UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

OFFICE OF
CHEMICAL SAFETY AND
POLLUTION PREVENTION

MEMORANDUM

Date: September 15, 2015

SUBJECT: **Flazasulfuron.** Human Health Draft Risk Assessment for Registration Review.

PC Code: 119011
Decision No.: 502405
Petition No.: NA
Risk Assessment Type: Single Chemical/ Aggregate
TXR No.: NA
MRID No.: NA

DP Barcode: D426196
Registration Nos.: 71512-12, 71512-18
Regulatory Action: Registration Review
Case No.: N/A

CAS No.: 104040-78-0
40 CFR: §180.655

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As part of Registration Review, the Pesticide Re-evaluation Division (PRD) of the Office of Pesticide Programs (OPP) has requested that HED evaluate the hazard and exposure data and conduct occupational and residential exposure assessments, as needed, to estimate the risk to human health that will result from the currently registered uses of pesticides. This memorandum serves as HED's draft human health risk assessment of the dietary, occupational, and residential exposure, and aggregate risk from the registered uses of flazasulfuron.

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1.0 Executive Summary

Flazasulfuron (*N*-[[(4,6-dimethoxy-2-pyrimidinyl)amino]carbonyl]-3-(trifluoromethyl)-2-pyridinesulfonamide) is a sulfonylurea herbicide which controls certain broad-leaf weeds and grasses. Flazasulfuron acts by inhibiting acetolactate synthase (ALS), which is not present in humans.

Flazasulfuron is currently registered (40 CFR §180.655) for use on citrus, grapes, sugarcane, and tree nuts. It is also registered for use on conifer (Christmas) trees, vegetation around industrial sites, and turf grass (including residential and recreational areas). ISK is the only registrant with flazasulfuron end-use products at this time.

A human health scoping document was conducted for flazasulfuron in 2012 (D399094, C. Walls, 4/26/2012). The most recent risk assessment was conducted in 2014 (D411772, C. Walls, 7/29/2014). Since the last risk assessment, there have been no changes to the flazasulfuron use, residue, or residential/occupational profile. Changes in the hazard profile since the previous risk assessment do not change the dose-response assessment; therefore, the endpoints selected for the previous risk assessment are still appropriate. There are no outstanding human health data deficiencies.

The toxicology database for flazasulfuron is adequate to support current registration requirements. Since the last human health risk assessment and scoping document, a new immunotoxicity study has been reviewed; the rat developmental studies have been re-evaluated according to current standards for toxicity evaluation; and the estimated maximum dermal absorption factor (DAF) has been changed from 45% to 20%. Since the new information does not change the dose-response assessment, endpoints selected for the previous risk assessment are still appropriate. The liver was the main target organ of flazasulfuron in most species tested, with effects ranging from non-adverse liver hypertrophy to more severe histopathological findings like inflammatory cell infiltration, hepatocellular necrosis and swelling, and bile duct proliferation. There was no evidence of neurotoxicity, reproductive toxicity, or carcinogenicity in the database. No dermal hazard has been identified. The Food Quality Protection Act (FQPA) Safety Factor has been reduced to 1X.

The residue chemistry database is adequate to support current Registration Review data requirements. Adequate metabolism, storage stability, magnitude of the residue, and processing data are available to support the registered uses. Adequate methods are available for enforcement of the currently established tolerances.

The dietary exposure data used in this risk assessment were taken unchanged from the previous dietary assessment (D417419, C. Walls, Ph.D., 2/5/2014). The unrefined acute and chronic dietary (food and drinking water) assessments for flazasulfuron used tolerance-level residues for foods and assumed that 100% of the crops were treated. For the acute assessment, the groundwater estimated drinking water concentration (EDWC) of 90.8 µg/L (ppb) from the Tier II Pesticide Root Zone Model – Ground Water (PRZM-GW) modeling system was used.

For the chronic assessment, the groundwater EDWC of 55.6 µg/L from the Tier II PRZM-GW model was used. The EDWCs were incorporated directly into the dietary assessments.

The acute and chronic dietary (food and drinking water) exposures to flazasulfuron are below HED's level of concern (i.e., <100% of the acute or chronic population-adjusted dose (aPAD or cPAD) for the general U.S. population and all population subgroups. The acute dietary exposure estimates at the 95th percentile are 1.0% of the aPAD for the general U.S. population and 3.1% of the aPAD for all infants (<1 year old), the most highly exposed population subgroup. The chronic dietary exposure estimates are 9.1% of the cPAD for the general U.S. population and 23% of the cPAD for all infants (<1 year old), the most highly exposed population subgroup.

The existing residential uses on turf have been adequately assessed. Residential handler and post-application scenarios resulted in margins of exposure (MOEs) greater than the level of concern (i.e., the LOC is an MOE <100); therefore, the exposures are not of concern to HED.

Aggregate risks were assessed. The acute aggregate exposure is equal to the acute dietary (food and drinking water) exposure. Similarly, the chronic aggregate exposure is equal to the chronic dietary (food and drinking water) exposure. The short-term aggregate exposures for adults and children include dietary (food and drinking water) exposures and residential exposures to turf. The short-term aggregate exposures are not of concern to HED (i.e., MOEs $\geq$ 100). Since intermediate-term residential exposures are not likely to occur, intermediate-term aggregate risks were not assessed.

The occupational handler and post-application exposure and risk estimates include dermal and inhalation exposures. However, dermal exposure during handling and post-application activities was not assessed for flazasulfuron because systemic toxicity was not observed at the limit dose in the 21-day dermal toxicity study. The occupational handler exposure and risk estimates indicate that short- and intermediate-term non-cancer inhalation MOEs are not of concern to HED (i.e., MOEs $\geq$ 100) at baseline (no respirator) attire. Based on the Agency's current practices, a quantitative occupational post-application inhalation exposure assessment was not performed for flazasulfuron at this time. If new policies or procedures are put into place, the Agency may revisit the need for a quantitative occupational post-application inhalation exposure assessment for flazasulfuron.

HED has not identified any risk concerns associated with the registered uses of flazasulfuron.

Potential areas of environmental justice concerns, to the extent possible, were considered in the preliminary human health risk assessment for flazasulfuron. Dietary and non-dietary exposures were considered.

This risk assessment relies in part on data from studies in which adult human subjects were intentionally exposed to a pesticide or other chemical. As indicated in Appendix C, these

studies have been determined to require a review of their ethical conduct, and have received that review.

2.0 HED Recommendations

2.1 Tolerance Considerations

The existing tolerances (40 CFR §180.655) are supported by the available residue chemistry data.

No Codex, Canadian, or Mexican maximum residue limits (MRLs) have been established for residues of flazasulfuron, as shown in Appendix F; therefore, there are no international tolerance/MRL harmonization issues.

2.2 Label Considerations

There are no label recommendations for registered products containing flazasulfuron.

2.3 Data Deficiencies

There are no data deficiencies for registered products containing flazasulfuron.

3.0 Introduction

3.1 Chemical Identity and Physical/Chemical Characteristics

Flazasulfuron (*N*-[[(4,6-dimethoxy-2-pyrimidinyl)amino]carbonyl]-3-(trifluoromethyl)-2-pyridinesulfonamide) is a pyrimidinylsulfonylurea herbicide. Flazasulfuron has a log octanol/water partition coefficient (log K_{ow}) of <1.0 and is considered relatively soluble in water. However, flazasulfuron has a molecular weight of 407.4 g/mol; therefore, the potential to cross biological barriers is somewhat limited. Based on laboratory and field studies, flazasulfuron was found to be long-lived and persistent under most environmental conditions. The vapor pressure of flazasulfuron is considered low ($<1x10^{-7}$ mm Hg at 20 ºC), limiting the potential for inhalation exposure to vapor. Refer to Appendix E for chemical identity and physical/chemical characteristics of flazasulfuron.

3.2 Pesticide Use Patterns and Anticipated Exposure Pathways

Flazasulfuron is currently registered (40 CFR §180.655) for use on citrus, grapes, sugarcane, and tree nuts. It is also registered for use on conifer (Christmas) trees, vegetation around industrial sites, and turf grass (including residential and recreational areas). Currently registered labels include one technical label and two formulated end use products. ISK Flazasulfuron Herbicide (EPA Reg. No. 71512-18) and Flazasulfuron 25WG (EPA Reg. No.

71512-12) are both water-dispersible granular (WDG/WG) formulations containing 25% active ingredient (ai).

In general, multiple applications may be made by ground, air, or chemigation up to a maximum yearly rate of 0.15 lb ai/A. Application timing varies depending on the target weed. For both formulated products, the restricted entry interval (REI) is 12 hours, and the personal protective equipment (PPE) includes long-sleeved shirt and long pants, shoes plus socks, protective eyewear and waterproof gloves. The uses are tabulated in Table 3.2 below.

Exposure to flazasulfuron is possible via the dietary, residential, and occupational pathways. Additionally, there is the potential for indirect exposure (incidental oral and dermal) to flazasulfuron related to spray drift.

Table 3.2. Summary of Directions for Use of Flazasulfuron

Applic. Timing, Type, and Equip.	Formulation [EPA Reg. No.]	Applic. Rate (lb ai/A)	Max. No. Applic. per Year	Max. Yearly Applic. Rate (lb ai/A)	Min. RTI (days)	PHI (days)	Use Directions and Limitations[1]
CITRUS (Navel Orange, Valencia Orange, Lemon, Mandarin, and Tangerine)							
Pre-emergence and Post-emergence; Soil application using ground spray equipment	ISK Flazasulfuron Herbicide, WDG/WG [71512-18]	0.033 - 0.045	Not reported	0.15	3 months	1	Apply only as a directed spray to the soil beneath the trees. Multiple applications can be made. Do not apply more than 2 applications at the maximum rate. Do not apply to stony soils or sandy soils (greater than 85% sand).
GRAPE							
Pre-emergence and Post-emergence; Soil application using ground spray equipment	ISK Flazasulfuron Herbicide, WDG/WG [71512-18]	0.033 - 0.045	Not reported	0.15	3 months	75	Apply only as a directed spray to the soil beneath the vines. Multiple applications can be made. Do not apply more than 2 applications at the maximum rate. Do not apply to stony soils.
SUGARCANE							
Postemergence; Over-the-Top; Ground equipment	ISK Flazasulfuron Herbicide, WDG/WG [71512-18]	0.014	Not reported	0.15	14	180	Over-the top:: Apply prior to spiking or on ratoon up to 24 inches tall. Post-directed: Apply to sugarcane that is 18 inches tall up through layby.

