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

OFFICE OF
CHEMICAL SAFETY AND
POLLUTION PREVENTION

MEMORANDUM

DATE: 24-JUN-2014

SUBJECT: **Saflufenacil.** Human-Health Risk Assessment in Support of Tolerances for Residues in/on Barley, Wheat, Grass, and Olives.

PC Code: 118203	**DP Barcode:** D418587
Decision Nos.: 480698, 481309, & 486544	**Registration Nos.:** 7969-275, 7969-276, & 7969-278
Petition Nos.: 3F8185, 3F8192, & 4F8229	**Regulatory Action:** Sec. 3 Registration
Risk Assessment Type: Single Chemical/ Aggregate	**Case No.:** 7277
TXR No.: NA	**CAS No.:** 372137-35-4
MRID No.: NA	**40 CFR:** §180.649

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The HED of the Office of Pesticide Programs (OPP) is charged with estimating the risk to human health from exposure to pesticides. The RD of OPP has requested that HED evaluate hazard and exposure data and conduct dietary, occupational, residential, and aggregate exposure assessments, as needed, to estimate the risk to human health that will result from the proposed tolerances for residues in/on barley, wheat, grass, and olives. The petitioner is BASF.

A summary of the findings and an assessment of human-health risk resulting from the proposed/registered uses of saflufenacil are provided in this document. The risk assessment, residue chemistry, and dietary exposure assessment were provided by George Kramer (RAB1), the hazard characterization by Chester Rodriguez (RAB1), the occupational/residential exposure assessment by Kelly Lowe (RAB1), and the drinking water assessment by Mohammed Ruhman of the Environmental Fate and Effects Division (EFED).

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1.0 Executive Summary

Saflufenacil (BAS 800 H) is a broad-spectrum herbicide developed by BASF. It belongs to the herbicide mode-of-action Group 14 (cell membrane disruptors). Saflufenacil acts through the inhibition of protoporphyrinogen oxidase (PPO), resulting in cell membrane damage and subsequent plant death. BASF has submitted a proposal to amend the established tolerances for saflufenacil on wheat and barley (PP#3F8185). The amended tolerances on these crops are the result of the proposed harvest-aid/desiccation use pattern for Sharpen® Powered by Kixor® Herbicide (EPA Reg. No. 7969-278 2.85 lb ai/gal; suspension concentrate (SC)); the currently registered uses are for preplant application. In addition, BASF has submitted a proposal for a new use of Sharpen® Powered by Kixor® Herbicide and Heat® Powered by Kixor® Herbicide (EPA Reg. No. 7969-297; 2.85lb ai/gal; SC) on grass group 17 as harvest aid/desiccant (PP#3F8192) and for a new use of Treevix® Powered by Kixor® Herbicide (EPA Reg. No. 7969-276; 30%; water-dispersible granule (WG)) to the base of olive trees (PP#4F8229).

Hazard Assessment: Saflufenacil was well absorbed and rapidly excreted via the oral route in rat metabolism studies. Maximum blood concentrations were reached within one hour and declined rapidly thereafter. Elimination was primarily urinary in female rats and via the feces in male rats. The sex-dependent excretion resulted in male rats having up to 3X higher internal levels and being, in some cases, more sensitive to toxicity than females.

Saflufenacil exhibited low acute toxicity via the oral, dermal, and inhalation routes of exposure (Toxicity Category III or IV). It was slightly irritating to the eye (Toxicity Category III), but was not a dermal irritant or a dermal sensitizer.

Subchronic and chronic toxicity studies in rats, mice, and dogs identified the hematopoietic system as the primary target of saflufenacil. Consistent with its proposed mode of toxicity involving PPO inhibition and subsequent disruption of heme biosynthesis, decreased hematological parameters [red blood cells (RBC), hematocrit (Ht), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC)] were seen at about the same dose level [lowest-observed adverse-effect levels (LOAELs) of 13-39 mg/kg/day] across species, except in the case of the dog, where the effects were seen at a slightly higher dose (LOAELs of 50-100 mg/kg/day). These effects occurred around the same dose level from short- through long-term exposures without increasing in severity. Effects were also seen in the liver (increased weight, centrilobular fatty change, lymphoid infiltrate) in mice, the spleen (increased spleen weight and extramedullary hematopoiesis) in rats, and in both of these organs (increased iron storage in the liver and extramedullary hematopoiesis in the spleen) in dogs. These effects also occurred around the same dose level from short- through long-term exposures without increasing in severity.

Increased fetal susceptibility was observed in the developmental toxicity studies in the rat and rabbit and in the two-generation reproduction study in the rat. Developmental effects (decreased fetal body weights and increased skeletal variations in rats and increased liver porphyrins in rabbits) occurred at doses that were not maternally toxic in the developmental studies, indicating increased quantitative susceptibility. In the two-generation reproductive toxicity study in rats, the reported offspring effects were more severe than the maternal effects at the same dose level, indicating evidence for increased qualitative susceptibility. An increased number of stillborn pups, decreased viability and lactation indices, decreased pre-weaning body weight, and changes

in hematological parameters occurred at the same dose level as maternal decrements in food intake, body weight, and changes in hematological parameters and organ weights indicative of anemia.

Saflufenacil was weakly clastogenic in the *in vitro* chromosomal aberration assay in V79 cells in the presence of S9 activation; however, the response was not evident in the absence of S9 activation. It was neither mutagenic in bacterial cells nor clastogenic in rodents *in vivo.* Carcinogenicity studies in rats and mice showed no evidence of increased incidence of tumors at the tested doses. Saflufenacil is classified as "not likely carcinogenic to humans."

Saflufenacil displayed no evidence of neurotoxicity in acute and subchronic neurotoxicity studies, did not produce any dermal or systemic effects in a 28-day dermal toxicity study, and failed to induce toxicity specific to the immune system in a recently submitted immunotoxicity study.

Dose-Response and Food Quality Protection Act (FQPA) Assessments: The RAB1 risk assessment team for saflufenacil determined that the FQPA Safety Factor (SF) should be reduced to 1X for all exposure scenarios for the following reasons (see Section 4.4 for a full discussion): the toxicological database is adequate for FQPA assessment, there is no evidence of neurotoxicity, there is low concern for offspring susceptibility, and there is no uncertainty in the exposure database.

A 100X uncertainty factor (UF) (10X for interspecies extrapolation and 10X for intraspecies variation) was incorporated into the acute reference dose (aRfD, 5.0 mg/kg) and chronic RfD (cRfD, 0.046 mg/kg/day). The acute population-adjusted dose (aPAD) and the chronic population-adjusted dose (cPAD) are equal to the acute and chronic RfDs, respectively, divided by the FQPA SF (1X). Saflufenacil is classified as "not likely carcinogenic to humans" by all relevant routes of exposure based on adequate studies in two animal species; therefore, cancer risk assessments are not required. In estimating margins of exposure (MOEs), the level of concern (LOC) is for MOEs $\leq$100 for the dermal and inhalation risk assessments. A 6% dermal-absorption factor (DAF) and a 100% inhalation-absorption factor were used in route-to-route extrapolations.

Food Residue Profile: The nature of the residue is adequately understood in the subject crops. Organization for Economic Co-operation and Development (OECD) tolerance-calculation procedures and the submitted residue data sets were used to calculate the HED-recommended tolerances. There are no residue chemistry issues that would preclude establishing permanent tolerances for residues of saflufenacil, as outlined in Table 2.2.2.

Exposure/Risk Assessment Characterization: Acute and chronic dietary risk assessments were conducted using the Dietary Exposure Evaluation Model - Food Consumption Intake Database (DEEM-FCID, ver. 3.16) which incorporates consumption data from the United States Department of Agriculture (USDA) National Health and Nutrition Examination Survey, What We Eat in America, (NHANES/WWEIA; 2003-2008). The acute and chronic analyses assumed 100% crop treated (CT), DEEM 7.81 default processing factors, and tolerance-level or tolerance-level residues adjusted to account for the residues of concern for risk assessment for all foods. Drinking water was incorporated directly into the dietary assessments using the concentration for surface water generated by Tier I Rice modeling. The resulting acute dietary (food + drinking

water) risk estimates using the DEEM-FCID model at the 95th percentile [<1% aPAD for all infants (<1-year old), the most highly exposed population subgroup] are not of concern (<100% aPAD). The chronic dietary risk assessment shows that the chronic dietary risk estimates are not of concern (i.e., <100% cPAD). The chronic dietary risk estimate for the highest exposed population subgroup, all infants (<1-year old), is 20% of the cPAD.

There are no residential uses proposed or currently registered for saflufenacil. Therefore, a residential risk assessment was not conducted.

