic. for total of 0.0369	**Chronic**	**1.3**

5.1.2 Food Residue Profile

The current proposed use on turfgrass is considered a non-food use. Since florasulam has tolerances on food commodities, the dietary exposure and risk assessment will include information from the previous assessments. Please see the most recent residue chemistry chapter (T. Morton, D333759, 05/31/2007) and the previous risk assessment (K. Bailey, D332983, 05/31/2007) for information regarding the food residue profile.

5.2 Dietary Exposure and Risk

The chronic dietary risk assessment (D. Wilbur, D364543, 04/30/2009) 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 analysis was performed to support a Section 3 registration action on turfgrass. The only difference from the previous dietary exposure and risk assessment (T. Morton, D338497, 04/05/2007) is a change in the estimated drinking water concentrations provided by EFED. The previous assessment was the first food use for florasulam.

5.2.1 Acute Dietary Exposure/Risk

No acute dietary endpoint of concern was identified in the toxicity database. Therefore, no acute dietary risk assessment was performed.

5.2.2 Chronic Dietary Exposure/Risk

An unrefined chronic dietary exposure assessment was performed for florasulam using DEEM-FCID™. The chronic analysis utilized tolerance value residues, empirical processing factors, 100% CT, and incorporated EDWC values. The resulting DEEM-FCID™ food plus drinking water chronic exposure estimates were below HED's level of concern for the US Population and all population subgroups. All infants (<1 year) (0.000107 mg/kg/day, <1 % cPAD) was the most highly exposed population subgroup. The results of this analysis are present in Table 5.2.

Table 5.2. Summary of Chronic Dietary Exposure and Risk (Food and Drinking Water) for Florasulam

Population Subgroup	cPAD (mg/kg/day)	Exposure (mg/kg/day)	% cPAD
General U.S. Population	0.05	0.000048	<1
All Infants (< 1 year old)	**0.05**	**0.000107**	**<1**
Children 1-2 years old	0.05	0.000089	<1

Table 5.2. Summary of Chronic Dietary Exposure and Risk (Food and Drinking Water) for Florasulam			
Population Subgroup	cPAD (mg/kg/day)	Exposure (mg/kg/day)	% cPAD
Children 3-5 years old	0.05	0.000086	<1
Children 6-12 years old	0.05	0.000059	<1
Youth 13-19 years old	0.05	0.000039	<1
Adults 20-49 years old	0.05	0.000043	<1
Females 13-49 years old	0.05	0.000041	<1
Adults 50+ years old	0.05	0.000041	<1

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

The unrefined dietary analysis utilized tolerance value residues, empirical processing factors, 100% CT, and incorporated EDWC values. No anticipated residues or percent crop treated data were incorporated into the assessment.

6.0 Residential (Non-Occupational) Exposure/Risk Characterization

Reference:
Florasulam: Occupational and Residential Exposure Assessment for proposed uses of florasulam on commercial and residential turfgrass and existing uses on cereal grains, including wheat (and duram), oats, barley, rye, and triticale. S. Recore. D364541.

HED assumes residential handlers are exposed to short-term exposures only. Intermediate-term and chronic exposures are not for residential handler and postapplication risk assessments.

6.1 Residential Handler Exposure

No short-term dermal point of departure was identified for florasulam. Therefore, no dermal risks were assessed for residential handlers.

For short-term inhalation residential exposure, the point of departure is 5 mg/kg/day. Since no inhalation absorption data are available, toxicity by the inhalation route is considered to be equivalent to the estimated toxicity by the oral route of exposure.

No chemical-specific handler exposure data were submitted in support of this registration. It is the policy of the HED to use data from the Pesticide Handlers Exposure Database (PHED) Version 1.1 as presented in PHED Surrogate Exposure Guide (8/98) to assess handler exposures for regulatory actions when chemical-specific monitoring data are not available (HED Science Advisory Council for Exposure Standard Operating Procedure (SOP) No. 7, dated 1/28/99). In addition, data from the Outdoor Residential Exposure Task Force (ORETF) were used.

All residential handler inhalation risks do not exceed HED's level of concern. MOEs were all greater than the target MOE of 100.