Table 3.2. Summary of Directions for Use of Flazasulfuron							
Applic. Timing, Type, and Equip.	**Formulation [EPA Reg. No.]**	**Applic. Rate (lb ai/A)**	**Max. No. Applic. per Year**	**Max. Yearly Applic. Rate (lb ai/A)**	**Min. RTI (days)**	**PHI (days)**	**Use Directions and Limitations[1]**
Postemergence; Directed spray; Ground equipment	ISK Flazasulfuron Herbicide, WDG/WG [71512-18]	0014 - 0.045	Not reported	0.15	14	180	Applications should minimize contact with the whorl of the sugarcane. Multiple applications can be made. Allow a 12 month interval between the last application and the planting of the rotational crop.
TREE NUTS (Hazelnut; Pecan; Pistachio; Black Walnut; English Walnut; African nut-tree; Beechnut; Brazil nut; Brazilian pine; Bunya; Bur oak; Butternut; Cajou nut; Candlenut; Cashew; Chestnut; Chinquapin; Coconut; Coquito nut; Dika nut; Ginkgo; Guiana chestnut; Heartnut; Hickory nut; Japanese horse-chestnut; Macadamia nut; Mongongo nut; Monkey-pot; Monkey puzzle nut; Okari nut; Pachira nut; Peach palm nut; Pequi; Pili nut; Pine nut; Sapucaia nut; Tropical almond; Yellowhorn)							
Pre-emergence and post-emergence; Soil application using ground spray equipment.	ISK Flazasulfuron Herbicide, WDG/WG [71512-18]	0.033 - 0.045	Not reported	0.15	3 months	130	Apply as a directed spray to the soil beneath the trees. Multiple applications can be made. Do not apply more than 2 applications at the maximum rate. Do not apply to stony soils.
ALMOND in California							
Pre-emergence or post-emergence; Soil application using ground spray equipment.	ISK Flazasulfuron Herbicide, WDG/WG [71512-18]	0.023 - 0.045	1	0.045	NA	Not reported	Apply as a directed spray to the soil beneath the trees. Apply in Oct. Nov, Dec. or Jan. Do not apply to stony soils or soils with 90% or greater sand concentration.
CONIFER (CHRISTMAS) TREES							

Table 3.2. Summary of Directions for Use of Flazasulfuron							
Applic. Timing, Type, and Equip.	**Formulation [EPA Reg. No.]**	**Applic. Rate (lb ai/A)**	**Max. No. Applic. per Year**	**Max. Yearly Applic. Rate (lb ai/A)**	**Min. RTI (days)**	**PHI (days)**	**Use Directions and Limitations[1]**
Pre-emergence and Post-emergence; Over the top or directed sprays; Ground equipment	ISK Flazasulfuron Herbicide, WDG/WG [71512-18]	0.033 -0.045	Not reported	0.15	3 months	NA	Do not apply to conifer seedbeds. Do not apply to trees within 1 year of seeding. May be applied over-the-top to conifers prior to spring bud break or when conifers are sufficiently hardened off. Directed sprays must be made to conifers that have new growth or are not sufficiently hardened off. Directed sprays are preferred and recommended to reduce phytotoxicity potential. Multiple applications can be made.
INDUSTRIAL VEGETATION MANAGEMENT/NON-AGRICULTURAL USES							
Post-emergence; Broadcast or directed spray; Ground equipment	ISK Flazasulfuron Herbicide, WDG/WG [71512-18]	0.047	Not reported	0.15	45 days	NA	Do not use near residential properties. Multiple applications can be made.
TURF - Non-residential							
Postemergence; Broadcast or spot treatments; Ground equipment	Flazasulfuron 25WG [71512-12]	0.0078 - 0.047 (broadcast) 0.024 – 0.047[2] (spot treatment)	Not reported	0.14	14 (broad-cast); 21 (spot treat-ment)	NA	Multiple applications can be made.
TURF - Residential							
Postemergence; Spot treatment with directed spray; Ground equipment	Flazasulfuron 25WG [71512-12]	0.024 – 0.047[2] 0.0011 lb ai/gal 1.1×10^{-6} lb ai/ft^2	Not reported	0.14	21	NA	Residential turf grass sites are limited to targeted or spot treatment wih spray directed to the weeds only. Spot treatments are limited to not more than 10% of a residential lawn. Multiple applications can be made.

[1] For both labels and all sites: Do not apply by air. Do not apply through any irrigation system. Use of an adjuvant is recommended for postemergence applications.
[2] Spot treatment rates are 0.03–0.068 oz product (1-2 g product) per 1000 sq ft.

3.3 Consideration of Environmental Justice

Potential areas of environmental justice concerns, to the extent possible, were considered in the preliminary human health risk assessment for flazasulfuron, in accordance with U.S. Executive Order 12898, "Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations," http://www.epa.gov/compliance/resources/policies/ej/exec_order_12898.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 National Health and Nutrition Examination Surveys/What We Eat in America (NHANES/WWEIA) 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 and ethnic group. Additionally, OPP is able to assess dietary exposure to smaller, specialized subgroups and exposure assessments are performed when conditions or circumstances warrant. Whenever appropriate, non-dietary 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 post-application 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.

4.0 Hazard Characterization

The toxicology database for flazasulfuron is complete. The latest risk assessment was conducted in 2014 (D411772, C. Walls, 7/29/2014). The data requirement for an inhalation toxicity study is waived (TXR: 0056483, 10/04/2012) based on a weight of evidence approach, considering the low acute inhalation toxicity and low vapor pressure of flazasulfuron, and the use of an oral POD that results in MOEs below the level of concern to HED. A new immunotoxicity study has been reviewed, and the rat developmental studies have been re-evaluated since the previous risk assessment according to current standards for toxicity evaluation. Since the newly submitted toxicity information, toxicity study waiver, and revised DAF do not change the dose-response assessment, endpoints selected for the previous risk assessment are still appropriate. A summary of the acute, subchronic, and chronic toxicity profile of flazasulfuron is presented in Appendix A.

4.1 Summary of Toxicological Effects

After oral administration to rats, more than 84% of the dose of flazasulfuron was excreted within 72 hours, mostly as parent compound. Urinary elimination accounted for about 80-90% of the dose and fecal elimination for about 10-20%. Females tended to eliminate more in the urine, and slightly more rapidly, than males. Tissue distribution was rapid but incomplete. While levels in tissue were generally low, the tissues with highest concentrations were the blood, liver, and muscle. Dermal absorption studies are not available for flazasulfuron; however, an estimated maximum DAF of 20% is used in this risk assessment, based on the range of DAFs available from dermal penetration studies for other sulfonylureas (9.1-17.7%; see Appendix H).

The liver was the main target organ of flazasulfuron in most species tested, with effects ranging from non-adverse liver hypertrophy to more severe histopathological findings like inflammatory cell infiltration, hepatocellular necrosis and swelling, and bile duct proliferation. Rats also showed kidney toxicity (nephropathy) after chronic exposure. No adverse effects were observed in most short and intermediate duration ($\leq$ 90 days) studies; only reduced body weight gain and non-adverse liver effects (increased weight and hepatocellular hypertrophy) were observed in some of the subchronic toxicity studies.

Developmental toxicity was observed in rats and abortions in rabbits; however, findings in rats were not consistent across strains. A small increase in the incidence of intraventricular septal defect was observed in Wistar rats but not in Sprague-Dawley rats. Significant decreases in mean fetal body weight were observed in both rat strains at the limit dose. In the same studies, the maternal animals showed no adverse effects. A high incidence of abortion and decreased food consumption, but no specific fetal effects, were observed in rabbits. While the developmental studies indicate there is offspring susceptibility in rats, both rat studies provide clear no-observed-adverse-effect levels (NOAELs) for the adverse fetal effects. Furthermore, the points of departure (PODs) used for risk assessment are lower than doses associated with fetal effects; therefore, the assessments are protective of the observed offspring effects.

No increase in tumor incidence was seen in rats or mice. Flazasulfuron was not genotoxic. There was no evidence of neurotoxicity or reproductive toxicity in the database. The acute toxicity data indicate that flazasulfuron has low acute oral, dermal, and inhalation toxicity. It was not found to be a skin irritant, but was a moderate eye irritant. Flazasulfuron was not a dermal sensitizer.

4.2 Safety Factor for Infants and Children (FQPA Safety Factor)

The toxicity database for flazasulfuron is complete and adequate to assess susceptibility in the young. While there is evidence of increased qualitative and quantitative susceptibility in the young based on rat developmental malformation and decreased fetal weight, the FQPA Safety Factor is reduced to 1X and is protective of the observed offspring susceptibility because: (1) there are clear NOAELs for the developmental effects in two rat studies and the PODs selected

for risk assessment are protective of those effects, (2) there is no evidence of neurotoxicity, and (3) exposure estimates are unlikely to underestimate risk.

4.3 Toxicity Endpoint and Point of Departure Selections

There have been no changes to the prior toxicity endpoint selections and cancer classification; however, the developmental studies were re-evaluated which resulted in re-evaluation of the dermal PODs. ***Some studies used for endpoint selection have conservative NOAEL/LOAEL values that have not been updated to reflect current standards for evaluating toxicity studies. Updates would result in higher NOAEL/LOAEL values and, given the current risk picture, would not impact the overall findings of the risk assessment.***

Dermal Endpoints for Occupational and Non-Occupational Exposure Scenarios: A dermal endpoint was not selected. No effects were observed in the 21-day dermal toxicity study up to the limit dose (1000 mg/kg/day). After re-evaluation of the developmental toxicity of flazasulfuron, quantitative offspring susceptibility was identified in two rat oral studies (as explained in section 4.1 above). *In utero* offspring susceptibility in animal studies is generally of concern for occupational risk assessment since *in utero* effects are not evaluated in the dermal toxicity study. However, in the case of flazasulfuron, dermal absorption is expected to be equal to or less than 20% of the oral absorption (as explained in section 4.1 above). Applying the 20% dermal absorption rate to the LOAELs of the rat and rabbit developmental studies gives estimated dermal equivalent doses well above the limit dose of 1000 mg/kg/day. Therefore, a dermal risk assessment was not conducted.