Since there are no residential exposures expected from the proposed or registered saflufenacil uses, the aggregate exposure assessment takes into consideration dietary food + drinking water exposure only. The acute and chronic dietary estimates represent acute and chronic aggregate risk, respectively.

There is potential for occupational handler short- and intermediate-term exposure resulting from the proposed uses of saflufenacil. Potential occupational handler exposure scenarios include mixing/loading liquids for aerial and ground applications, applications via aerial and ground equipment, and flagging. The occupational handler exposure and risk estimates indicate that the short- and intermediate-term dermal and inhalation combined MOEs are not of concern to HED (i.e., MOE $\geq$ 100). At the baseline level of personal protection (i.e., no gloves and no respirator), all scenarios result in combined MOEs (dermal + inhalation) $\geq$ 250.

The occupational post-application dermal exposure and risk estimates are greater than the LOC of 100 on the day of application, ranging from 3,000 to 5,200 depending on crop and activity. Since the post-application assessment is not a concern on Day 0 (12 hours following application), the restricted-entry interval (REI) is based on the acute toxicity of saflufenacil technical material. Saflufenacil is classified as Toxicity Category III for acute oral, acute dermal toxicity, and acute eye irritation. It is classified as Toxicity Category IV for acute inhalation toxicity and acute dermal irritation. It is not a dermal sensitizer. Therefore, the acute toxicity categories for this chemical require a 12-hour REI under 40 CFR §156.208 (c) (2) (iii). The 12-hour REI, which currently appears on the labels, is adequate for the proposed uses.

Based on the Agency's current practices, a quantitative non-cancer occupational post-application inhalation exposure assessment was not performed for saflufenacil 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 saflufenacil.

This risk assessment relies in part on data from studies in which adult human subjects were intentionally exposed to a pesticide or other chemical. Please refer to Appendix C for a discussion of the human study data used in this risk assessment.

2.0 HED Recommendations

Pending submission of revised Section Fs, there are no other residue chemistry, occupational, or toxicology data deficiencies that would preclude the establishment of permanent tolerances for residues of saflufenacil and it metabolites and degradates as outlined in Table 2.2.2.

2.1 Data Deficiencies

860.1550 Proposed Tolerances (PP#s 3F8185 & 3F8192)

- The petitioner is requested to submit revised Section Fs specifying revised tolerances, as presented in Table 2.2.2.

2.2 Tolerance Considerations

2.2.1 Enforcement Analytical Method

The petitioner has submitted two liquid chromatography/mass spectroscopy/mass spectroscopy (LC-MS/MS) analytical methods for the determination of residues of the parent and its metabolites in/on plant and livestock commodities. BASF Method D0603/02 was developed for determination of residues of saflufenacil and its metabolites M800H11 and M800H35 in different plant matrices using LC-MS/MS. The limit of quantitation (LOQ) was 0.01 ppm for each analyte in food matrices and 0.025 ppm for each analyte in feed matrices. BASF analytical Method No. L0073/01 was developed for determination of saflufenacil in livestock matrices using LC-MS/MS. The LOQ was 0.01 ppm in all matrices. These methods were used as the data-collection methods in the analysis of samples for residues of concern from the various studies associated with the current petitions. Each method has been adequately validated by the petitioner as well as by independent laboratories and were adequately radiovalidated using weathered samples obtained from metabolism studies.

HED has determined that Methods D0603/02 and L0073/01 are suitable enforcement methods for the plant and livestock commodities associated with this petition, respectively, as defined in SOP No. ACB-019 (9/15/08).

2.2.2 Recommended Tolerances

The proposed uses and the submitted data support the following permanent tolerances for residues of saflufenacil in or on the commodities summarized in Table 2.2.2.

Table 2.2.2. Tolerance Summary for Saflufenacil.

Commodity	Proposed Tolerance (ppm)	HED-Recommended Tolerance (ppm)	Correct Commodity Definition/Comments
PP#3F8185			
Barley, bran	1.53	1.5	
Barley, grain	1	1.0	
Barley, straw	15	15	
Grain, aspirated fractions	-	50	Grain, aspirated grain fractions
Grain, cereal group 15 (except barley and wheat grain)	0.03	0.03	
Grain, cereal, forage, fodder and straw group 16 (except barley, wheat and rice straw)	0.10	0.10	Grain, cereal, forage, fodder and straw group 16 (except barley and wheat straw)
Wheat, grain	0.6	0.60	
Wheat, straw	6	6.0	

Table 2.2.2. Tolerance Summary for Saflufenacil.			
Commodity	Proposed Tolerance (ppm)	HED-Recommended Tolerance (ppm)	Correct Commodity Definition/Comments
PP#3F8192			
Grass forage	15	15	
Grass hay	20	20	
Grass seed screenings	0.9	0.15	
Grass straw	1.5	0.15	
Cattle, fat	0.05	0.04	
Cattle, liver	45	50	
Cattle, meat byproducts, except liver	0.5	0.30	
Cattle, meat	-	0.02	
Goat, fat	0.05	0.04	
Goat, liver	45	50	
Goat, meat byproducts, except liver	0.5	0.30	
Goat, meat	-	0.02	
Sheep, fat	0.05	0.04	
Sheep, liver	45	50	
Sheep, meat byproducts, except liver	0.5	0.30	
Sheep, meat	-	0.02	
Horse, fat	0.05	0.04	
Horse, liver	45	50	
Horse, meat byproducts, except liver	0.5	0.30	
Horse, meat	-	0.02	
Hog, fat	0.05	0.01	0.01 ppm is the currently established value
Hog, liver	45	2.0	
Hog, meat byproducts, except liver	0.5	0.02	0.02 ppm is the currently established value
PP#4F8229			
Olive	0.03	0.03	

2.2.3 Revisions to Petitioned-For Tolerances

HED is recommending for the following revisions to the petitioned-for tolerances: 1) the value for barley bran should be rounded to 1.5 ppm; 2) the commodity definition "Grain, cereal, forage, fodder, and straw group 16 (except barley, wheat and rice straw)" should be revised to "Grain, cereal, forage, fodder and straw group 16 (except barley and wheat straw)" as rice straw is not a significant livestock feed item; 3) the HED-recommended values for grass straw and seed screenings are lower because the petitioner included data from trials in which the samples were harvested at a significantly shorter preharvest interval (PHI) than that allowed on the label; 4) the existing tolerance of 10 ppm for residues in/on grain, aspirated fractions should be increased to 50 ppm; and 5) the recommended tolerances for residues in livestock, calculated by HED based on the maximum reasonably balanced diets (MRBDs) and the results of the ruminant feeding study, differ from the petitioned-for tolerances, especially in hog commodities (where the petitioner over-estimated residues as a result of using the cattle MRDB).

2.2.4 International Harmonization

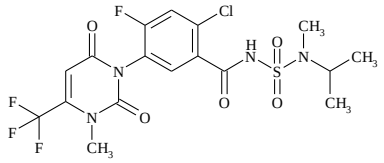
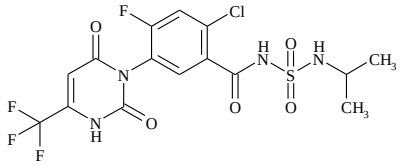
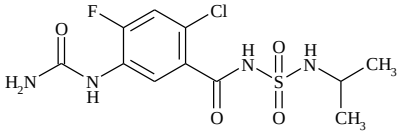
There are Codex maximum residue limits (MRLs) established for residues of saflufenacil *per se* in wheat and barley (as members of the cereal grain crop group) grain, straw, and fodder; and livestock commodities. Canadian MRLs are established for residues of saflufenacil and its metabolites in/on wheat and barley grain (as members of the cereal grain crop group) and for residues of saflufenacil *per se* in/on livestock commodities. Harmonization is not possible as the U.S. use pattern (harvest-aide/burndown application) results in significantly higher residues than the Codex/Canadian use pattern (pre-emergence application). In addition, the U.S. and Canadian residue definition for crops contains additional metabolites not included in the Codex residue definition.