Table 6.1. Florasulam Residential Handler Risks - Short- Term Inhalation Risks						
Exposure Scenario	**Crop**	**Application Rate (lb ai/A)**	**Area Treated Daily (acres)**	**Baseline Inhalation Unit Exposure (ug/lb ai)**	**Baseline Inhalation Dose[a] (mg/kg/day)**	**Baseline Inhalation MOE[b] (LOC = 100)**
Mixer/Loader/Applicator						
Mixing/Loading/Applying Liquid Concentrates with Low Pressure Handwand (PHED)	turfgrass	0.013	0.5	30	0.0000028	1,800,000
Mixing/Loading/Applying Liquid Concentrates with Low Pressure Handwand (ground directed)	turfgrass	0.013	0.5	2.7	0.00000025	20,000,000
Mixing/Loading/Applying with a Hose-End Sprayer (PHED)	turfgrass	0.013	0.5	9.5	0.00000088	5,700,000
Mixing/Loading/Applying Liquid Concentrates with Hose-End Sprayer (Residential ORETF data)	turfgrass	0.013	0.5	17	0.0000016	3,200,000

a Baseline Inhalation Dose (mg/kg/day) = ((application rate * acres treated daily * baseline unit exposure in µg/lb ai) /1000 mg/µg)) * inhalation absorption (100%) / BW (70 kg for adult)

b Baseline Inhalation MOE = inhalation NOAEL (5 mg/kg/day) / baseline inhalation dose (mg/kg/day). LOC = 100.

6.2 Residential Postapplication Exposure

HED uses the term "postapplication" to describe exposures to individuals that occur as a result of being in an environment that has been previously treated with a pesticide. Florasulam can be used in many areas that can be frequented by the general population including residential areas (e.g., home lawns and gardens). As a result, individuals can be exposed by entering these areas if they have been previously treated.

6.2.1 Residential Postapplication Exposure Scenarios

HED determined there is a potential for exposure from entering florasulam-treated residential areas, such as lawns, sports fields, and golf courses that could lead to postapplication exposures to adults and children.

No short-term dermal point of departure was identified for florasulam. Therefore, no dermal risks were assessed for residential postapplication exposures.

HED assumes that inhalation exposures are minimal following outdoor applications of an active ingredient with low vapor pressure. Since the proposed use of florasulam include only outdoor applications and florasulam has a low vapor pressure, postapplication inhalation exposures and risks were not assessed.

Short-term incidental oral risks were assessed for toddlers after applications of florasulam to lawns. Short-term incidental oral risks to toddlers do not exceed HED's level of concern.

HED combines risk values resulting from separate postapplication exposure scenarios when it is likely they can occur simultaneously based on the use-pattern and the behavior associated with the exposed population. The combined risk assessment for incidental oral exposures to toddlers following home lawn applications was calculated. The combined risks do not exceed HED's level of concern.

Table 6.2.1 Florasulam: Toddler Residential Risk Estimates for Postapplication Exposure

Exposure Scenario	Route of Exposure	Formulation	Application Rate (lb ai/A)	Average Daily Dose[a] (mg/kg/day)	MOE Day 0[b] LOC =
Hand to Mouth Activity on Turf	Oral	Spray	0.013	0.00019	26,000
Object to Mouth Activity on Turf				0.000049	100,000
Incidental Soil Ingestion				0.00000065	7,700,000
Combined (Hand to Mouth + Object to Mouth + Incidental Soil Ingestion)				0.00024	21,000[c]

a Average Daily Dose $_{\text{hand to mouth}}$ = application rate (lb ai/A) * 5% ai dislodgeable * 20 cm^2 surface area of hands * 20 events/hr * 2 hr/day * CF1 (1.0E-3 mg/ µg) * CF2 (4.54E+8 µg/lb) * CF3 (2.47E-8 A/cm^2) / BW 15 kg
Average Daily Dose $_{\text{object to mouth}}$ = application rate (lb ai/A) * 20% ai dislodgeable * 25 cm^2 surface area of turf mouthed * CF1 (1.0E-3 mg/ µg) * CF2 (4.5E+8 µg/lb) * CF3 (2.47E-8 A/cm^2) / BW 15 kg
Average Daily Dose $_{\text{incidental soil ingestion}}$ = application rate (lb ai/A) * 100% of app rate present in top 1 cm of soil % 100 mg/day ingestion rate * CF2 (4.54E+8 µg/lb) * CF3 (2.47E-8 A/cm^2) * CF4 (0.67 cm^3/ gm soil) * CF5 (1.0^{E}-6 (gm/ µg) / BW 15 kg