Table 4.3. Summary of Toxicity Endpoints and Points of Departure for Flazasulfuron for Use in Human Risk Assessment.

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	NOAEL =50 mg/kg	UF_A = 10X UF_H = 10X FQPA SF = 1X	Acute RfD = 0.5 mg/kg aPAD = 0.5 mg/kg	Acute Neurotoxicity – Rat LOAEL = 1000 mg/kg based on transient decrease in motor activity 5 hours post-dosing.
Chronic Dietary: All populations	NOAEL= 1.3 mg/kg/day	UF_A = 10X UF_H = 10X FQPA SF = 1X	Chronic RfD = 0.013 mg/kg/day cPAD = 0.013 mg/kg/day	Combined Chronic/ Carcinogenicity – Rat LOAEL = 13 mg/kg/day based on kidney effects (chronic nephropathy).

Table 4.3. Summary of Toxicity Endpoints and Points of Departure for Flazasulfuron for Use in Human Risk Assessment.				
Exposure Scenario	**Point of Departure**	**Uncertainty/ FQPA Safety Factors**	**RfD, PAD, Level of Concern for Risk Assessment**	**Study and Toxicological Effects**
Incidental Oral: Short- and Intermediate-Term) *and* Inhalation Exposure: Short-, Intermediate- and Long-Term	NOAEL= 2 mg/kg/day Inhalation toxicity assumed to be equivalent to oral.	UF_A = 10 UF_H = 10 FQPA SF = 1X	Residential LOC for MOE = 100 Occupational LOC for MOE = 100	90-day toxicity study – Dog LOAEL = 10 mg/kg/day based on based on liver effects (inflammatory cell infiltration, hepatocellular necrosis, hepatocellular swelling, bile duct proliferation).
Dermal Exposure: Short-, Intermediate- and Long-Term	No dermal toxicity was observed in the 21-day dermal toxicity study up to the limit dose. Increased susceptibility was seen in rat developmental studies; however, applying a 20% dermal absorption rate to developmental LOAELs gives estimated dermal equivalent doses well above the limit dose of 1000 mg/kg/day. Therefore, a dermal risk assessment was not conducted.			
Cancer (oral, dermal, inhalation)	No evidence of carcinogenicity to humans based on lack of carcinogenic effects in the rat and mouse carcinogenicity studies and lack of a mutagenicity concern.			

Point of Departure (POD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. 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 = Food Quality Protection Act Safety Factor. PAD = population adjusted dose (a = acute, c = chronic). RfD = reference dose. MOE = margin of exposure. LOC = level of concern.

4.4 Endocrine Disruption

As required by FIFRA and FFDCA, EPA reviews numerous studies to assess potential adverse outcomes from exposure to chemicals. Collectively, these studies include acute, subchronic and chronic toxicity, including assessments of carcinogenicity, neurotoxicity, developmental, reproductive, and general or systemic toxicity. These studies include endpoints which may be susceptible to endocrine influence, including effects on endocrine target organ histopathology, organ weights, estrus cyclicity, sexual maturation, fertility, pregnancy rates, reproductive loss, and sex ratios in offspring. For ecological hazard assessments, EPA evaluates acute tests and chronic studies that assess growth, developmental and reproductive effects in different taxonomic groups. As part of Registration Review for flazasulfuron, EPA reviewed these data and selected the most sensitive endpoints for relevant risk assessment scenarios from the existing hazard database. However, as required by FFDCA section 408(p), flazasulfuron is subject to the endocrine screening part of the Endocrine Disruptor Screening Program (EDSP).

EPA has developed the EDSP to determine whether certain substances (including pesticide active and other ingredients) may have an effect in humans or wildlife similar to an effect produced by a "naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." The EDSP employs a two-tiered approach to making the statutorily required determinations. Tier 1 consists of a battery of 11 screening assays to identify the potential of a chemical substance to interact with the estrogen, androgen, or thyroid (E, A, or T) hormonal systems. Chemicals that go through Tier 1 screening and are found to have the potential to interact with E, A, or T hormonal systems will proceed to the next stage of the EDSP where EPA will determine which, if any, of the Tier 2 tests are necessary based on the available data. Tier 2 testing is designed to identify any adverse endocrine-related effects caused by the substance, and establish a dose-response relationship between the dose and the E, A, or T effect.

Under FFDCA section 408(p), the Agency must screen all pesticide chemicals. Between October 2009 and February 2010, EPA issued test orders/data call-ins for the first group of 67 chemicals, which contains 58 pesticide active ingredients and 9 inert ingredients. A second list of chemicals identified for EDSP screening was published on June 14, 2013[1] and includes some pesticides scheduled for Registration Review and chemicals found in water. Neither of these lists should be construed as a list of known or likely endocrine disruptors.

For further information on the status of the EDSP, the policies and procedures, the lists of chemicals, future lists, the test guidelines and the Tier 1 screening battery, please visit our website.[2]

5.0 Dietary Exposure and Risk Assessment

5.1 Residue Chemistry

The nature of the residue in plants and ruminants is adequately understood based on metabolism studies in grapes, sugarcane, tomatoes, and goats. The residue of concern for plants and ruminants for both the tolerance expression and risk assessment is parent. Since no poultry feed items have been registered or proposed, residues in poultry have not been defined. Resides in the drinking water exposure assessment include parent and all identified degradates/metabolites (i.e., flazasulfuron, DTPU, DTPP, HTPP, TSPA, ADMP, and 2,3-GTF). Refer to Appendix E for chemical names and structures of the flazasulfuron degradates.

The existing residue chemistry database for flazasulfuron is adequate to support current Registration Review data requirements. Adequate metabolism, enforcement methods, storage stability, field trials, and processing data are available to support the registered uses. The

[1] See http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPPT-2009-0477-0074 for the final second list of chemicals.
[2] http://www.epa.gov/endo/

requirement of a confined rotational crop study to support the use on sugarcane (the only registered crop which is rotated) has been waived since an adequate 12-month plant-back restriction was placed on the label. (This waiver was based on low residues in metabolism studies, no detectable residues in field studies, and limited sugarcane acreage.) An analytical reference standard for flazasulfuron with an expiration date of 5/3/2018 is available at EPA's National Pesticide Standards Repository (e-mail dated 2/4/2014 from Theresa Cole, Analytical Chemistry Branch/Biological and Economic Analysis Division).

5.2 Drinking Water Residue Profile

Flazasulfuron may reach surface and/or groundwater. The drinking water residues used in the dietary assessment were provided by the Environmental Fate and Effects Division (EFED) in the following memorandum: "Drinking Water Assessment for Flazasulfuron Use on Tree Nuts" (A. Shelby, D411771, 12/3/2013) and were incorporated directly into the dietary assessment. Water residues were incorporated in the DEEM Food Commodity Intake Database (FCID) into the food categories "water, direct, all sources" and "water, indirect, all sources." The EDWCs were determined for groundwater and surface water based on the Delmarva corn scenario (0.045 lb ai/A with 3 applications per year). EDWCs include total toxic residues of flazasulfuron in accordance with the most recent memo of the Residues of Concern Knowledgebase Subcommittee (ROCKS; D386767, 2/15/2011). The toxic residues include DTPU, DTPP, HTPP, TPSA, ADMP, and 2,3-GTF. For surface water, EDWCs were generated from the Pesticide Root Zone Model and Exposure Analysis Modeling System (PRZM-EXAMs). For groundwater, EDWCs were generated from a Tier II provisional groundwater model (PRZM-GW). The EDWCs for groundwater were used in the dietary assessment since they were higher than those for surface water. The surface and groundwater EDWCs are shown in Table 5.2.

Table 5.2. Summary of Estimated Surface Water and Groundwater Concentrations for Flazasulfuron

	Surface Water Conc., ppb [a]	Tier II Groundwater Conc., ppb [b]
Acute	26.9	90.8 (highest daily value)
Chronic	4.67 (non-cancer, 1 in 10 year annual average)	55.6 (post breakthrough average)

a From the Tier I PRZM-EXAMs modeling system.
b From the Tier II provisional groundwater model (PRZM-GW).

5.3 Dietary (Food and Drinking Water) Exposure Assessment

An updated dietary exposure assessment is not needed for flazasulfuron for the draft risk assessment since an assessment was recently completed. The use pattern, PODs, and residue inputs to the dietary assessment have not changed since the previous assessment.

The recent assessment included unrefined acute and chronic dietary (food and drinking water) assessments for flazasulfuron using tolerance-level residues for foods and assuming that 100% of the crops were treated (D417419, C. Walls, 2/5/2014). For the acute assessment, the groundwater EDWC of 90.8 µg/L from the Tier II PRZM-GW modeling was incorporated directly into the dietary assessment. For the chronic assessment, the groundwater EDWC of 55.6 µg/L from the Tier II PRZM-GW modeling was incorporated directly into the dietary assessment.

Exposure and risk estimates were obtained from the Dietary Exposure Evaluation Model using the Food Commodity Intake Database (DEEM-FCID, version 3.16). The model uses food consumption data from the 2003-2008 NHANES/WWEIA (National Health and Nutrition Examination Survey, What We Eat in America) database, coupled with recipe files and residues in foods, to derive estimates of dietary exposure and risk. Generally, HED is concerned when the dietary exposure estimates exceed 100% of the acute or chronic population adjusted dose (aPAD or cPAD). The acute and chronic dietary (food and drinking water) exposures to flazasulfuron are below HED's level of concern (i.e., <100% of the aPAD or cPAD) for the general U.S. population and all population subgroups. The acute dietary exposure estimates at the 95th percentile are 1.0% of the aPAD for the general U.S. population and 3.1% of the aPAD for all infants (<1 year old), the most highly exposed population subgroup. The chronic dietary exposure estimates are 9.1% of the cPAD for the general U.S. population and 23% of the cPAD for all infants (<1 year old), the most highly exposed population subgroup. Because of the conservative assumptions used in the analyses, actual exposures and risks are expected to be lower than shown in Table 5.3. The residue input files are included in Appendix B.

Flazasulfuron is classified as "not likely to be carcinogenic to humans"; therefore, a cancer dietary assessment was not conducted.