2.3 Label Recommendations

None

3.0 Introduction

3.1 Chemical Identity

TABLE 3.1. Saflufenacil Nomenclature.	
Chemical Structure	
Common name	Saflufenacil
Company experimental name	BAS 800 H (synonyms: AC 433 379, BASF Reg. No. 4054449)
IUPAC name	*N*'-[2-chloro-4-fluoro-5-(3-methyl-2,6-dioxo-4-(trifluoromethyl)-3,6-dihydro-1(2*H*)-pyrimidinyl)benzoyl]-*N*-isopropyl-*N*-methylsulfamide
CAS name	2-chloro-5-[3,6-dihydro-3-methyl-2,6-dioxo-4-(trifluoromethyl)-1(2*H*)-pyrimidinyl]-4-fluoro-*N*-[[methyl(1-methylethyl)amino]sulfonyl]benzamide
CAS registry number	372137-35-4
End-use product (EP)	BAS 800 04 H (342 g ai/L SC formulation)
Chemical Structure	
Common name	M800H11
Chemical name	*N*-[2-chloro-5-(2,6-dioxo-4-(trifluoromethyl)-3,6-dihydro-1(2*H*)-pyrimidinyl)-4-fluorobenzoyl]-*N*'-isopropylsulfamide
Chemical Structure	
Common name	M800H35
Chemical name	*N*-[4-chloro-2-fluoro-5-({[(isopropylamino)sulfonyl]amino}carbonyl)phenyl]urea

3.2 Physical/Chemical Characteristics

Saflufenacil is a broad-spectrum herbicide developed by BASF. It belongs to the herbicide mode-of-action Group 14 (cell membrane disruptors). Saflufenacil acts through the inhibition of PPO, resulting in cell membrane damage and subsequent plant death. Saflufenacil is a uracil herbicide that is expected to be mobile to highly mobile. Its major routes of degradation are alkaline hydrolysis and biodegradation in aerobic soil. The compound is expected to degrade with a half-life of 1 to 5 weeks in aerobic soil environments and a half-life of 7 to 15 weeks (2 to 4 months) in aerobic aquatic environments. Its vapor pressure is 4.5×10^{-15} Pa at 20 ºC. Because it is a low-volatile herbicide, saflufenacil could be less prone to atmospheric transport than more-volatile herbicides. A summary of the physicochemical properties can be found in Appendix B.

3.3 Pesticide Use Pattern

BASF has submitted draft labels for Sharpen® Powered by Kixor® Herbicide (EPA Reg. No. 7969-278), Heat® Powered by Kixor® Herbicide (EPA Reg. No. 7969-297), and Treevix® Powered by Kixor® Herbicide (EPA Reg. No. 7969-276). A summary of the proposed use patterns is detailed in Table 3.3.1.

Table 4. Summary of Directions for Use of Saflufenacil.

Applic. Timing, Type, and Equip.	EPA Reg. No.	Max Single App. Rate (lb ai/A)	Max. # Apps per year	Max Seasonal App. Rate (lb ai/A)	RTI (days)	PHI (days)	Use Directions and Limitations
Barley, Wheat, and Triticale (PP# 3F8185)							
Harvest aid/ Desiccation	7969-278	2 fl. oz./A (0.045 lbs. ai/A)	2 per crop season	2 fl. oz./A (0.045 lbs. ai/A)	NS	3	-A single app. of 2.0 fl. oz./A or sequential apps. of 1.0 fl. oz./A may be made, but do not exceed 2.0 fl. oz./A in a cropping season from desiccation uses. -MSO plus ammonium-based adjuvant are required for optimum desiccation activity. -Make GROUND application at a minimum spray volume of 10 gallons per acre. -Make Aerial application at a min. spray volume of 5 gallons per acre.
Grass Grown for Pasture & Rangeland (forage, silage and hay) (PP# 3F8192)							
Broadcast **burndown** apps. to **established** stands during **dormant period.** For cool and warm-season grasses	7969-278 7969-297	4 fl. oz./A (0.090 lbs. ai/A)	2 per dormant season	4 fl. oz./A (0.090 lbs. ai/A)	14	N/A	-Apply 1.0 to 2.0 fl. oz./A as a broadcast burndown spray to emerged weeds in the dormant season. -MSO plus AMS is required.
In-season growing period postemergence broadcast burn-down apps. to **established cool-season**	7969-278 7969-297	2 fl. oz./A (0.045 lb ai/A)	2 per In-season	2 fl. oz./A (0.045 lb ai/A)	14	0	-Apply 1.0 to 2.0 fl. oz./A as a broadcast burndown spray to emerged weeds in growing season (Spring after greenup and before weeds reach max. size). -MSO at 1% v/v is required.

Table 4. Summary of Directions for Use of Saflufenacil.							
Applic. Timing, Type, and Equip.	EPA Reg. No.	Max Single App. Rate (lb ai/A)	Max. # Apps per year	Max Seasonal App. Rate (lb ai/A)	RTI (days)	PHI (days)	Use Directions and Limitations
grass							
In-season growing period postemergence broadcast burndown apps. to **established warm-season grasses**	7969-278 7969-297	2 fl. oz./A (0.045 lb ai/A) (except Bermudagrass is just 1 fl. oz./A)	2 per In-season (except Bermudagrass is just 1 app/in-season	2 fl. oz./A (0.045 lb ai/A) (except Bermudagrass is just 1 fl. oz./A)	14	0	-Apply 1.0 to 2.0 fl. oz./A as a broadcast burndown spray to emerged weeds in growing season (Spring after greenup and before weeds reach max. size). -DO NOT exceed 1 fl. oz./A for in-season apps to forage Bermudagrass. -MSO at 1% v/v.
Split program for established stands of warm and cool-season grasses	7969-278 7969-297	Split program (dormant + in-season) apps. may be made, but do not exceed the maximum cumulative amount of **6.0 fl. oz./A (0.134 lb ai) per crop season** (up to 4.0 fl. oz./A/dormant period and 2.0 fl. oz./A/in-season). -All sequential applications must be separated by 14 days. -DO NOT apply to mixed stands containing forage legumes or other desirable broadleaf species (including alfalfa & clover). -DO NOT apply to stands containing annual forage species (e.g., forage sorghum, Sudangrass).					
Grasses Grown for Seed (PP# 3F8192)							
Broadcast **burndown** apps. in **newly planted** grass stands grown for seed	7969-278	2.0 fl. oz./A (0.045 lb ai/A)	2	2.0 fl. oz./A (0.045 lb ai/A)	14	50	-Apply to new seedling grass fields after the first tiller is established in cool-season grasses and after the first rhizome or stolon is established in warm-season grasses. -Burndown applications require an adjuvant system (MSO at 1% v/v).
Broadcast **postemergence** apps. in **established** grass stands grown for seed	7969-278	2.0 fl. oz./A (0.045 lb ai/A)	2	2.0 fl. oz./A (0.045 lb ai/A)	14	50	-Apply postemergence apps to established grass fields any time after spring greenup to 1 week before boot stage. -Postemergent applications require an adjuvant system (MSO at 1% v/v).
Dormant apps. in **established** grass seed stands	7969-278	4.0 fl. oz./A (0.090 lb ai/A)	2	4.0 fl. oz./A (0.090 lb ai/A)	NS	50	-Apply to established grass seed stands in the dormant season. -Sequential app. may be made for residual control in the dormant season. -An adjuvant system is required for optimum burndown activity.
-DO NOT apply more than a **max. cumulative amount of 6.0 fl. oz./A per cropping season on established** grass seed stands. -DO NOT apply more than a **max. cumulative amount of 4.0 fl. oz./A per cropping season on seedling** grass seed stands. -Treated forage and hay may be grazed and/or fed to livestock- no pre-harvest or pre-grazing interval. -Treated grass straw remaining after seed harvest may be used as livestock bedding and/or grazed/fed to livestock. -Grass seed screenings in treated fields may be fed to livestock.							
Pre-emergence Broadleaf Weed Control in newly planted Cool-Season Grass Stands [forage & seed production] (PP# 3F8192)							
Preplant, preplant incorporated, or preemergence in the fall or spring while establishing **new stands** of **cool-season grasses**	7969-278	4.0 fl. oz./A (0.090 lb ai/A)	2	6.0 fl. oz./A (0.134 lb ai/A)	NS	0	-Apply as a broadcast spray to the soil surface before grasses emerge. If burndown of established weeds is desired, add an adjuvant system. -Sequential/Split apps can be made, but not to exceed a max. cumulative amount of 6.0 fl. oz./A/cropping season (preplant/in-season). -No preharvest or pregrazing interval for forage and hay.

Table 4. Summary of Directions for Use of Saflufenacil.							
Applic. Timing, Type, and Equip.	EPA Reg. No.	Max Single App. Rate (lb ai/A)	Max. # Apps per year	Max Seasonal App. Rate (lb ai/A)	RTI (days)	PHI (days)	Use Directions and Limitations
Olive Trees (PP#4F8229)							
Post, Directed to Orchard Floor	7969-276	1.0 fl. oz./A (0.044 lb ai/A)	3	3.0 fl. oz./A (0.132 lb ai/A)	21	0	A fourth application during dormancy is permitted.