b Incidental Oral MOE = incidental oral NOAEL (5.0 mg/kg/day) / average daily dose

c Aggregate MOE = 1 / ((1/$MOE_{\text{hand-to-mouth})+}$ + 1/$MOE_{\text{object-to-mouth}}$ + 1/$MOE_{\text{incidental soil ingestion}}$))

Residential Postapplication Exposure to Turfgrass from Sod Farms

An additional postapplication assessment was not performed to assess the potential exposure of toddlers to turf transplanted from sod farms into residential areas. The maximum application rate for sod farm turfgrass is the same as the maximum application rate for residential turfgrass.

Since the postapplication incidental oral risks to toddlers did not exceed HED's level of concern, no additional assessment for transplanted sod farm turfgrass is warranted.

6.3 Other (Spray Drift, *etc.*)

Spray drift is always a potential source of exposure to residents nearby to spraying operations. This is particularly the case with aerial application, but to a lesser extent, could also be a potential source of exposure from the airblast and groundboom application method additionally employed for florasulam. The Agency has been working with the Spray Drift Task Force, EPA Regional Offices, and State Lead Agencies for pesticide regulation and other parties to develop the best spray drift management practices. The Agency is now requiring interim mitigation measures for aerial applications that must be placed on product labels/labeling. The Agency has completed its evaluation of the new database submitted by the Spray Drift Task Force, a membership of U.S. pesticide registrants, and is developing a policy on how to appropriately apply the data and the AgDRIFT computer model to its risk assessments for pesticides applied by air, orchard airblast and ground hydraulic methods. After the policy is in place, the Agency may impose further refinements in spray drift management practices to reduce off-target drift and risks associated with aerial as well as other application types where appropriate.

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

Short-term aggregate risk is made up of dietary and non-dietary sources of exposure. Since florasulam is proposed for use on turfgrass, post-application residential exposure is expected. Short-term aggregate risk is made up of average dietary exposures from food and drinking water sources, inhalation and oral (children only) residential exposures. A short-term dermal endpoint was not selected and therefore, was not included in the aggregate risk estimates. Dietary (food + drinking water) exposure estimates are based on a conservative, unrefined chronic dietary exposure assessment (see Table 5.2). Residential exposure estimates are conservative estimates due to the standard assumptions that were built into the calculations (see Section 6.0). Incidental oral exposure was factored into the short-term aggregate risk calculations for children, as incidental oral exposure is possible for this population. Incidental oral exposure is not expected for adults from residues on turfgrass; therefore, this exposure scenario was not factored into the short-term aggregate risk calculation.

Table 7.2. Short-Term Aggregate Risk Calculations

Population	*Short*- Term Scenario					
	NOAEL mg/kg/day	LOC[1]	Max Allowable Exposure[2] mg/kg/day	Average Food & Water Exposure mg/kg/day	Residential Exposure[3] mg/kg/day	Aggregate MOE (food and residential)[4]
General U.S. Population	5	100	0.05	0.000048	0.0000028	98,000
Adult Female	5	100	0.05	0.000041	0.0000028	114,000
Child	5	100	0.05	0.000107	0.00024	14,000

[1] HED applies a 10X factor to account for inter-species extrapolation and a 10X factor to account for intra-species sensitivity. The total uncertainty factor that has been applied to the non-cancer risk assessment for florasulam is 100.
[2] Maximum Allowable Exposure (mg/kg/day) = NOAEL (5 mg/kg/day)/LOC (100)
[3] Residential Exposure = [Oral exposure + Inhalation Exposure]. No short-term dermal endpoint selected. General U.S. Population and Adult Female exposures are inhalation only. Child exposures are incidental oral only.
[4] Aggregate MOE = [NOAEL (5 mg/kg/day) / (Avg Food & Water Exposure + Residential Exposure)]

7.3 Intermediate-Term Aggregate Risk

Intermediate-term aggregate risk is made up of average dietary exposures from food and drinking water sources, and incidental oral (toddlers only) residential exposures. Because of the use pattern associated with the application of florasulam on residential lawns and because of mowing and rainfall events, intermediate-term post-application exposure to turf is not anticipated.