Table 5.3. Summary of Dietary (Food and Drinking Water) Exposure Analysis for Flazasulfuron Using DEEM-FCID

Population Subgroup	Acute Dietary (95th Percentile)		Chronic Dietary	
	Dietary Exposure (mg/kg/day)	% aPAD	Dietary Exposure (mg/kg/day)	% cPAD
General U.S. Population	0.004982	1.0	0.001187	9.1
All Infants (< 1 year old)	**0.015502**	**3.1**	**0.003022**	**23**
Children 1-2 years old	0.007755	1.6	0.001769	14
Children 3-5 years old	0.006309	1.3	0.001485	11
Children 6-12 years old	0.004777	<1.0	0.001054	8.1
Youth 13-19 years old	0.004142	<1.0	0.000867	6.7
Adults 20-49 years old	0.004891	<1.0	0.001177	9.1
Adults 50-99 years old	0.004370	<1.0	0.001165	9.0
Females 13-49 years old	0.004969	<1.0	0.001173	9.0

6.0 Residential (Non-Occupational) Exposure/Risk Characterization

There are existing residential uses that have been previously assessed to reflect HED's 2012 Residential SOPs[3] along with policy changes for body weight assumptions (DP399890, C. Walls, 10/09/2012). Residential handler scenarios resulted in margins of exposure (MOEs) greater than the level of concern (i.e., the LOC is an MOE <100), ranging from 27,000 to 6,800,000, and therefore are not of concern to HED. The residential short-term post-application incidental oral scenario for children resulted in an MOE greater than the LOC of 100 and therefore is not of concern to HED (MOEs ranged from 2,900 to 1,300,000). A summary of the worst-case residential exposure estimates are provided in Table 6.0. The recommended residential exposure for use in the adult aggregate assessment reflects inhalation exposure from applications to turf via backpack or manually pressurized handwand. The recommended residential exposure for use in the children 1 to <2 years old aggregate assessment reflects hand-to-mouth exposures from post-application exposure to turf treatments. A turf transferable residues (TTR) study is not required for flazasulfuron at this time since there was no dermal hazard identified and the hand-to-mouth MOE is greater than 1,000 based on default values for the fraction of application rate available for transfer after a turf application.

Table 6.0. Scenarios Recommended for Aggregate Risk Assessment of Flazasulfuron (Short-Term Only)

Scenario	Daily Dose[a]	MOE[b]
	mg/kg/day	*LOC = 100*
Adults		
Handler: Inhalation Only Exposure (Mixer/Loader/Applicator of Liquids via Backpack or Manually Pressurized Handwand to Residential Turf)	0.000073	27,000
Children 1 to < 2 years old		
Post-Application: Hand-to-Mouth Only Exposure (Liquid Application to Residential Turf)	0.00069	2,900

[a] Daily Dose = inhalation dose for adults, hand-to-mouth dose for children 1 to <2 years old.

[b] MOE = NOAEL/Daily Dose (mg/kg/day). ST Inhalation NOAEL = ST Incidental Oral NOAEL = 2 mg/kg/day. LOC = 100.

Spray Drift

Off-target movement of pesticides can occur via many types of pathways and it is governed by a variety of factors. Sprays that are released and do not deposit in the application area end up off-target and can lead to exposures to those it may directly contact. They can also deposit on surfaces where contact with residues can eventually lead to indirect exposures (e.g. children playing on lawns where residues have deposited next to treated fields). The potential risk estimates from these residues can be calculated using drift modeling coupled with methods employed for residential risk assessments for turf products.

[3] Available: http://www.epa.gov/pesticides/science/residential-exposure-sop.html

The approach to be used for quantitatively incorporating spray drift into risk assessment is based on a premise of compliant applications which, by definition, should not result in direct exposures to individuals because of existing label language and other regulatory requirements intended to prevent them.[4] Direct exposures would include inhalation of the spray plume or being sprayed directly. Rather, the exposures addressed here are thought to occur indirectly through contact with impacted areas, such as residential lawns, when compliant applications are conducted. Given this premise, exposures for children (1 to 2 years old) and adults who have contact with turf where residues are assumed to have deposited via spray drift thus resulting in an indirect exposure are the focus of this analysis analogous to how exposures to turf products are considered in risk assessment.

EPA Reg. No. 71512-12 is an existing label for use on turf; thus, it was evaluated to determine whether the risk assessment for that use may be considered protective of any type of exposure that would be associated with spray drift. If the maximum application rate on crops, adjusted by the amount of drift expected, is less than or equal to existing turf application rates, the existing turf assessment is considered protective of spray drift exposure. For flazasulfuron, the registered residential uses on turf result in estimated exposure levels that are greater than the potential exposure from spray drift; therefore, no new residential assessment needs to be completed. The currently registered maximum single application rate of flazasulfuron for all registered crops is 0.047 lb ai/A. The highest degree of spray drift noted for any application method immediately adjacent to a treated field (Tier 1 output from the aerial application using fine to medium spray quality) results in a deposition fraction of 0.26 of the application rate. A quantitative spray drift assessment for flazasulfuron is not required because the maximum non-turf application rate to a crop/target site multiplied by the adjustment factor for drift of 0.26 is less than the maximum registered direct spray residential turf application rate of 0.047 lb ai/A for any flazasulfuron products. The turf post-application MOEs have been previously assessed and are based on the 2012 Residential SOPs.

7.0 Aggregate Exposure/Risk Characterization

The Food Quality Protection Act of 1996 directs EPA to assess aggregate exposure to pesticide chemical residues, including all anticipated dietary exposures and all other exposures for which there is reliable information. Aggregate exposure and risk estimates, as calculated in D411772 (C. Walls, 7/29/2014), are shown below.

7.1 Acute Aggregate Risk

The acute aggregate risk is equal to the acute dietary (food and drinking water) exposure. Refer to Section 5.3.

[4] This approach is consistent with the requirements of the EPA's Worker Protection Standard which, when included on all labels, precludes direct exposure pathways.

7.2 Short- and Intermediate-Term Aggregate Risk

There is potential short-term aggregate exposure to flazasulfuron via the dietary pathway (which is considered background exposure) and the residential pathway (which is considered the primary pathway). Since intermediate-term residential exposures are not likely to occur, intermediate-term aggregate risks were not assessed. Since there is no dermal endpoint, the short-term aggregate exposure assessment for adults includes dietary (food and drinking water) and inhalation handler exposures. The most conservative scenario was chosen for each population (e.g., hand-to-mouth exposure from treated turf for children 1-2 years old). For a description of the residential exposure scenarios considered in the aggregate assessment, see Section 6.0.

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 and Water Exposure mg/kg/day[3]	Residential Exposure mg/kg/day[4]	Total Exposure mg/kg/day[5]	Aggregate MOE (food, water, and residential)[6]
Adult	2	100	0.02	0.001187	0.000073	0.001259	1,600
Child	2	100	0.02	0.001769	0.00069	0.002459	810

[1] LOC includes standard inter- (10X) and intra- (10X) species uncertainty factors totaling 100.
[2] Maximum Allowable Exposure (mg/kg/day) = NOAEL/LOC
[3] Table 5.4.6
[4] Residential Exposure (with no dermal exposure) = [Oral exposure + Inhalation Exposure]. Source of residential exposure values used in the aggregate assessment (Table 7.0). Exposure estimate for adults (general U.S. population) includes handler exposures from treating turf with flazasulfuron. Exposure estimate for Children 1-2 years old includes post-application exposure via hand-to-mouth to treated turf.
[5] Total Exposure = (Avg Food & Water Exposure + Residential Exposure)
[6] Aggregate MOE = NOAEL÷ (Avg Food & Water Exposure + Residential Exposure), NOAEL = 2 mg/kg/day

7.3 Chronic Aggregate Risk

The chronic aggregate risk is equal to the chronic dietary (food and drinking water) exposure. Refer to Section 5.3.

7.4 Cancer Aggregate Risk

A cancer aggregate risk assessment was not conducted because there was no evidence of carcinogenicity to humans based on lack of carcinogenic effects in the rat and mouse carcinogenicity studies.

8.0 Cumulative Exposure/Risk Characterization

In 2015, EPA's Office of Pesticide Programs released a guidance document entitled, *Pesticide Cumulative Risk Assessment: Framework for Screening Analysis*

[http://www.epa.gov/oppfead1/cb/csb_page/updates/2015/framework-for-screening-analysis.html]. This document provides guidance on how to screen groups of pesticides for cumulative evaluation using a two-step approach beginning with the evaluation of available toxicological information and if necessary, followed by a risk-based screening approach. This framework supplements the existing guidance documents for establishing common mechanism groups (CMGs)[1] and conducting cumulative risk assessments (CRA)[2]. The Agency has utilized this framework to evaluate the SUs of which flazasulfuron is a member (J. D'Agostino; D428798; 9/9/15). Although the SUs share some chemical and toxicological characteristics, the toxicological database does not support a testable hypothesis for a common mechanism of action. No further mechanistic data are required and no further cumulative evaluation is necessary.

9.0 Occupational Exposure/Risk Characterization

Although exposures are expected for occupational handlers from the agricultural and turf uses of flazasulfuron, dermal exposure during handling activities was not considered in this assessment because systemic toxicity was not observed at the limit dose in the dermal study. The occupational handler exposure and risk estimates (Appendix D) indicate that short- and intermediate-term non-cancer inhalation MOEs are not of concern to HED (i.e., MOEs $\geq$ 100) at baseline (no respirator) attire. The lowest MOE of 4,800 represents the most protective worst-case occupational scenario: mixing/loading dry flowables (water-dispersible granules) to support groundboom applications to sod. These risk estimates are not of concern to HED.

Dermal exposure during post-application activities was not considered because no systemic toxicity was observed at the limit dose in the 21-day dermal toxicity study. Based on the Agency's current practices, a quantitative occupational post-application inhalation exposure assessment was not performed for flazasulfuron at this time. Since there was no dermal POD selected for flazasulfuron, no additional Dislodgeable Foliar Residue (DFR) data are required and the 40 CFR DFR data requirement (discussed in Appendix G) is waived. Also, a TTR study is not required for flazasulfuron at this time since there was no dermal hazard identified and the hand-to-mouth MOE is greater than 1,000 based on default values for the fraction of application rate available for transfer after a turf application (also discussed in Appendix G). If new policies or procedures are put into place, the Agency may revisit the need for a quantitative occupational post-application inhalation exposure assessment for flazasulfuron.