NS = not specified; PHI = preharvest interval; RTI = retreatment interval; AMS = ammonium sulfate; MSO = methylated seed oil.

Conclusions: The proposed use patterns are adequate to allow evaluation of the residue data submitted in support of these petitions.

3.4 Anticipated Exposure Pathways

RD has requested that HED evaluate hazard and exposure data and conduct dietary, occupational, residential, and aggregate exposure assessments, as needed, to estimate the risk to human health that will result from the tolerance petitions for residues in/on barley, wheat, grass, and olives. Humans may be exposed to saflufenacil in food and drinking water, since saflufenacil may be applied directly to growing crops and application may result in saflufenacil reaching surface and ground water sources of drinking water. There are no residential uses of saflufenacil, so exposure in residential or non-occupational settings is not likely. In an occupational setting, applicators may be exposed while handling the pesticide prior to application, as well as during application. There is also a potential for post-application exposure for workers re-entering treated fields.

This risk assessment considers all of the aforementioned exposure pathways based on the proposed new uses of saflufenacil and considers the existing registered uses as well for the dietary and residential exposure assessments.

3.5 Consideration of Environmental Justice

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://epa.gov/compliance/ej/resources/policy/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 U.S. Department of Agriculture (USDA) under the National Health and Nutrition Examination Survey, What We Eat in America, (NHANES/WWEIA; 2003-2008) 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. 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 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.

4.0 Hazard Characterization and Dose-Response Assessment

Saflufenacil is a pre- and post-emergence herbicide that acts by inhibiting the enzyme PPO, leading to disruption of chlorophyll biosynthesis, and ultimately bleaching of emerging foliar tissue. PPO is a key enzyme in porphyrin biosynthesis for the production of chlorophyll in plants and heme in mammals. When PPO is inhibited in mammals, hemoglobin biosynthesis is reduced, resulting in anemia and accumulation of different porphyrins and their precursors in various organs.

4.1 Toxicology Studies Available for Analysis

The toxicology database for saflufenacil is complete and adequate for hazard characterization, toxicity endpoint selection, and FQPA SF evaluation. In previous risk assessments (Kramer *et al*., DP# 384602; 04-AUG-2011) and in the current assessment, an oral toxicity study is used for the inhalation endpoint. The HED Hazard and Science Policy Council (HASPOC) concluded, based on a weight-of-evidence approach, that a 28-day inhalation toxicity study is not required at this time (A. Dunbar, 02-AUG-2013; TXR #0056720).

4.2 Absorption, Distribution, Metabolism, and Excretion (ADME)

In rat metabolism/pharmacokinetic studies via the oral route, radiolabeled saflufenacil was well absorbed and rapidly excreted. Following a single dose and regardless of the dose administered, maximum blood concentrations were reached within 1 hour of dosing and declined rapidly thereafter. Excretion of saflufenacil was essentially complete within 96 hours, with the majority eliminated within the first 24-48 hours. The blood and plasma data demonstrated that the majority of the saflufenacil residues occurred in the plasma and were not bound to cellular elements of the blood such as red blood cells. Following single or repeated low- and high-dose administration, the main route of elimination in male rats was via the feces, whereas urinary excretion was the major route of elimination in females. There was significantly higher biliary excretion of saflufenacil residues in males than in females. This sex-dependent difference in excretion was more pronounced at the low-dose level and resulted in males having up to 3X higher internal exposures than females as measured by the plasma area under the concentration-time curve (AUC). Increasing the administered dose by a factor of 25 resulted in less than proportional increases in plasma AUC values at 6.1 in males and 12.4 in females. Saflufenacil residues remained very low in tissues at 168 hours after dosing, occurring mainly in carcass, liver, skin, and gut contents.

4.2.1 Dermal Absorption

A DAF of 6% was estimated for saflufenacil based on the highest degree of skin penetration at the lowest dose tested in a rat dermal absorption study. Immediately after a 10-hour exposure, the estimated DAF was 3.4%. However, about 50% of the radioactivity remaining at the end of exposure penetrated through the skin during a 120-hour (5-day) observational period, indicating

that skin-bound residues of saflufenacil are available for dermal absorption. With skin-bound residues included, a DAF of 6% should be applied for converting oral doses to dermal equivalent doses to assess the potential risk associated with dermal exposures to saflufenacil.

4.3 Toxicological Effects

4.3.1 Summary of Toxicological Effects

The effects observed following repeated oral exposures to saflufenacil are consistent with the proposed mode of toxicity involving inhibition of PPO in mammals, resulting in disruption of heme biosynthesis. Toxicological effects from subchronic and chronic toxicity studies in rats, mice and dogs consisted of decreased hematological parameters (RBC, Ht, MCV, MCH, and MCHC) at approximately the same dose level (13-39 mg/kg/day), except in the case of the dog, where the effects were seen at a slightly higher dose (50-100 mg/kg/day). In line with the ADME findings suggesting that male rats achieve a greater systemic exposure than females, males were the most sensitive sex in mice and rats, with LOAELs approximately 3-4X lower than their female counterparts. The hematological effects resulting from oral exposures to saflufenacil occurred around the same dose level from short- through long-term exposures without increasing in severity. Toxic effects were also seen in the liver (increased organ weight, centrilobular fatty change, lymphoid infiltrate) in mice, the spleen (increased organ weight and extramedullary hematopoiesis) in rats, and in both of these organs (increased iron storage in the liver and extramedullary hematopoiesis in the spleen) in dogs. These effects also occurred around the same dose level from short- through long-term exposures without a progression in severity.

Evidence for increased pre- and/or postnatal susceptibility was noted from the developmental toxicity studies in the rat and rabbit and in the two-generation reproduction study in the rat. Decreased fetal body weights and increased skeletal variations occurred at doses (20 mg/kg/day) that were not maternally toxic in the developmental study in rats. Similarly, in rabbits, increased liver porphyrins in fetuses were observed at doses (200 mg/kg/day) that were not maternally toxic. In the two-generation reproductive toxicity study in rats, there was evidence of increased qualitative susceptibility based on an increased number of stillborn pups, decreased pup viability and lactation indices, decreased pre-weaning body weight and/or body-weight gain, and changes in hematological parameters at the same dose level as less severe maternal effects consisting of decrements in food intake, body weight, body-weight gain, and changes in organ weights and hematological parameters indicative of anemia.

In an acute neurotoxicity (ACN) study in rats, a decrease in motor activity was observed on the day of dosing at the limit dose (2000 mg/kg/day) in males only. However, the finding was not accompanied by any neuropathological changes and was considered a reflection of a mild and transient general systemic toxicity and not a substance-specific neurotoxic effect. In the subchronic neurotoxicity (SCN) study, systemic toxicity (anemia) was seen at 1000 ppm (66.2 mg/kg/day) and 1350 ppm (101 mg/kg/day) in males and females, respectively. There was no evidence of neurotoxicity or neuropathology in either the acute or subchronic neurotoxicity study.

In a 28-day dermal toxicity study in rats, saflufenacil did not induce any type of dermal or systemic toxicity up to the limit dose of 1000 mg/kg bw/day.

Based on the results of acute toxicity studies, saflufenacil was ranked low for acute toxicity (Toxicity Category III or IV) via the oral, dermal, and inhalation route of exposure. It was not classified as a dermal irritant or dermal sensitizer.

In a 28-day immunotoxicity study in mice, saflufenacil failed to induce toxicity specific to the immune system at the highest dose tested (i.e., 52 mg/kg bw/day).

Saflufenacil was weakly clastogenic in the *in vitro* chromosomal aberration assay in V79 cells in the presence of S9 activation; however, the response was not evident in the absence of S9 activation. It was neither mutagenic in bacterial cells nor clastogenic in rodents *in vivo.* Carcinogenicity studies in rats and mice showed no evidence of increased incidence of tumors at the tested doses. Saflufenacil is classified as "not likely carcinogenic to humans."

4.4 Safety Factor for Infants and Children (FQPA SF)

The saflufenacil risk assessment team recommends that the FQPA SF be reduced to 1X for all exposure scenarios based on the following rationale: the toxicological database is adequate for FQPA assessment, there is no evidence of neurotoxicity, there is low concern for offspring susceptibility, and there is no uncertainty in the exposure database.

4.4.1 Completeness of the Toxicology Database

The toxicology database for saflufenacil is complete and adequate for FQPA SF consideration.