7.4 Long-Term Aggregate Risk

Since residential post-application exposure over the long-term duration (more than 6 months) is not expected based on the use pattern (i.e., application to golf course turf), the long-term aggregate risk assessment includes food and drinking water only. 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. (from 2007 flurasulam RA).

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

Reference:
Florasulam: Occupational and Residential Exposure Assessment for proposed uses of florasulam on commercial and residential turfgrass and existing uses on cereal grains, including wheat (and duram), oats, barley, rye, and triticale. S. Recore. D364541.

The proposed turf use and current use on cereal grains is expected to result in both occupational handler and postapplication exposure to florasulam. Handlers may be exposed during mixing, loading and application activities to turfgrass and cereal grains. The application method, maximum application rate, and use site are summarized in Table 2.1. Handler exposure is expected to be short- or intermediate-term based on information provided on proposed and existing label.

9.1 Occupational Handler Exposure

There is a potential for exposure to florasulam during mixing, loading, and application activities. No chemical-specific handler exposure data were submitted in support of this registration. It is the policy of the HED to use data from the Pesticide Handlers Exposure Database (PHED) Version 1.1 as presented in PHED Surrogate Exposure Guide (8/98) to assess handler exposures for regulatory actions when chemical-specific monitoring data are not available (HED Science Advisory Council for Exposure Standard Operating Procedure (SOP) No. 7, dated 1/28/99). In addition, data from the Outdoor Residential Exposure Task Force (ORETF) were used.

The inhalation risks to handlers do not exceed HED's level of concern at baseline (no respirator) for any of the handler scenarios where baseline data are available. Only engineering control (enclosed cockpit) data are available to assess inhalation risks to handlers operating aircraft. The inhalation risks do not exceed HED's level of concern for pilots using enclosed cockpits and wearing no respirator.

The intermediate-term dermal and combined intermediate-term dermal plus intermediate-term inhalation risks to handlers do not exceed HED's level of concern with baseline attire (i.e., long-sleeve shirt, long pants, shoes, and socks) where baseline data are available. The only data available for applying with handgun equipment and mixing/loading/applying with handgun equipment is baseline attire plus chemical-resistant gloves. The dermal and combined intermediate-term dermal plus intermediate-term inhalation risks to handlers do not exceed HED's level of concern with the addition of gloves to baseline attire for these two scenarios. Only engineering control (enclosed cockpit) data are available to assess dermal (and therefore combined risks) to handlers operating aircraft. The dermal and combined risks do not exceed HED's level of concern for pilots using enclosed cockpits and wearing baseline attire.

Table 9.1. Florasulam Occupational Handler Risks - Intermediate-Term Dermal Risks, Short- and Intermediate-Term Inhalation Risks, and Combined Intermediate-term D and Inhalation Risks