10.0 Public Health and Pesticide Epidemiology Data

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[1] *Guidance For Identifying Pesticide Chemicals and Other Substances that have a Common Mechanism of Toxicity* (USEPA, 1999)

[2] *Guidance on Cumulative Risk Assessment of Pesticide Chemicals That Have a Common Mechanism of Toxicity* (USEPA, 2002)

The evaluation of the OPP Incident Data System (IDS) indicated no incidents identified in the United States for flazasulfuron in either Main or Aggregate IDS, from January 1, 2006 to December 14, 2011 (D399369, S. Recore, 02/14/2012). Flazasulfuron is not included in the Agricultural Health Study (AHS); therefore, no information is provided in that report. No concern was identified that would warrant further investigation.

11.0 References

Author	Barcode	Date	Title
C. Walls	D411772	7/29/2014	Flazasulfuron: Human Health Risk Assessment for Proposed Uses on Tree Nuts
N. Dodd	D412475	7/29/2014	Flazasulfuron. Petition for the Establishment of Permanent Tolerances and Registration for Use on Tree Nuts. Summary of Analytical Chemistry and Residue Data.
C. Walls	D417419	2/5/2014	Flazasulfuron: Acute & Chronic Aggregate Dietary (Food and Drinking Water) Exposure and Risk Assessment for a Proposed New Use on Tree Nuts
C. Walls	D417418	1/31/2014	Flazasulfuron: Occupational and Residential Exposure Assessment for a Proposed Use on Tree Nuts.
C. Walls	D399358	10/15/2012	Flazasulfuron: Human Health Risk Assessment for First Residential Use on Turf Grass
C. Walls	D399890	10/9/2012	Flazasulfuron: Occupational and Residential Exposure/Risk Assessment for the First Residential Use on Turf Grass.
C. Walls	D399094	4/26/2012	Flazasulfuron. Human Health Assessment Scoping Document in Support of Registration Review
N. Dodd	D394885	11/8/2011	Flazasulfuron. Amendment to Review of Analytical Chemistry and Residue Data for Use on Citrus, Grapes and Sugarcane
C. Walls	D372903	6/12/2011	Flazasulfuron: Human Health Risk Assessment for Proposed Uses on Citrus, Grapes, Sugarcane, Christmas Trees, and Industrial Vegetation Management
N. Dodd	D372901	2/16/2011	Flazasulfuron. Summary of Analytical Chemistry and Residue Data for Use on Citrus, Grapes and Sugarcane.
K. Rury	TXR # 0056483	10/4/2012	Flazasulfuron: Summary of Hazard and Science Policy Council (HASPOC) Meeting of October 4, 2012: Recommendations on the Requirement of Repeated Exposure Inhalation Study.

Appendix A. Toxicology Profile and Executive Summaries

A.1. Toxicology Data Requirements

Table A.1. Flazasulfuron Data Requirements

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	yes	waived[1]
870.3700	Developmental Toxicity (rodent)	yes	yes
870.3700	Developmental Toxicity (nonrodent)	yes	yes
870.3800	Reproduction	yes	yes
870.4100a	Chronic Toxicity (rodent)	yes	yes[2]
870.4100b	Chronic Toxicity (nonrodent)	yes	yes
870.4200a	Carcinogenicity (rat)	yes	yes[2]
870.4200b	Carcinogenicity (mouse)	yes	yes
870.4300	Chronic Toxicity/Carcinogenicity (rodent)	no	yes[2]
870.5100	Mutagenicity—Gene Mutation - bacterial	yes	yes
870.5300	Mutagenicity—Gene Mutation - mammalian	yes	yes
870.5385	Mutagenicity—Structural Chromosomal Aberrations	yes	yes
870.5550	Mutagenicity—Other Genotoxic Effects	yes	yes
870.6100	Acute Delayed Neurotox. (hen)	no	---
870.6100	90-Day Neurotoxicity (hen)	no	---
870.6200a	Acute Neurotox. Screening Battery (rat)	yes	yes
870.6200b	90-Day Neurotoxicity Screening Battery (rat)	yes	yes
870.6300	Developmental Neurotoxicity	no	---
870.7485	General Metabolism	yes	yes
870.7600	Dermal Penetration	no	---
870.7800	Immunotoxicity	yes	yes

[1] The requirement for this study has been waived by the HASPOC (TXR: 0056483, 10/04/2012).
[2] A chronic/oncogenicity study is available for the rat, thus separate chronic and oncogenicity studies are not necessary.

A.2. Toxicity Profiles

Table A.2.1. Acute Toxicity Profile – Flazasulfuron

Guideline No.	Study Type	MRID(s)	Results	Toxicity Category
870.1100	Acute oral – rat	46220908	LD_{50} > 5000 mg/kg	IV
870.1200	Acute dermal – rabbit	46220909	$LD_{50} \geq$ 2000 mg/kg	III
870.1300	Acute inhalation – rat	46220910	$LC_{50} \geq$ 5 mg/L	IV
870.2400	Acute eye irritation – rabbit	46220911	Minimal conjunctivitis through 48 hours. Clear by 72 hours.	III
870.2500	Acute dermal irritation – rabbit	46220912	Not an irritant	IV
870.2600	Skin sensitization – guinea pig	46220913	Not a sensitizer	NA

Table A.2.2 Subchronic, Chronic and Other Toxicity Profile – Flazasulfuron

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.3100 90-Day Oral Toxicity in Rodents (rat)	46220920 (1988) Acceptable/guideline 0, 40, 200, 1000, 5000 ppm M: 0, 2.3, 11.7, 57, 287 F: 0, 2.5, 12.8, 62, 309 mg/kg/day	NOAEL = 11.7/62 mg/kg/day (M/F) LOAEL = 57/309 mg/kg/day based on reduced body weight gains in both sexes and slight anemia due to decrease in hemoglobin in females.
870.3150 90-Day Oral Toxicity in nonrodent (dog)	46220921 (1994) Acceptable/guideline M: 0, 2, 10, 50, 250 F: 0, 2, 10, 50, 100 mg/kg/day (capsule)	NOAEL = 2/10 mg/kg/day (M/F) LOAEL = 10/50 mg/kg/day based on liver effects (brown pigments deposition, inflammatory cell infiltration, microgranulomas; increased serum levels of glutamic pyruvic transaminase, creatine phosphokinase).
870.3200 21-Day dermal toxicity (rabbit)	46220922 (1994) Acceptable/guideline M: 0, 250, 500, 250, 1000 mg/kg/day	NOAEL = 1000 mg/kg/day LOAEL could not be established
870.3700a Prenatal developmental in rodent (rat) Wistar	46220924 (1988) Acceptable/non-guideline 0, 100, 300, 1000 mg/kg/day	**Maternal** NOAEL = 1000 mg/kg/day LOAEL could not be established. **Developmental** NOAEL = 100 mg/kg/day LOAEL = 300 mg/kg/day based on increased incidence of interventricular septal defect.

Table A.2.2 Subchronic, Chronic and Other Toxicity Profile – Flazasulfuron		
Guideline No./ Study Type	**MRID No. (year)/ Classification /Doses**	**Results**
870.3700a Prenatal developmental in rodent (rat) Sprague-Dawley	46220925 (1996) Acceptable/guideline 0, 100, 300, 1000 mg/kg/day	**Maternal** NOAEL = 1000 mg/kg/day LOAEL could not be established. **Developmental** NOAEL = 100 mg/kg/day LOAEL = 300 mg/kg/day based on reduced fetal weights.
870.3700b Prenatal developmental in nonrodent (rabbit)	46220923 (1988) Acceptable/guideline 0, 50, 150, 450 mg/kg/day	**Maternal** NOAEL = 150 mg/kg/day LOAEL = 450 mg/kg/day based on high incidence of abortion and decrease food consumption. **Developmental** NOAEL = 150 mg/kg/day LOAEL = 450 mg/kg/day based on high incidences of abortion.
870.3800 Reproduction and Fertility Effects (rat)	46220926 (1995) Acceptable/guideline 0, 200, 2000, 10000 ppm F_0 M: 0, 14, 135, 675 F_0 F: 0, 16, 155, 760 mg/kg/day F_1 M: 0, 15, 148, 761 F_1 F: 0, 16, 165, 842 mg/kg/day	**Parental** NOAEL = 155 mg/kg/day in <u>females only</u>; was not established in males LOAEL = 14/760 mg/kg/day (male/female) based on increased incidence of nephropathy in F_0 males, kidney abnormalities in F_1 females and decreased body weights in both generations of females. **Reproductive** NOAEL = 842 mg/kg/day LOAEL could not be established. **Offspring** NOAEL = 135 mg/kg/day LOAEL = 675 mg/kg/day based on decreased body weight during lactation in both sexes and generations.
870.4100 Chronic toxicity (dog)	46220927 (1995) Acceptable/guideline M: 0, 0.4, 2, 10, 50 F: 0, 2, 10, 50 mg/kg/day (capsule)	NOAEL = 2 mg/kg/day LOAEL = 10 mg/kg/day based on based on liver effects (inflammatory cell infiltration, hepatocellular necrosis, hepatocellular swelling, bile duct proliferation).
870.4200 Carcinogenicity (mouse)	46220928 (1995) Acceptable/guideline 0, 500, 3500, 7000 ppm M: 0, 77, 553, 1054 F: 0, 94, 660, 1208 mg/kg/day	NOAEL = 77 mg/kg/day LOAEL = 553 mg/kg/day based on decreased body weight, body weight gain, food consumption, and liver effects (increased weight and hepatocellular hypertrophy). **No evidence of carcinogenicity.**
870.4300 Chronic Toxicity/Carcinogenicity (rat)	46220929 (1995) Acceptable/guideline 0, 40, 400, 2000 ppm M: 0, 1.3, 13, 70 F: 0, 1.6, 16., 173 mg/kg/day	NOAEL = 1.3 mg/kg/day LOAEL = 13 based on kidney effects (chronic nephropathy, enlargement, dark color). **No evidence of carcinogenicity.**