4.4.2 Evidence of Neurotoxicity

There was no evidence of neurotoxicity or neuropathology in the acute and subchronic neurotoxicity study. The decrease in motor activity observed in the ACN study on the day of dosing at the limit dose (2000 mg/kg/day) in males is considered a reflection of a mild and transient general systemic toxicity and not a substance-specific neurotoxic effect. No neurotoxic effects were seen in the SCN study.

4.4.3 Evidence of Sensitivity/Susceptibility in the Developing or Young Animal

The concern for increased susceptibility following prenatal or postnatal exposure is low because clear no-observed adverse-effect levels (NOAELs)/LOAELs were established for the developmental effects seen in rats and rabbits as well as for the offspring effects seen in the two-generation reproductive toxicity study. Further, the dose-response relationship for the effects of concern are also well characterized and being used for assessing risks. The point of departure for risk assessments would be protective of the developmental and offspring effects.

4.4.4 Residual Uncertainty in the Exposure Database

There are no additional residual uncertainties with respect to exposure data. The dietary food exposure assessment utilizes recommended tolerance-level residues and 100% CT information for all commodities. By using these screening-level assessments, acute and chronic exposures/risks will not be underestimated. The dietary drinking water assessment utilizes values generated by models and associated modeling parameters that are designed to provide

conservative, health-protective, high-end estimates of water concentrations. There are no registered residential uses of saflufenacil; therefore, residential exposures are not anticipated.

4.5 Toxicity Endpoint and Point of Departure Selections

4.5.1 Dose-Response Assessment

Acute Dietary Endpoint (General population including infants and children): An acute dietary endpoint was established for this population group based on decreased motor activity observed at the LOAEL of 2000 mg/kg bw in male rats in the ACN study. The NOAEL was 500 mg/kg bw. A combined UF of 100 was applied to account for interspecies (10X) and intraspecies (10X) extrapolation. The FQPA SF was reduced to 1X for this exposure scenario (see Section 4.4). Thus, the aPAD is estimated at 5.0 mg/kg bw.

Acute Dietary Endpoint (Females 13-49 years old): An acute dietary endpoint, separate from that defined above, was not established for this population group. The developmental effects following saflufenacil exposure are unlikely to be the result of a single dose event. The skeletal variations (e.g., misshapen bones, delays in ossification, and wavy ribs) observed in the prenatal developmental study in the rat are not considered to be the result of a single dose. The process of bone deposition begins with cartilage deposition followed by calcification and does not occur during a single day. Unlike supernumerary ribs or missing bones, which may be caused by the activation or inactivation of genes and could be the outcome of a single exposure, the process of bone deposition occurs over several days and, therefore, is not considered appropriate for this endpoint.

Chronic Dietary Endpoint: This endpoint was based on decreases in red blood cells, hemoglobin, and hematocrit as well as porphyria observed in males in the satellite group (sacrificed at 10 months) at the LOAEL of 13.8 mg/kg bw/day in a mouse chronic/carcinogenicity study. The NOAEL is 4.6 mg/kg bw/day. A combined UF of 100 was applied to account for interspecies (10X) and intraspecies (10X) extrapolation. The FQPA SF was reduced to 1X for this exposure scenario (see Section 4.4). Thus, the cPAD is estimated at 0.046 mg/kg bw/day. This point of departure is protective of the developmental and offspring effects.

Dermal (Short- and Intermediate-Term): Although a 28-day dermal toxicity study with non-pregnant adult rats yielded no evidence of toxicity (dermal or systemic), there is concern for developmental toxicity following exposure to saflufenacil. Decreased fetal weights and increased skeletal variations were observed in the rat oral prenatal developmental toxicity study at the LOAEL of 20 mg/kg/day (NOAEL of 5 mg/kg/day). The concern for developmental toxicity is also supported by findings at higher doses from the rabbit developmental toxicity study and the rat two-generation reproductive toxicity study. A DAF of 6% was estimated based on a dermal penetration study in rats. Thus, the equivalent dermal NOAEL based on the rat prenatal developmental toxicity study can be estimated at 83.3 mg/kg/day. The LOC is 100 based on a combined UF of 100 applied to account for interspecies (10X) and intraspecies (10X) extrapolation.

Inhalation (Short- and Intermediate-Term): The inhalation risk for saflufenacil is being assessed using the rat prenatal developmental toxicity study with 100% absorption assumed via the

inhalation route. The HASPOC decided, based on a weight-of-evidence approach, that a 28-day inhalation toxicity study is not required at this time (TXR #0056720). The effects in the rat prenatal developmental toxicity study consisted of decreased fetal weights and increased skeletal variations at the LOAEL of 20 mg/kg/day (NOAEL of 5 mg/kg/day). The LOC is 100 based on a combined UF of 100 applied to account for interspecies (10X) and intraspecies (10X) extrapolation.

4.5.2 Recommendation for Combining Routes of Exposures for Risk Assessment

Dermal and inhalation exposures should be combined since the dermal and inhalation endpoints are based on the same study.

4.5.3 Cancer Classification and Risk Assessment Recommendation

Carcinogenicity studies in rats and mice showed no evidence of increased incidence of tumors at the tested doses. Saflufenacil is classified as "not likely carcinogenic to humans"; therefore, a cancer risk assessment is not required.

4.5.4 Summary of Points of Departure and Toxicity Endpoints Used in Human Risk Assessment

Table 4.5.4.1. Summary of Toxicological Doses and Endpoints for Saflufenacil for Use in Dietary Human-Health Risk Assessments.

Exposure Scenario	Point of Departure	UFs/ FQPA SF	RfD, PAD, LOC for Risk Assessment	Study and Toxicological Effects
Acute Dietary (General Population, including Infants and Children)	NOAEL = 500 mg/kg bw	UF_A = 10X UF_H = 10X FQPA SF = 1X	**aRfD** = 5.0 mg/kg **aPAD** = 5.0 mg/kg	Acute Neurotoxicity Study - rats NOAEL = 500 mg/kg bw. LOAEL = 2000 mg/kg bw based on decreased motor activity representing mild and transient systemic toxicity in males.
Chronic Dietary (All Populations)	NOAEL = 4.6 mg/kg/day	UF_A = 10X UF_H = 10X FQPA SF = 1X	**cRfD** = 0.046 mg/kg/day **cPAD** = 0.046 mg/kg/day	Chronic/Carcinogenicity (mouse) NOAEL = 4.6 mg/kg bw/day. LOAEL = 13.8 mg/kg bw/d based on decreased red blood cells, hemoglobin, hematocrit, and porphyria observed in the satellite group.
Cancer (oral, dermal, inhalation)	Classification: Not likely carcinogenic to humans based on the lack of tumors in the mouse and rat carcinogenicity studies and lack of mutagenicity.			

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. FQPA SF = FQPA Safety Factor. PAD = population-adjusted dose (a = acute, c = chronic). RfD = reference dose.

Table 4.5.4.2. Summary of Toxicological Doses and Endpoints for Saflufenacil for Occupational Human-Health Risk Assessment.

Exposure/ Scenario	Point of Departure	UFs/ FQPA SF	LOC for Risk Assessment	Study and Toxicological Effects
Dermal Short- and Intermediate-Term (1-30 days and 1-6 months, respectively)	NOAEL = 5 mg/kg/day Dermal absorption factor = 6%	UF_A = 10X UF_H = 10X FQPA SF = 1X	Occupational LOC for MOE = 100	Developmental study -Rat NOAEL = 5 mg/kg bw/day. LOAEL = 20 mg/kg bw/day based on decreased fetal bodyweight and increased skeletal variations.
Inhalation Short- and Intermediate-Term (1-30 days and 1-6 months, respectively)	NOAEL = 5 mg/kg/day Inhalation-absorption = Assumed to be equivalent with oral absorption	UF_A = 10X UF_H = 10X FQPA SF = 1X	Occupational LOC for MOE = 100	Developmental study -Rat NOAEL = 5 mg/kg bw/day. LOAEL = 20 mg/kg bw/day based on decreased fetal bodyweight and increased skeletal variations.
Cancer (oral, dermal, inhalation)	Classification: Not likely carcinogenic to humans based on the lack of tumors in the mouse and rat carcinogenicity studies and lack of mutagenicity.			

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.

5.0 Dietary Exposure and Risk Assessment

An overview of the metabolism and environmental degradation of saflufenacil can be found in the 22-JUL-2009 human-health risk assessment (L. Austin, *et al.*, D367317).