Exposure Scenario	Crop or Target	Application Rate	Area Treated Daily	Unit Exposures		Doses [a,b]		MOEs [c,d,e,f,g,h] Dermal LOC = 100 Inhalation LOC = 100		
				Baseline Dermal (mg/lb ai)	Baseline Inhalation (ug/lb ai)	Baseline Absorbed Dermal[a]	Baseline Inhalation[b]	Baseline Dermal[c]	Baseline Inhalation[d]	Baseline Der Baselin Inhalatio
Mixer/Loader										
Mixing/Loading Liquid Concentrates for Aerial Applications	wheat, barley, oats, rye, triticale	0.00446	1200	2.9	1.2	0.00086	0.000092	5,800	54,000	5,200
Mixing/Loading Liquids Concentrates for Groundboom Applications	wheat, barley, oats, rye, triticale	0.00446	200	2.9	1.2	0.00014	0.000015	35,000	330,000	31,000
Mixing/Loading Liquids Concentrates for Groundboom Applications	sod farms	0.013	80	2.9	1.2	0.00017	0.000018	30,000	280,000	27,000
Mixing/Loading Liquids Concentrates for Groundboom Applications	golf courses	0.013	40	2.9	1.2	0.000085	8.9E-06	59,000	560,000	53,000
Mixing/Loading Liquid Concentrates to Support LCO Handgun Applications (mixing/loading supports 20 LCOs)	turfgrass	0.013	100	2.9	1.2	0.00021	0.000022	24,000	220,000	21,000
Applicator										
Applying Sprays via Aerial Equipment	wheat, barley, oats, rye, triticale	0.00446	1200	0.005[h] (Eng cont)	0.068[h] (Eng cont)	0.0000015[h] (Eng cont)	0.0000052[h] (Eng cont)	3,400,000[h] (Eng cont)	960,000[h] (Eng cont)	750,000 (Eng con
Applying Sprays via Groundboom Equipment	wheat, barley, oats, rye, triticale	0.00446	200	0.014	0.74	7.0E-07	9.4E-06	7,200,000	530,000	490,00(

Table 9.1. Florasulam Occupational Handler Risks - Intermediate-Term Dermal Risks, Short- and Intermediate-Term Inhalation Risks, and Combined Intermediate-term D and Inhalation Risks

Exposure Scenario	Crop or Target	Application Rate	Area Treated Daily	Unit Exposures	Doses [a,b]			MOEs [c,d,e,f,g,h] Dermal LOC = 100 Inhalation LOC = 100		
				Baseline Dermal (mg/lb ai)	Baseline Inhalation (ug/lb ai)	Baseline Absorbed Dermal[a]	Baseline Inhalation [b]	Baseline Dermal[c]	Baseline Inhalation[d]	Baseline Der Baselin Inhalatio
Applying Sprays via Groundboom Equipment	sod farms	0.0131	80	0.014	0.74	8.2E-07	0.000011	6,100,000	450,000	420,00(
Applying Sprays via Groundboom Equipment	golf courses	0.013	40	0.014	0.74	4.1E-07	5.5E-06	12,000,000	900,000	840,00(
Applying Sprays via Handgun Equipment	turfgrass	0.013	5	0.34[g] (gloves)	1.4	0.0000012[g] (gloves)	1.3E-06	4,000,000[g] (gloves)	3,800,000	2,000,00((gloves)
Flagger										
Flagging for Aerial Sprays Applications	wheat, barley, oats, rye, triticale	0.00446	350	0.011	0.35	9.6E-07	7.8E-06	5,200,000	640,000	570,00(
Mixer/Loader/Applicator										
Mixing/Loading/Applying Liquid Concentrates with Low Pressure Handwand (PHED)	turfgrass	0.013	5	100	30	0.00036	0.000028	14,000	180,000	13,000
Mixing/Loading/Applying Liquid Concentrates with Low Pressure Handwand (ORETF)	turfgrass	0.013	5	15	2.7	0.000055	2.5E-06	91,000	2,000,000	87,000
Mixing/Loading/Applying Liquid Concentrates with a Handgun Sprayer (LCO ORETF data)	turfgrass	0.013	5	0.45[g] (gloves)	1.8	0.0000016[g] (gloves)	1.6E-06	3,100,000[g] (gloves)	3,000,000	1,500,00((gloves)