Table A.2.2 Subchronic, Chronic and Other Toxicity Profile – Flazasulfuron		
Guideline No./ Study Type	**MRID No. (year)/ Classification /Doses**	**Results**
870.5100 Bacterial Reverse Mutation Test (*S. typhimurium* and *E. coli*)	46220933 (1987) Acceptable/guideline 20 -5000 µg/plate	Flazasulfuron was not cytotoxic with or without metabolic activation in four *S. typhimurium* strains and one strain of *E. coli*, and did not induce a genotoxic response in any strain.
870.5300 *In vitro* Mammalian Cell Gene Mutation Test (mouse lymphoma cells)	46220930 (1993) Acceptable/guideline 20 - 5000 µg/mL	There was no evidence of biologically significant induction of mutant colonies.
870.5375 *In vitro* Mammalian Chromosome Aberration Test (Chinese hamster lung cells)	46220931 (1988) Acceptable/guideline 0.000021 – 0.00033 M	Flazasulfuron did not induce chromosome aberrations in the presence or absence of metabolic activation.
870.5395 Mammalian Erythrocyte Micronucleus Test (mouse)	46220932 (1995) Acceptable/guideline 0, 1250, 2500, 5000 mg/kg	There was no statistically significant increase in the frequency of micronucleated polychromatic erythrocytes in mouse bone marrow at any dose or collection time.
870.6200a Acute Neurotoxicity Screening Battery (rat)	46220934 (2002) Acceptable/non-guideline 0, 50, 1000, or 2000 mg/kg	NOAEL = 50 mg/kg/day LOAEL = 1000 mg/kg based on transient decrease in motor activity observed 5 hours post-dosing.
870.6200b Subchronic Neurotoxicity Screening Battery (rat)	49030001 (2012) Acceptable/guideline 0, 300, 3000, or 10000 ppm M: 0, 19, 190, 649 F: 0, 22, 229, 732 mg/kg/day	NOAEL = 229 mg/kg/day (M/F) LOAEL = 732 mg/kg/day based on decreased body weight and body weight gain.

Table A.2.2 Subchronic, Chronic and Other Toxicity Profile – Flazasulfuron		
Guideline No./ Study Type	**MRID No. (year)/ Classification /Doses**	**Results**
870.7485 Metabolism and Pharmacokinetics (rat)	46220936 (1995) 46220938 (1994) 46220940 (1994) 46220942 (1995) Acceptable/guideline 2 or 50 mg/kg pyridinyl ring label (P) 46220937 (1995) 46220939 (1995) 46220941 (1995) 46220943 (1995) Acceptable/guideline 2 or 50 mg/kg pyrimidinyl ring label (Pm)	Generally no difference between dose levels or single versus repeated dose, but differences were noted between males and females, and between P and Pm labels. Both labels rapidly absorbed: males 84-99% females 93-95% by 48 hr. P t_{max} was 30 min at 2 mg/kg both sexes; 4 hr in females and 6 hr in males at 50 mg/kg. Pm t_{max} was slightly higher: 6 hrs at 2 mg/kg and 4 hrs at 50 mg/kg. Males had slightly longer t½ (27/28 and 36/26 hr, for P/Pm) than females (18.8/17 and 33.8/17 hr); and greater AUC (304/361 and 4440/6630 µg-eq/g·hr) than females (189/259 and 3080/5710 µg-eq/g·hr). Excretion was also rapid (48-72 hrs): urine was major route: 73-80% males, 89-94% females; feces 18-24% male, 9-10% female; bile 8.4-17.0% with males slightly more than females. Tissue distribution was rapid but incomplete. Total body burdens ≤4/2% males and ≤1/0.3% females (P/Pm). Blood, liver, and muscle had highest concentrations (0.03-1.0% per tissue); the carcass had up to 2.5%.
870.7485 Metabolism and Pharmacokinetics (rat)	46220935 (1995) Acceptable/guideline 2 or 50 mg/kg P or Pm	Parent compound was primary component in urine (19-40% males, 51-67% females), feces (1-5%), and bile (0.6-2%). Most prevalent metabolite was HDTG+TPPG (6.5-17% urine, 0.4-9.7% feces, 6.5-14% in bile), with minor amounts (<5%) of DTPU, HDPU and HTTP for both labels; TPSA and MTMG for P only; and ADMP and HDU for Pm only. Unidentified fraction < 2% of dose in urine and bile except high dose Pm males was 12%; up to 35% in feces. Proposed metabolic pathway: intramolecular rearrangement within the sulfonylurea bridge, cleavage at the sulfonylurea bridge, pyrimidine hydroxylation followed by glucuronidation at the 5-position or the at methoxy group, displacement reaction by glutathione at the 2-position of the pyridine ring followed by formation of glucuronic acid conjugate of pyridine thiol.
870.7800 Immunotoxicity (female mouse)	48870301 (2012) Acceptable/guideline 0, 600, 3000, 6000 ppm 0, 123, 663, 1198 mg/kg/day	NOAEL = 1198 mg/kg/day LOAEL could not be established.

A.3 Hazard Identification and Endpoint Selection

The Hazard Identification and Endpoint Selection sections are presented a previous risk assessment document (D303573, Burke G.V., 11/16/05).

A.4 Executive Summaries

The following executive summaries are from studies that have been recently re-evaluated, leading to changes in their NOAEL/LOAEL statements. Executive summaries for other flufenacet studies are presented in the previous risk assessment document (D303573, Burke G.V., 11/16/05).

A.4.1 Prenatal Developmental Toxicity

870.3700a Prenatal Developmental Toxicity Study – Rat

In a developmental toxicity study (**MRID 46220924**), SL-160 Technical (96.3% a.i., lot # 8706) was administered to 23 female Wistar rats/dose by gavage at dose levels of 0, 100, 300, or 1000 mg/kg bw/day on days 6 through 15 of gestation. On gestational day (GD) 21, all surviving dams were sacrificed and examined grossly. Each fetus was weighed and examined externally for abnormalities and for sex determination. Approximately one-half of the fetuses in each litter were examined viscerally after fixation in Bouin's solution. The remaining one-half of the fetuses in each litter were eviscerated and processed for skeletal examination.

In maternal animal, no treatment-related deaths or clinical signs of toxicity were observed and gross necropsy was unremarkable. Mid dose animals had transient decreases in body weight gain (50%; $p \leq 0.01$) and food consumption (11%; $p \leq 0.05$) compared to controls during GD 6-9, but mean absolute body weight was not different from controls. Absolute body weight of the high dose group was significantly less than that of the controls (6-7%; $p \leq 0.01$) beginning on GD 9 and continuing until termination; body weight gains and food consumption were also less than controls for the GDs 6-9 and 12-15 intervals. However mean food consumption for the high dose group increased significantly (13%) on GD 18-21 and body weight gain was similar to controls during the same time period, suggesting a recovery. There were no abortions or other indications of maternal toxicity. **The maternal LOAEL for Wistar rats was not observed. The maternal NOAEL is ≥ 1000 mg/kg/day.**

No treatment-related differences were noted between the treated and control groups for numbers of corpora lutea and implantations, placental weight, fetal sex ratios, and pre-implantation losses. Male and female fetal body weights of the high-dose group were significantly less (8% for each sex; $p \leq 0.01$) than control. The high-dose group showed a non-statistically significant increases in fetal mortality (20.8% vs 5.5% for controls),

resorptions (69 vs 19 for controls), and post-implantation loss (21.6% vs 6% for controls). While most dams in the control, low and mid dose groups had 10-17 live fetuses and 0-3 resorptions each, two high dose dams had complete litter resorption of 16 and 17 implantations, respectively, and two other dams had partial but significant resorptions of 9/12 implants and 5/18, respectively.

Only a few malformations/variations seemed to increase with dose, and the incidence was generally low. A significantly ($p \leq 0.05$) greater number of high dose litters contained fetuses with interventricular septal defect (ISD), and the litter incidences seem to be dose-dependent starting at the mid dose ($p > 0.5$), with 1, 1, 6, and 7 litters in control, low, mid, and high dose groups, respectively. The fetal incidence of ISD at the high dose (6.6%, 8/122 fetuses) was slightly higher than the laboratory historical control incidence (0-5.3%). A significantly ($p \leq 0.05$) greater number of high dose litters contained fetuses with an extra 14^{th} rib, compared to no litters in the control and low dose groups, and 2 litters in the mid dose group; however this variation is usually reversible as pups mature (Wickramaratne, 1988; J Appl Toxicol. 1988 Apr;8(2):91-4) especially when it does not co-occurs with sacral vertebrae variations (Foulon et. al., 2000 J. Appl. Toxicol. 20, 205–209) as is noted in the current study, and is therefore not considered adverse. Delayed ossification in high dose fetuses was indicated by a significantly ($p \leq 0.05$) lower percentage of fetuses with 5 ossified metatarsals (72.8% vs 99.4% for the controls), however this is also a reversible effect and is not considered adverse. **The developmental LOAEL in Wistar rats is 1000 mg/kg/day based on increased incidence of interventricular septal defect. The developmental toxicity NOAEL is 300 mg/kg/day.**

This developmental toxicity study in the rat is classified **acceptable (non-guideline)** and only partially satisfies the guideline requirements for a developmental toxicity study (OPPTS 870.3700; OECD 414) in rats. This study is upgradable if laboratory methods and data are provided for concentration and homogeneity analyses of the test substance in the dosing solution.