5.1 Residues of Concern Summary and Rationale

Plants (Primary Crops): The previously submitted metabolism data for corn, soybean, and tomato were adequate to elucidate the nature of the residue in plants resulting from pre-plant/pre-emergence application. The main reactions involved in the metabolic pathway of saflufenacil were *N*-demethylation at the uracil ring, stepwise degradation (*N*-dealkylation) of the *N*-methyl-*N*-isopropyl group, hydrolytic cleavage of the uracil ring generating a urea side chain, and hydroxylation of the phenyl ring. The HED ROCKS determined that residues of concern for the tolerance expression and risk assessment consist of saflufenacil, M800H11, and M800H35 (Memo, B. Daiss, 01-JUN-2009; D359645). The metabolic pathway of radiolabeled saflufenacil in soybean following a late-season post-emergence treatment follows the same initial pathways, but is not as extensive. No new metabolites were observed following post-emergence treatment; however, an additional major metabolite (M800H02), that is not included in the tolerance expression, was observed in soybean seed. As the structure of M800H02 is closely related to the parent compound and it is the precursor of the regulated metabolite M800H11, HED concluded that M800H02 is a residue of concern for risk-assessment purposes in seed commodities following late-season post-emergence treatment.

Subsequently, the petitioner submitted a rice metabolism study following post-emergence foliar

application of saflufenacil. The combined residues of saflufenacil, M800H11, and M800H35 (the current residues of concern for the tolerance expression and risk assessment) in rice forage were 71-89% of the total radioactive residue (TRR). The only other major metabolite was M800H02, which accounted for 4-16% of the TRR in forage. In rice grain, the combined residues of saflufenacil and all identified metabolites was <10% of the TRR (≤0.01 ppm). HED thus concludes that the current tolerance expression adequately accounts for the residues of concern following post-emergence foliar application to rice and related crops (i.e., cereal grains and grass). Additional metabolism data may be required to support foliar application to crops other than grasses and legume vegetables.

Plants (Rotational Crops): The metabolism of saflufenacil in rotational crops appears to be consistent with the pathway observed in the plant metabolism studies. The previously submitted confined and field rotational crop data are adequate to satisfy the data requirements for application rates up to 0.137 lb ai/A (1X). The available data indicate that residues of saflufenacil and its metabolites M800H11 and M800H35 were each <LOQ in/on all rotational crop matrices at a 120-day PBI. These data support the labeled rotational crop restriction of 4 months for all non-labeled crops. Unless the petitioner requests PBIs shorter than 120 days, no additional data are required, and tolerances for inadvertent residues in/on rotational crops need not be established in conjunction with the currently proposed uses.

Livestock: The nature of the residue in livestock is adequately understood based on acceptable metabolism studies conducted on lactating goats and laying hens. Saflufenacil was metabolized by several dealkylation steps occurring at two different sites in the molecule (*N*-isopropyl-*N*-methylsulfamide side chain and at the uracil ring) and via hydrolytic opening of the uracil ring (goat only). In the ruminant metabolism study, saflufenacil was a major residue in all matrices. M800H04, a ring opening product, was the only significant metabolite (>10% total radioactive residue, TRR) found (liver). In the poultry metabolism study, saflufenacil was a major residue in all matrices and no significant metabolites were found. The HED ROCKS determined that saflufenacil *per se* is the only residue of concern for the tolerance expression and risk assessment (Memo, B. Daiss, 01-JUN-2009; D359645). The decision to exclude the plant metabolites M800H11 and M800H35 as residues of concern in livestock was based on the low potential for exposure associated with the previously proposed uses and should be reevaluated if additional proposed uses result in a significant increase in the livestock dietary burden. The proposed post-emergence uses will result in a significant increase in the livestock dietary burden; however, metabolites M800H11 and M800H35 are not major residues in crops following desiccation application. M800H02 does not need to be included as a residue of concern as its concentration in the subject crops is >6X lower than the parent compound. HED thus concludes that saflufenacil *per se* is still the only residue of concern for the tolerance expression and risk assessment in livestock.

Drinking Water: Saflufenacil is slowly photolyzed in water (half-life of 57 days at pH 5) and on soil (half-lives of 83 and 87 days) at 22 °C. In addition, the compound is relatively stable to hydrolysis at pH 5, almost stable at pH 7 (half-life of 248 days), and readily hydrolyzed at pH 9 (half-life of 4.9 days). Therefore, alkaline hydrolysis is a major degradation route for saflufenacil in high pH environments.

Saflufenacil biodegrades in 1 to 5 weeks in aerobic soil (half-lives of 8.5-34 days) and less quickly in aerobic aquatic environments of pH 5.6 to 6.4 (half-lives of 50 and 107 days).

Therefore, aerobic soil metabolism is another major degradation route for saflufenacil that will operate in the environment at any pH value.

Dissipation occurred with half-lives of 2.4 to 22 days in terrestrial field dissipation studies conducted in the continental U.S., which is consistent with the submitted, laboratory-derived data. Dissipation was slower in Canadian field plots (half-lives of 25 days and >>20 days).

Major degradates that are structurally similar to the parent compound include M01, M02, M04, M07, M08, M15, M22, and the soil photolysis product number 8. Major cleavage products of saflufenacil include M26, trifluoroacetic acid, M31, M33, and TFP. Another major aqueous photolysis product was isolated as well (unknown 3/4/7/6), but not identified. Major degradates that did not decline in amount in unsterile study conditions include M7, M29, and product 8 (see Appendix B: Metabolism Assessment, Table B.1.2 of L. Austin, *et al.*, 22-JUL-2009; D367317).

Table 5.1. Summary of Metabolites and Degradates to be Included in the Risk Assessment.

Matrix		Residues Included in Risk Assessment	Residues Included in Tolerance Expression
Plants	Registered/proposed Primary Crops (preplant application)*	Saflufenacil + M800H11, M800H35	Saflufenacil + M800H11, M800H35
	Registered/proposed Primary Crops (foliar application)	Saflufenacil + M800H11, M800H02, M800H35	
	Rotational Crops	Saflufenacil + M800H11, M800H35	
Livestock	Ruminants	Saflufenacil	Saflufenacil
	Poultry		
Drinking Water		Saflufenacil + M800H01, M800H02, M800H07, M800H08, M800H15, M800H22, Product 8	Not Applicable

* Plus post-emergence foliar application to cereal grains and grasses.

5.2 Food Residue Profile

The new uses/use patterns associated with the subject result in significant increases in the livestock MRBDs. Consequently, the petitioner submitted new ruminant and poultry feeding studies. The feeding study data indicate that the established tolerances should be increased in all livestock commodities except hog meat, fat, and meat byproducts, except liver; and that there is no reasonable expectation of finite residues in poultry commodities.

The submitted crop field trial data are adequate to fulfill data requirements. The available data will support the proposed use patterns. The residue data were analyzed using the OECD tolerance-calculation procedures. The HED-recommended tolerances differed from the petitioner-for tolerances in some cases (Table 2.2.2). A revised Section F is requested.

The submitted wheat and barley processing studies are adequate to fulfill data requirements. A tolerance is required for barley bran, and the established aspirated-grain fractions tolerance (10 ppm) for the combined residues of saflufenacil and its metabolites M800H11 and M800H35 should be increased to 50 ppm.

The previously submitted confined and field rotational crop data are adequate to satisfy data requirements for application rates up to 0.137 lb ai/A (1X). The available data indicate that residues of saflufenacil and its metabolites M800H11 and M800H35 (residues of concern in rotational crops) were each <LOQ in/on all rotational crop matrices at a 120-day PBI. These data support the labeled rotational crop restriction of 4 months for all non-labeled crops.

5.3 Water Residue Profile

The Estimated Drinking Water Concentrations (EDWCs) used in the dietary exposure risk assessment were provided by EFED in a memorandum dated 12-MAR-2014 (Memo, M. Ruhman; DP# 414485). Water residues were incorporated directly into the DEEM-FCID in the food categories "water, direct, all sources" and "water, indirect, all sources."

Screening EDWCs (Table 5.3) of saflufenacil were generated by Tier I Rice modeling for surface water and with Pesticide Root Zone Model-Ground Water (PRZM-GW) for ground water. Modeled application rates represent the maximum use patterns for dry-seeded rice: the 1st application at planting, the second application 14 days after planting and flooding at 45 days after planting. Remaining model input parameters were chosen according to current guidance (USEPA, 2002). EDWCs reflect exposure to saflufenacil and all degradates of concern in drinking water (Table 5.1).

Table 5.3. Tiered EDWCs for Proposed Saflufenacil Uses.