a. Absorbed Dermal Dose (mg/kg/day) = daily unit exposure (mg/lb ai) x application rate (lb ai/acre) x acres treated * dermal absorption (0.39%) / body weight (70 kg).
b. Inhalation Dose (mg/kg/day) = daily unit exposure (µg/lb ai) x application rate (lb ai/acre) x acres treated * inhalation absorption (100%) x conversion factor (1 mg/1,000 µg) / body weight (70 kg).
c Intermediate-term dermal MOE = NOAEL (5.0 mg/kg/day) / dermal daily dose (mg/kg/day). Level of concern = 100.
d Short- and Intermediate-Term Inhalation MOE = NOAEL (5.0 mg/kg/day) / inhalation daily dose (mg/kg/day). Level of concern = 100.
e Combined Intermediate-term dermal plus intermediate-term inhalation MOE = 1/ ((1/dermal MOE) + (1/inhalation MOE))
f. Baseline Dermal: Long-sleeve shirt, long pants, and no gloves; Baseline Inhalation: no respirator.
g Baseline plus Gloves Dermal: Baseline plus chemical-resistant gloves.
h Only engineering control (enclosed cockpit) data are available to assess dermal and inhalation risks to handlers operating aircraft.

9.2 Occupational Postapplication Exposure

HED assumes that inhalation exposures are minimal following outdoor applications of an active ingredient with low vapor pressure. Since the proposed use of florasulam include only outdoor applications and florasulam has a low vapor pressure, postapplication inhalation exposures and risks were not assessed.

No short-term dermal point of departure was identified for florasulam; therefore, postapplication occupational risks were assessed using the intermediate-term dermal point of departure.

No chemical-specific dislodgeable foliar residue data are available for florasulam to assess postapplication dermal risks following applications to turfgrass or cereal grains. Using the default assumption that 20 percent of the application rate is retained on foliage on day 0, postapplication risks do not exceed HED's level of concern on Day 0 (12 hours following application).

Since systemic postapplication risks do not exceed HED's level of concern on day 0 (12 hours following application), the restricted entry interval (REI) is based on the acute toxicity of florasulam technical material. Florasulam is classified as Toxicity Category III for acute dermal and Category IV for skin irritation and eye irritation potential. 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.

Table 9.2.2. Occupational Postapplication Exposure and Risk for Florasulam

Crop	Activity	Transfer Coefficient[1] (cm^2/hr)	DAT[2]	DFR[3] ($\mu g/cm^2$)	Intermediate-Term	
					Daily Dermal Dose[4] (mg/kg/day)	MOE[5]
Sod Farm Turfgrass	Mowing	500	0 (12 hours)	0.007	1.6×10^{-6}	3,100,000
	Transplanting, Hand Weeding, Hand or Mechanical Harvesting	16,500	0 (12 hours)	0.007	5.4×10^{-5}	93,000
Cereal Grains	Hand weeding	100	0 (12 hours)	0.01	4.5×10^{-7}	11,000,000
	Scouting, Irrigation	1500	0 (12 hours)	0.01	6.7×10^{-6}	750,000

1 Transfer coefficients and associated activities from ExpoSAC Policy Memo #003.1 "Agricultural Transfer Coefficients", 8/17/2000.

2 DAT = Days after treatment needed to reach the LOC of 100; DAT 0 = the day of treatment after sprays have dried; assumed to be approximately 12 hours.

3 DFR ($\mu g/cm^2$) = Application rate (lb ai/A) x (1- daily dissipation rate)^t x CF (4.54E+8 µg/lb) x CF (2.47E-8 A/cm^2) x 20% DFR after initial treatment.

4 Daily Dermal Dose = [(DFR x Tc x Dermal absorption x 8-hr Exposure Time)] / [(CF: 1000 µg/mg) x (70-kg Body Weight)] (Intermediate-term dermal absorption factor = 0.39%).

5 MOE = NOAEL/Daily Dose (Intermediate-term Dermal NOAEL = 5 mg/kg/day).

10.0 Data Needs and Label Recommendations

10.1 Toxicology

An immunotoxicity study is now required under the revised CFR 158.

10.2 Residue Chemistry

There are no residue chemistry data gaps

10.3 Occupational and Residential Exposure

HED recommends that the product label establish a retreatment interval.

References:

Florasulam: Occupational and Residential Exposure Assessment for proposed uses of florasulam on commercial and residential turfgrass and existing uses on cereal grains, including wheat (and duram), oats, barley, rye, and triticale. S. Recore. D364541.

Florasulam: Human Health Risk Assessment for Proposed Use on Cereal Grains (Wheat, Oats, Barley, Rye, and Triticale). K. Bailey, T. Morton, M Collantes. D332983.