Appendix B. Dietary Exposure/Risk Modeling Input Files

Acute Food and Water Residue Input File

```
Filename: C:\Documents and Settings\cwalls\My Documents\Cassi\HED\Flazasulfuron\2014 tree
nuts\acute FLAZ 012914.R08
Chemical: Flazasulfuron
RfD(Chronic): .013 mg/kg bw/day  NOEL(Chronic): 1.3 mg/kg bw/day
RfD(Acute): .5 mg/kg bw/day  NOEL(Acute):  50 mg/kg bw/day
Date created/last modified: 01-23-2014/16:41:25       Program ver. 3.16, 03-08-d
```

EPA Code	Crop Grp	Commodity Name	Def Res (ppm)	Adj.Factors #1	#2	Comment
1001106000	10A	Citron	0.010000	1.000	1.000	
1001107000	10A	Citrus hybrids	0.010000	1.000	1.000	
1001108000	10A	Citrus, oil	0.010000	1.000	1.000	
1001240000	10A	Orange	0.010000	1.000	1.000	
1001241000	10A	Orange, juice	0.010000	1.000	1.000	
1001241001	10A	Orange, juice-babyfood	0.010000	1.000	1.000	
1001242000	10A	Orange, peel	0.010000	1.000	1.000	
1001369000	10A	Tangerine	0.010000	1.000	1.000	
1001370000	10A	Tangerine, juice	0.010000	1.000	1.000	
1002197000	10B	Kumquat	0.010000	1.000	1.000	
1002199000	10B	Lemon	0.010000	1.000	1.000	
1002200000	10B	Lemon, juice	0.010000	1.000	1.000	
1002200001	10B	Lemon, juice-babyfood	0.010000	1.000	1.000	
1002201000	10B	Lemon, peel	0.010000	1.000	1.000	
1002206000	10B	Lime	0.010000	1.000	1.000	
1002207000	10B	Lime, juice	0.010000	1.000	1.000	
1002207001	10B	Lime, juice-babyfood	0.010000	1.000	1.000	
1003180000	10C	Grapefruit	0.010000	1.000	1.000	
1003181000	10C	Grapefruit, juice	0.010000	1.000	1.000	
1003307000	10C	Pummelo	0.010000	1.000	1.000	
1304175000	13D	Grape	0.010000	1.000	1.000	
1304176000	13D	Grape, juice	0.010000	1.000	1.000	
1304176001	13D	Grape, juice-babyfood	0.010000	1.000	1.000	
1304179000	13D	Grape, wine and sherry	0.010000	1.000	1.000	
1400003000	14	Almond	0.010000	1.000	1.000	
1400003001	14	Almond-babyfood	0.010000	1.000	1.000	
1400004000	14	Almond, oil	0.010000	1.000	1.000	
1400004001	14	Almond, oil-babyfood	0.010000	1.000	1.000	
1400059000	14	Brazil nut	0.010000	1.000	1.000	
1400068000	14	Butternut	0.010000	1.000	1.000	
1400081000	14	Cashew	0.010000	1.000	1.000	
1400092000	14	Chestnut	0.010000	1.000	1.000	
1400155000	14	Hazelnut	0.010000	1.000	1.000	
1400156000	14	Hazelnut, oil	0.010000	1.000	1.000	
1400185000	14	Hickory nut	0.010000	1.000	1.000	
1400213000	14	Macadamia nut	0.010000	1.000	1.000	
1400269000	14	Pecan	0.010000	1.000	1.000	
1400278000	14	Pine nut	0.010000	1.000	1.000	
1400282000	14	Pistachio	0.010000	1.000	1.000	
1400391000	14	Walnut	0.010000	1.000	1.000	
8601000000	86A	Water, direct, all sources	0.090800	1.000	1.000	
8602000000	86B	Water, indirect, all sources	0.090800	1.000	1.000	
9500177000	O	Grape, leaves	0.010000	1.000	1.000	
9500178000	O	Grape, raisin	0.010000	1.000	1.000	
9500362000	O	Sugarcane, sugar	0.010000	1.000	1.000	
9500362001	O	Sugarcane, sugar-babyfood	0.010000	1.000	1.000	

```
9500363000 O    Sugarcane, molasses                0.010000   1.000  1.000
9500363001 O    Sugarcane, molasses-babyfood       0.010000   1.000  1.000
```

Chronic Food and Water Residue Input File

Filename: C:\Documents and Settings\cwalls\My Documents\Cassi\HED\Flazasulfuron\2014 tree nuts\chronic FLAZ 012914.R08
Chemical: Flazasulfuron
RfD(Chronic): .013 mg/kg bw/day NOEL(Chronic): 1.3 mg/kg bw/day
RfD(Acute): .5 mg/kg bw/day NOEL(Acute): 50 mg/kg bw/day
Date created/last modified: 01-23-2014/16:40:39 Program ver. 3.16, 03-08-d

EPA Code	Crop Grp	Commodity Name	Def Res (ppm)	Adj.Factors #1	#2	Comment
1001106000	10A	Citron	0.010000	1.000	1.000	
1001107000	10A	Citrus hybrids	0.010000	1.000	1.000	
1001108000	10A	Citrus, oil	0.010000	1.000	1.000	
1001240000	10A	Orange	0.010000	1.000	1.000	
1001241000	10A	Orange, juice	0.010000	1.000	1.000	
1001241001	10A	Orange, juice-babyfood	0.010000	1.000	1.000	
1001242000	10A	Orange, peel	0.010000	1.000	1.000	
1001369000	10A	Tangerine	0.010000	1.000	1.000	
1001370000	10A	Tangerine, juice	0.010000	1.000	1.000	
1002197000	10B	Kumquat	0.010000	1.000	1.000	
1002199000	10B	Lemon	0.010000	1.000	1.000	
1002200000	10B	Lemon, juice	0.010000	1.000	1.000	
1002200001	10B	Lemon, juice-babyfood	0.010000	1.000	1.000	
1002201000	10B	Lemon, peel	0.010000	1.000	1.000	
1002206000	10B	Lime	0.010000	1.000	1.000	
1002207000	10B	Lime, juice	0.010000	1.000	1.000	
1002207001	10B	Lime, juice-babyfood	0.010000	1.000	1.000	
1003180000	10C	Grapefruit	0.010000	1.000	1.000	
1003181000	10C	Grapefruit, juice	0.010000	1.000	1.000	
1003307000	10C	Pummelo	0.010000	1.000	1.000	
1304175000	13D	Grape	0.010000	1.000	1.000	
1304176000	13D	Grape, juice	0.010000	1.000	1.000	
1304176001	13D	Grape, juice-babyfood	0.010000	1.000	1.000	
1304179000	13D	Grape, wine and sherry	0.010000	1.000	1.000	
1400003000	14	Almond	0.010000	1.000	1.000	
1400003001	14	Almond-babyfood	0.010000	1.000	1.000	
1400004000	14	Almond, oil	0.010000	1.000	1.000	
1400004001	14	Almond, oil-babyfood	0.010000	1.000	1.000	
1400059000	14	Brazil nut	0.010000	1.000	1.000	
1400068000	14	Butternut	0.010000	1.000	1.000	
1400081000	14	Cashew	0.010000	1.000	1.000	
1400092000	14	Chestnut	0.010000	1.000	1.000	
1400155000	14	Hazelnut	0.010000	1.000	1.000	
1400156000	14	Hazelnut, oil	0.010000	1.000	1.000	
1400185000	14	Hickory nut	0.010000	1.000	1.000	
1400213000	14	Macadamia nut	0.010000	1.000	1.000	
1400269000	14	Pecan	0.010000	1.000	1.000	
1400278000	14	Pine nut	0.010000	1.000	1.000	
1400282000	14	Pistachio	0.010000	1.000	1.000	
1400391000	14	Walnut	0.010000	1.000	1.000	
8601000000	86A	Water, direct, all sources	0.055600	1.000	1.000	
8602000000	86B	Water, indirect, all sources	0.055600	1.000	1.000	
9500177000	O	Grape, leaves	0.010000	1.000	1.000	
9500178000	O	Grape, raisin	0.010000	1.000	1.000	
9500362000	O	Sugarcane, sugar	0.010000	1.000	1.000	
9500362001	O	Sugarcane, sugar-babyfood	0.010000	1.000	1.000	
9500363000	O	Sugarcane, molasses	0.010000	1.000	1.000	
9500363001	O	Sugarcane, molasses-babyfood	0.010000	1.000	1.000	

Appendix C. 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 data are subject to ethics review pursuant to 40 CFR 26, have received that review, and are compliant with applicable ethics requirements. For certain studies that review may have included review by the Human Studies Review Board. Descriptions of data sources as well as guidance on their use can be found at: http://www.epa.gov/pesticides/science/handler-exposure-data.html and http://www.epa.gov/pesticides/science/post-app-exposure-data.html.

Appendix D. Occupational Non-cancer Handler Exposure Estimates and Algorithms.

Potential daily exposures for occupational handlers are calculated using the following formulas:

$$E = UE * AR * A * 0.001\ mg/ug$$

where:

E	=	exposure (mg ai/day),
UE	=	unit exposure (µg ai/lb ai),
AR	=	maximum application rate according to registered labels (lb ai/A), and
A	=	area treated or amount handled (e.g., A/day).

The daily doses are calculated using the following formula:

$$ADD = \frac{E * AF}{BW}$$

where:

ADD	=	average daily dose absorbed in a given scenario (mg ai/kg/day),
E	=	exposure (mg ai/day),
AF	=	absorption factor (inhalation), and
BW	=	body weight (kg).

Margin of Exposure: Non-cancer risk estimates for each application handler scenario are calculated using a Margin of Exposure (MOE), which is a ratio of the toxicological endpoint to the daily dose of concern. The daily inhalation dose received by occupational handlers is compared to the appropriate POD (i.e., NOAEL) to assess the risk to occupational handlers. All MOE values are calculated using the following formula:

$$MOE = \frac{POD}{ADD}$$

where:

MOE	=	margin of exposure: value used by HED to represent risk estimates (unitless),
POD	=	point of departure (mg/kg/day), and
ADD	=	average daily dose absorbed in a given scenario (mg ai/kg/day).