Source (Tier: Model)	1-in-10-year Peak Exposure (ppb)	1-in-10-year Annual Mean Exposure (ppb)
Surface water (Tier I: Rice Model)	133 (used in acute analysis)	120 (used in chronic analysis)
Ground water (Tier II: PRZM GW)	69.2	51.5

5.4 Dietary Risk Assessment

5.4.1 Description of Residue Data Used in Dietary Assessment

The unrefined acute and chronic analyses assumed DEEM 7.81 default concentration factors and tolerance-level residues for all commodities [except for cottonseed; sunflower subgroup 20B; soybean, seed; vegetable, legume, subgroup 6C, pea and bean (except soybean); and rapeseed subgroup 20A for which the recommended tolerance levels were multiplied by a correction factor to account for a metabolite of concern which is not included in the tolerance expression]. Drinking water was incorporated directly into the dietary assessment using the concentration for surface water generated by Tier I Rice modeling.

5.4.2 Percent Crop Treated Used in Dietary Assessment

The acute and chronic dietary analyses assumed 100% CT for all commodities.

5.4.3 Acute Dietary Risk Assessment

The acute dietary risk for food and drinking water utilized <1% of the aPAD for the U.S. population. The acute dietary risk for the highest exposed population subgroup, all infants (<1-

year old), is <1% of the aPAD at the 95th percentile. A summary table of acute dietary exposure and risk for saflufenacil can be found in Section 5.4.6. Although further refinement to the analysis is not required at this time, future assessments could be refined using average field trial values, use of empirical processing factors, incorporation of %CT data, or monitoring data.

5.4.4 Chronic Dietary Risk Assessment

The chronic dietary risk for food and drinking water utilized 9.2% of the cPAD for the U.S. population. The chronic dietary risk for the highest exposed population subgroup, all infants (<1-year old), is 20% of the cPAD. A summary table of chronic dietary exposure and risk for saflufenacil can be found in Section 5.4.6. Although further refinement to the analysis is not required at this time, future assessments could be refined using average field trial values, use of empirical processing factors, incorporation of %CT data, or monitoring data.

5.4.5 Cancer Dietary Risk Assessment

Saflufenacil is classified as "not likely carcinogenic to humans." Therefore, cancer risk is not a concern for this chemical.

5.4.6 Summary Table

Table 5.4.6. Summary of Dietary (Food and Drinking Water) Exposure Risk for Saflufenacil.

Population Subgroup	Acute Dietary (95th Percentile)		Chronic Dietary	
	Dietary Exposure (mg/kg/day)	% aPAD	Dietary Exposure (mg/kg/day)	% cPAD
General U.S. Population	0.010106	<1	0.004223	9.2
All Infants (<1-year old)	**0.026582**	**<1**	**0.009099**	**20**
Children 1-2 years old	0.017044	<1	0.008368	18
Children 3-5 years old	0.013965	<1	0.006993	15
Children 6-12 years old	0.010852	<1	0.004872	11
Youth 13-19 years old	0.008383	<1	0.003409	7.4
Adults 20-49 years old	0.009103	<1	0.003946	8.6
Adults 50-99 years old	0.007781	<1	0.003679	8.0
Females 13-49 years old	0.009078	<1	0.003759	8.2

*The values for the highest exposed population for each type of risk assessment are bolded.

6.0 Residential (Non-Occupational) Exposure/Risk

6.1 Residential Exposure/Risk Characterization

Saflufenacil has no registered or proposed residential uses; therefore, a quantitative non-occupational exposure assessment was not performed.

6.2 Residential Bystander Post-Application Inhalation Exposure

Based on the Agency's current practices, a quantitative post-application inhalation exposure assessment was not performed for saflufenacil at this time primarily because of the low acute inhalation toxicity (Toxicity Category IV) and the low vapor pressure (4.5×10^{-15} Pa, 20°C).

However, volatilization of pesticides may be a source of post-application inhalation exposure to individuals nearby pesticide applications. The Agency sought expert advice and input on issues related to volatilization of pesticides from its Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) Scientific Advisory Panel (SAP) in December 2009, and received the SAP's final report on March 2, 2010[1]. The Agency is in the process of evaluating the SAP report and may, as appropriate, develop policies and procedures to identify the need for and, subsequently, the way to incorporate post-application inhalation exposure into the Agency's risk assessments. If new policies or procedures are developed, then the Agency may revisit the need for a quantitative post-application inhalation exposure assessment for saflufenacil.

6.3 Spray Drift

Spray drift is a potential source of exposure to those nearby pesticide applications. This is particularly the case with aerial application, but, to a lesser extent, spray drift can also be a potential source of exposure from the ground application methods (e.g., groundboom and airblast) employed for saflufenacil. The Agency has been working with the Spray Drift Task Force (a task force composed of various registrants which was developed as a result of a Data Call-In issued by EPA), EPA Regional Offices and State Lead Agencies for pesticide regulation and other parties to develop the best spray drift management practices (see the Agency's Spray Drift website for more information).[2] The Agency is also taking means to address quantitatively and qualitatively spray drift as a potential source of exposure in risk assessments for pesticides through existing programs such as AgDRIFT® and chemical-specific properties of pesticides. The potential for spray drift will be quantitatively evaluated for each pesticide during the *Registration Review* process that ensures that all uses for that pesticide will be considered concurrently. The Agency has also developed a policy on how appropriately to consider spray drift as a potential source of exposure in risk assessments for pesticides.

The potential for spray drift will be quantitatively evaluated for each pesticide during the Registration Review process that ensures that all uses for that pesticide will be considered concurrently. The approach is outlined in the revised (2012) *Standard Operating Procedures For Residential Risk Assessment (SOPs) - Residential Exposure Assessment Standard Operating Procedures Addenda 1: Consideration of Spray Drift*[3]. This document outlines the quantification of indirect non-occupational exposure to drift.

7.0 Aggregate Exposure/Risk Characterization

In accordance with the FQPA, HED must consider and aggregate pesticide exposures and risks from three major sources: food, drinking water, and residential exposures. In an aggregate assessment, exposures from relevant sources are added together and compared to quantitative estimates of hazard (e.g., a NOAEL or PAD), or the risks themselves can be aggregated. When aggregating exposures and risks from various sources, HED considers both the route and duration of exposure.

For saflufenacil, aggregate exposure and risk assessments were assessed by incorporating the

[1] Available: http://www.epa.gov/scipoly/SAP/meetings/2009/120109meeting.html
[2] Available: http://www.epa.gov/opp00001/factsheets/spraydrift.htm
[3] Available: http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2013-0676-0001

drinking water directly into the dietary-exposure assessment for the following scenarios: acute and chronic aggregate exposure (food + drinking water). Short-, intermediate-, and long-term aggregate-risk assessments were not performed because there are no registered or proposed uses of saflufenacil that result in residential exposures. A cancer aggregate-risk assessment was not performed because saflufenacil is not a carcinogen and cancer risk is not a concern.

7.1 Acute Aggregate Risk

The acute aggregate risk assessment takes into account average exposure estimates from dietary consumption of saflufenacil (food and drinking water). The acute dietary exposure estimates are not of concern to HED (<100% cPAD) for the general U.S. population and all population subgroups (see Table 5.4.6).

7.2 Chronic Aggregate Risk

The chronic aggregate risk assessment takes into account average exposure estimates from dietary consumption of saflufenacil (food and drinking water). The chronic dietary exposure estimates are not of concern to HED (<100% cPAD) for the general U.S. population and all population subgroups (see Table 5.4.6).

8.0 Cumulative Risk Characterization/Assessment

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 saflufenacil and any other substances and saflufenacil does not appear to produce a toxic metabolite produced by other substances. For the purposes of this tolerance action, therefore, EPA has not assumed that saflufenacil 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 Characterization

9.1 Short- and Intermediate-Term Handler Risk

The occupational handler exposure and risk estimates indicate that the short- and intermediate-term dermal and inhalation combined MOEs are not of concern to HED (i.e., MOE $\geq$ 100). At the baseline level of personal protection (i.e., no gloves and no respirator), all scenarios result in combined MOEs (dermal + inhalation) $\geq$ 250.

HED has no data to assess exposures to pilots using open cockpits. The only data available is for exposure to pilots in enclosed cockpits. Therefore, risks to pilots are assessed using the engineering control (enclosed cockpits) and baseline attire (long-sleeve shirt, long pants, shoes, and socks); per the Agency's Worker Protection Standard stipulations for engineering controls,

pilots are not required to wear protective gloves for the duration of the application. With this level of protection, there are no risk estimates of concern for applicators.

The Agency matches quantitative occupational exposure assessment with appropriate characterization of exposure potential. While HED presents quantitative risk estimates for human flaggers where appropriate, agricultural aviation has changed dramatically over the past two decades. According the 2012 National Agricultural Aviation Association (NAAA) survey of their membership, the use of Global Positioning System (GPS) for swath guidance in agricultural aviation has grown steadily from the mid-1990s. Over the same time period, the use of human flaggers for aerial pesticide applications has decreased steadily from ~15% in the late 1990s to only 1% in the most recent (2012) NAAA survey. The Agency will continue to monitor all available information sources to best assess and characterize the exposure potential for human flaggers in agricultural aerial applications.