Florasulam. Chronic Aggregate Dietary (Food and Drinking Water) Exposure and Risk Assessment for the Section 3 Registration Action on Turfgrass. D. Wilbur. D364543.

Florasulam. Chronic Aggregate Dietary and Drinking Water Exposure and Risk Assessment for the New Active Ingredient. T. Morton. D338497.

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.

Revised Tier I Drinking Water Assessment for the Florasulam Proposed Section 3 New Use Registration for Use on Turfgrass. C. Sutton. D356624.

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
870.7800	Immunotoxicity	yes (01/01/2010)	no

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. **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.

Table A.2.2 Subchronic, Chronic, and Other Toxicity Profile for Florasulam Technical		
Guideline No./Study Type	**MRID No. (year) Classification/Doses**	**Results**
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**
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.**

Table A.2.2 Subchronic, Chronic, and Other Toxicity Profile for Florasulam Technical		
Guideline No./Study Type	**MRID No. (year) Classification/Doses**	**Results**
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 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

Table A.2.2 Subchronic, Chronic, and Other Toxicity Profile for Florasulam Technical		
Guideline No./Study Type	**MRID No. (year) Classification/Doses**	**Results**
		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

For detailed information on executive summaries please refer to *Florasulam: Human Health Risk Assessment for Proposed Use on Cereal Grains (Wheat, Oats, Barley, Rye, and Triticale)*. K. Bailey, T. Morton, M Collantes. D332983.

A.4 DCI Rationale

Table 4. **Guideline Number: 870.7800** **Study Title: Immunotoxicity**
Rationale for Requiring the Data
This is a new data requirement under 40 CFR Part 158 as a part of the data requirements for registration of a pesticide (food and non-food uses). The Immunotoxicity Test Guideline (OPPTS 870.7800) prescribes functional immunotoxicity testing and is designed to evaluate the potential of a repeated chemical exposure to produce adverse effects (i.e., suppression) on the immune system. Immunosuppression is a deficit in the ability of the immune system to respond to a challenge of bacterial or viral infections such as tuberculosis (TB), Severe Acquired Respiratory Syndrome (SARS), or neoplasia. Because the immune system is highly complex, studies not specifically conducted to assess immunotoxic endpoints are inadequate to characterize a pesticide's potential immunotoxicity. While data from hematology, lymphoid organ weights, and histopathology in routine chronic or subchronic toxicity studies may offer useful information on potential immunotoxic effects, these endpoints alone are insufficient to predict immunotoxicity.
Practical Utility of the Data
How will the data be used? Immunotoxicity studies provide critical scientific information needed to characterize potential hazard to the human population on the immune system from pesticide exposure. Since epidemiologic data on the effects of chemical exposures on immune parameters are limited and are inadequate to characterize a pesticide's potential immunotoxicity in humans, animal studies are used as the most sensitive endpoint for risk assessment. These animal studies can be used to select endpoints and doses for use in risk assessment of all exposure scenarios and are considered a primary data source for reliable reference dose calculation. For example, animal studies have demonstrated that immunotoxicity in rodents is one of the more sensitive manifestations of TCDD (2,3,7,8-tetrachlorodibenzo-p-dioxin) among developmental, reproductive, and endocrinologic toxicities. Additionally, the EPA has established an oral reference dose (RfD) for tributyltin oxide (TBTO) based on observed immunotoxicity in animal studies (IRIS, 1997). **How could the data impact the Agency's future decision-making?** If the immunotoxicity study shows that the test material poses either a greater or a diminished risk than that given in the interim decision's conclusion, the risk assessments for the test material may need to be revised to reflect the magnitude of potential risk derived from the new data. If the Agency does not have this data, a 10X database uncertainty factor may be applied

for conducting a risk assessment from the available studies.

13544

R170472

Chemical Name: Florasulam

PC Code: 129108
HED File Code: 14000 Risk Reviews
Memo Date: 5/21/2009
File ID: 00000000
Accession #: 000-00-0127

HED Records Reference Center
6/8/2009