Appendix E. Nomenclature and Physical/Chemical Properties

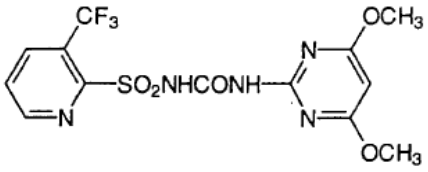
Table E.1. Flazasulfuron Nomenclature.	
Chemical Structure	
Empirical Formula	$C_{13}H_{12}F_3N_5O_5S$
Common Name	flazasulfuron
IUPAC Name	1-(4,6-dimethoxypyrimidin-2-yl)-3-(3-trifluoromethyl-2-pyridylsulfonyl)urea
CAS Name	*N*-[[(4,6-dimethoxy-2-pyrimidinyl)amino]carbonyl]-3-(trifluoromethyl)-2-pyridinesulfonamide
CAS Registry Number	104040-78-0
Chemical Class	Sulfonylurea herbicide

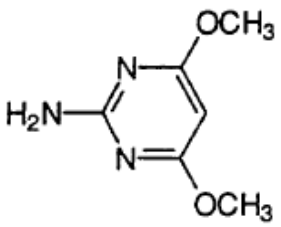
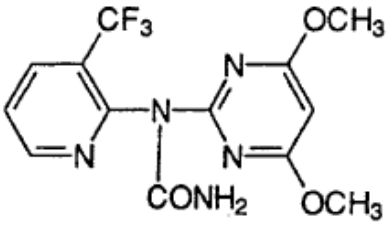
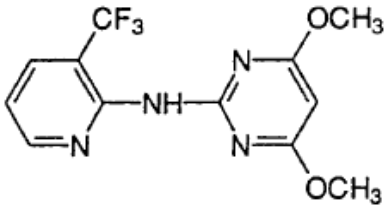
Table E.2. Chemical Names and Structures for Flazasulfuron Metabolites		
Common name/code	Chemical name	Chemical structure
ADMP	2-amino-4,6-dimethoxypyrimidine	
DTPU	*N*-(4,6-dimethoxy-2-pyrimidinyl)-*N*-[3-(trifluoromethyl)-2-pyridinyl]urea	
DTPP	4,6-dimethoxy-*N*-[3-(trifluoromethyl)-2-pyridinyl]-2-pyrimidinamine	

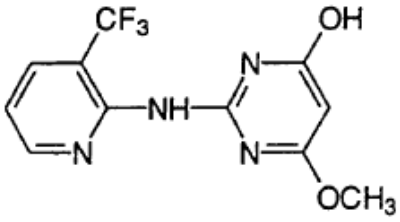
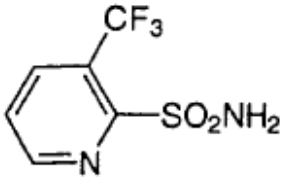
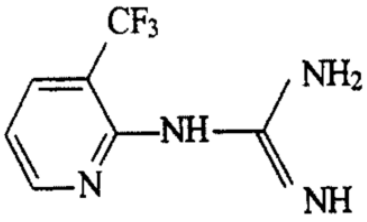
Table E.2. Chemical Names and Structures for Flazasulfuron Metabolites		
Common name/code	Chemical name	Chemical structure
HTPP	6-methoxy-2-[[3-(trifluoromethyl)-2-pyridinyl]amino]-4-pyrimidinol	
TPSA	3-(trifluoromethyl)-2-pyridinesulfonamide	
2,3-GTF	3-trifluoromethyl-2-pyridylguanidine	

Table E.3. Physical/Chemical Properties of Flazasulfuron.		
Parameter	**Value**	**Reference (MRID)**
Color	Cream	46220905
Physical State	Granular solid	
Odor	Strong lawn fertilizer	
Melting point	150°C	
pH	4.01 at 25°C (1% w/w)	
Density	0.66 g/cm^3 at 25°C (bulk density)	
Water solubility at 20°C	pH 5 buffer 0.027 mg/mL pH 7 buffer 2.1 mg/mL pH 9 buffer not stable	
Solvent solubility at 20°C	Acetone 22.7 mg/mL Acetonitrile 8.7 mg/mL Dichloromethane 22.1 mg/mL Ethyl acetate 6.9 mg/mL Hexanes* 0.50 µg/mL Methanol 4.2 mg/mL Octanol 0.20 mg/mL Toluene 0.56 mg/mL	
Vapor pressure	<1 x 10^{-7} mmHg (<1.33 x 10^{-5} Pa) at 25, 35, and 45°C	
Dissociation constant, pKa	4.37 at 20°C	
Octanol/water partition coefficient, Log(K_{OW})	K_{ow} = 20.0 in pH 5 buffer K_{ow} = <10 in pH 7 buffer	
UV/visible absorption spectrum	Not reported	

*n-hexane with various methylpentanes

Appendix F. International Harmonization

Flazasulfuron (119011; 4/06/2015)

Summary of US and International Tolerances and Maximum Residue Limits				
Residue Definition:				
US		Canada	Mexico[1]	Codex
40 CFR §180.655 Compliance with the tolerance levels specified below is to be determined by measuring only flazasulfuron (*N*-[[(4,6-dimethoxy-2-pyrimidinyl)amino]carbonyl]-3-(trifluoromethyl)-2-pyridinesulfonamide)		None		None
Commodity	*Tolerance (ppm) /Maximum Residue Limit (mg/kg)*			
	US	Canada	Mexico[2]	Codex
Almond, hulls	0.01			
Fruit, citrus, group 10-10	0.01			
Grape	0.01			
Nut, tree, group 14-12	0.01			
Sugarcane	0.01			
Completed: M. Negussie; 4/10/2015				

[1] Mexico adopts US tolerances and/or Codex MRLs for its export purposes.

Appendix G. DFR and TTR Data Waiver Rationales

Dislodgeable Foliar Residue (DFR): In accordance with 40 CFR §158, DFR data are required for all occupational (e.g., crop, nursery, greenhouse use sites) or residential (e.g., ornamental and vegetable gardens, pick your own farms, retail tree farms) uses that could result in post-application exposure to foliage. In the absence of chemical-specific DFR data, EPA uses default values. The 2012 Standard Operating Procedures for Residential Pesticide Exposure Assessment includes an analysis of a number of DFR studies, which resulted in the selection of revised default values for the fraction of the application rate available for transfer after a foliar application (FAR). These values are based on an analysis of 19 DFR studies. Since that time, the Agricultural Re-entry Task Force has submitted information (MRID 49299201) that corrects an application rate error made in the original submission of "ARF039 – Determination of Dermal and Inhalation Exposure to Reentry Workers During Chrysanthemum Pinching in a Greenhouse" (EPA MRID 45344501). As a result, the range of FAR values was revised from 2% - 89% to 2% - 47%. In the data, a large range of transferability is observed and this variability can potentially be attributable to many factors such as active ingredient, formulation, field conditions in the studies, weather conditions (e.g., humidity), or many other difficult to quantify factors. Although witnessed across multiple chemicals, this range in FAR values is not expected when considering DFR data for a single chemical. At this time, the ARTF submission did not alter the selection of 25% as the reasonable, high-end default value.

Since there was no dermal POD selected for flazasulfuron, an occupational post-application assessment is not required at this time. Therefore, no additional DFR data are required and the 40 CFR DFR data requirement is waived.

Turf Transferable Residue (TTR): In accordance with the updated Part 158 data requirements (2007), a TTR study is required for all occupational (e.g., sod farms, golf courses, parks, and recreational areas) or residential turf uses. As part of the recent revision to the *Health Effects Division's 2012 Standard Operating Procedures for Residential Pesticide Exposure Assessment*, HED analyzed all available data and selected new liquid and granular default values for the fraction of the application rate available for transfer after a turf application (F_{AR}).[5] These defaults are 1% for formulations applied as liquids (i.e., emulsifiable concentrates, liquids, wettable powders, dry flowables, etc.) and 0.2% for granular formulations. Of the available TTR studies submitted to the Agency, the maximum F_{AR} value seen using a liquid product was 6.1% or 6.1 times higher than the default residue transfer value. The maximum F_{AR} value seen in a TTR study using a granular product was 0.69% or 3.5X the default residue transfer value. Therefore, for both liquid and granular formulations, a calculated MOE of approximately 10 times higher than the level of concern (e.g., an MOE > 1,000 if the LOC = 100) using the default residue transfer values would provide an adequate margin of safety for any potentially higher residues seen in a chemical-specific TTR study (*Guidance for Requiring/Waiving Turf Transferrable Residue (TTR) and Dislodgeable Foliar Residue (DFR) Studies*. 6/7/2012, Exposure Science Advisory Council). A TTR study is not required for flazasulfuron at this time

[5] http://www.epa.gov/pesticides/science/residential-exposure-sop.html

since there was no dermal hazard identified and hand-to-mouth MOE is greater than 1,000 based on default values for the fraction of application rate available for transfer after a turf application.

Appendix H. Estimated Dermal Absorption Factors (DAF)

Table H. Structure-Activity Relationship (SAR) Data for Sulfonylureas Technical Formulations with Available Experimental or Estimated Dermal Absorption Factors (DAF)

Chemical	MW	Log Kow[1]	DAF	DAF Basis/Dermal Penetration
Bensulfuron-methyl	410.4	0.79	4.7%	Unpublished *in vivo* rat study not submitted to EPA (DuPont HLR 120-90[2]).
Chlorimuron-ethyl	414.8	2.50	4.8%	Dermal NOAEL / oral LOAEL extrapolation[3]
Flazasulfuron	407.3	1.08	20%	Estimated maximum per SAR analysis (Log Kp = -4.46) based on tribenuron-methyl (Log Kp = -4.51, DAF = 17.7%).
Iodosulfuron-methyl-sodium	529.2	-0.70	11%	1-6% per *in vivo* rat study; however 11% used because data indicates absorption continues after exposure.
Mesosulfuron-methyl	503.6	-0.48	NA	An unacceptable/guideline rat *in vivo* study indicates 11.9-26.3%. European document indicates 9% (SANCO/1 0298/2003-final[2]).
Nicosulfuron	410.4	-1.74	0.021-0.23%	Unpublished *in vitro* human studies not submitted to EPA (DuPont 21540 and 25519[2]).
Oxasulfuron	406.4	-0.81	1%	Unpublished *in vitro* rat and human, and *in vivo* rat studies not submitted to EPA (EC SANC0/4323/2002[2]).
Primisulfuron	468.3	1.15 (pH 5.0)	30%	Dermal NOAEL / oral LOAEL extrapolation[3]
Rimsulfuron	431.4	-1.46	20%	Estimated maximum per SAR analysis (Log Kp = -6.41) based on iodosulfuron (Kow = -6.24, DAF = 11%). 0.18-0.4% per unpublished *in vitro* human skin not submitted to EPA (DuPont 24335, 25519 and 24600[2]).
Tribenuron-methyl	395.4	0.78	17.7%	Per *in vivo* rat study
Trifloxysulfuron-sodium	459.3	-0.42	30%	Dermal NOAEL / oral LOAEL extrapolation[3]
Tritosulfuron	445.3	0.62	1%	Unpublished *in vitro* rat and human, and *in vivo* rat studies not submitted to EPA (EC SANC0/1256/08-rev.1[2]).

[1] Log Kow measured at pH=7 unless otherwise indicated.

[2] Concentrate chemical data excerpted in a DuPont submission, MRID 48904001. That document also has some dilute formulation DAFs, which were not considered here.

[3] Calculated by dividing the dermal study NOAEL (when no LOAEL was observed) by a subchronic oral LOAEL. Because no dermal toxicity was observed, this will lead to an artificially high DAF.