Table 9.1. Occupational Handler Non-Cancer Exposure and Risk Estimates for Saflufenacil.

Exposure Scenario	Crop or Target	Dermal Unit Exposure (µg/lb ai)[1]	Inhalation Unit Exposure (µg/lb ai)[1]	Maximum Applic. Rate (lb ai/A)[2]	Area Treated (acres)[3]	Dermal (LOC = 100)		Inhalation (LOC = 100)		Total (LOC = 100)
		Mitigation Level	Mitigation Level			Dose (mg/kg/day)[4]	MOE[5]	Dose (mg/kg/day)[6]	MOE[7]	MOE[8]
Mixer/Loader										
Aerial application of liquid formulation	Forage Grasses Grown in Pastures and Rangeland, or in Fields Grown for Forage, Silage and Hay Production	220 (baseline)	0.219 (baseline)	0.089	1200	0.0204	250	0.000339	15,000	250
Groundboom application of liquid formulation					200	0.00341	1,500	0.0000565	88,000	1,500
Groundboom application of dry flowable formulation	Olive trees	227 (baseline)	8.96 (baseline)	0.044	80	0.000695	7,200	0.000457	11,000	4,400
Commercial Impregnation of Dry Bulk Fertilizers (closed system)	Forage Grasses Grown in Pastures and Rangeland, or in Fields Grown for Forage, Silage and Hay Production	8.6 (engineering control)	0.083 (engineering control)	0.89 lb ai/ton	960 tons	0.00639	780	0.00103	4,900	670
On-farm Impregnation of Dry Bulk Fertilizers		220 (baseline)	0.219 (baseline)	0.089	160	0.00272	1,800	0.0000452	110,000	1,800
Applicator										
Aerial spray application	Forage Grasses Grown in Pastures and Rangeland, or in Fields Grown for Forage, Silage and Hay Production	2.08 (engineering control)	0.0049 (engineering control)	0.089	1200	0.000193	26,000	0.00000758	660,000	25,000
Groundboom spray application		78.6 (baseline)	0.34 (baseline)		200	0.00122	4,100	0.0000877	57,000	3,800
	Olive trees			0.044	80	0.000241	21,000	0.0000174	290,000	20,000
Commercial Impregnation of Dry Bulk Fertilizers	Forage Grasses Grown in Pastures and Rangeland, or in Fields Grown for Forage, Silage and Hay Production	9.9 (baseline)	1.2 (baseline)	0.089	320	0.000245	20,000	0.000496	10,000	6,700
On-farm Impregnation of Dry Bulk Fertilizers					160	0.000123	41,000	0.000248	20,000	13,000
Flagger										
Flagger for aerial spray application	Forage Grasses Grown in Pastures and Rangeland, or in Fields Grown for Forage, Silage and Hay Production	11 (baseline)	0.35 (baseline)	0.089	350	0.000298	17,000	0.000158	32,000	11,000

Table 9.1. Occupational Handler Non-Cancer Exposure and Risk Estimates for Saflufenacil.

Exposure Scenario	Crop or Target	Dermal Unit Exposure (µg/lb ai)[1]	Inhalation Unit Exposure (µg/lb ai)[1]	Maximum Applic. Rate (lb ai/A)[2]	Area Treated (acres)[3]	Dermal (LOC = 100)		Inhalation (LOC = 100)		Total (LOC = 100)
		Mitigation Level	Mitigation Level			Dose (mg/kg/day)[4]	MOE[5]	Dose (mg/kg/day)[6]	MOE[7]	MOE[8]
Mixer/Loader/Applicator										
Mixing/loading/applying dry flowables via backpack applications	Olive trees (ground-directed)	8260	2.58	0.00044 lb ai/gallon	40 gallons	0.000126	40,000	0.000000658	7,600,000	40,000
Mixing/loading/applying dry flowables via manually-pressurized handwand applications		100,000	30			0.00153	3,300	0.00000765	650,000	3,300

1 Based on the "Occupational Pesticide Handler Unit Exposure Surrogate Reference Table" (March 2013); Level of mitigation: Baseline, Eng. Controls.
2 Based on proposed labels (Reg. No. 7969-278, 7969-276, and 7969-297).
3 Exposure Science Advisory Council Policy #9.1 and petitioner information.
4 Dermal Dose = Dermal Unit Exposure (µg/lb ai) × Conversion Factor (0.001 mg/µg) × Application Rate (lb ai/acre) × Area Treated (A/day) × DAF (6%) ÷ BW (69 kg).
5 Dermal MOE = Dermal NOAEL (5 mg/kg/day) ÷ Dermal Dose (mg/kg/day).
6 Inhalation Dose = Inhalation Unit Exposure (µg/lb ai) × Conversion Factor (0.001 mg/µg) × Application Rate (lb ai/acre) × Area Treated (A/day) ÷ BW (69 kg).
7 Inhalation MOE = Inhalation NOAEL (5 mg/kg/day) ÷ Inhalation Dose (mg/kg/day).
8 Total MOE = NOAEL (5 mg/kg/day) ÷ (Dermal Dose + Inhalation Dose).

9.2 Short- and Intermediate-Term Post-Application Risk

9.2.1 Dermal Post-Application Risk

A post-application exposure assessment has not been conducted for the proposed use on olive trees since the use directions indicate that the product is to be applied to the base of the tree trunk and is not to contact the foliage. Currently, HED has no transfer coefficients or other data to assess post-application dermal exposures to soil by occupational workers. In general, such exposures are considered negligible. Therefore, for the soil-directed uses, post-application exposures and risks to occupational workers were not assessed.

The proposed use on wheat and barley is for application of saflufenacil as a harvest aid/desiccant. As such, postapplication exposure to foliage is not expected because harvesting is done mechanically. Therefore, occupational post-application dermal exposure was not assessed at this time.

The proposed uses on grass/forage are not specifically soil directed and, therefore, could result in potential post-application exposures. These exposures have been assessed.

The short- and intermediate-term post-application exposure scenarios associated with the proposed uses for saflufenacil are summarized in Table 9.2.1. All scenarios resulted in MOEs greater than the LOC of 100 (ranging from 3,000 to 5,200) on day 0 (12 hours after application) and, therefore, are not of concern to HED.

Table 9.2.1. Occupational Post-application Non-Cancer Exposure and Risk Estimates for Saflufenacil.

Crop/Site	Activities	Transfer Coefficient (cm^2/hr)	Proposed Application Rate (lb ai/A)	DFR[1]	Dermal Dose (mg/kg/day)[2]	MOE[3] (LOC = 100)
Short- and Intermediate-term						
Forage crop	Scouting	1,100	0.045	0.13	0.00097	5,200
	Irrigation (hand set)	1,900			0.00167	3,000

1 DFR = Application Rate × F × $(1\text{-}D)^t$ × 4.54E8 µg/lb × 2.47E-8 acre/cm^2; where F = 0.25 and D = 0.10 per day.
2 Daily Dermal Dose = [DFR (µg/cm^2) × Transfer Coefficient × 0.001 mg/µg × 8 hrs/day × dermal absorption (6%)] ÷ BW (69 kg).
3 MOE = POD (5 mg/kg/day) / Daily Dermal Dose.

9.2.2 Inhalation Post-Application Risk

Based on the Agency's current practices, a quantitative occupational post-application inhalation exposure assessment was not performed for saflufenacil at this time primarily because of the low acute inhalation toxicity (Toxicity Category IV) and low vapor pressure (4.5×10^{-15} Pa, 20°C). However, there are multiple potential sources of post-application inhalation exposure to individuals performing post-application activities in previously treated fields. These potential sources include volatilization of pesticides and resuspension of dusts and/or particulates that contain pesticides. The Agency sought expert advice and input on issues related to volatilization of pesticides from its FIFRA SAP in December 2009, and received the SAP's final report on March 2, 2010[4]. The Agency is in the process of evaluating the SAP report as well as available post-application inhalation exposure data generated by the Agricultural Reentry Task Force (ARTF) and may, as appropriate, develop policies and procedures, to identify the need for and,

[4] Available: http://www.epa.gov/scipoly/SAP/meetings/2009/120109meeting.html

subsequently, the way to incorporate occupational post-application inhalation exposure into the Agency's risk assessments. 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 saflufenacil.

Although a quantitative occupational post-application inhalation exposure assessment was not performed, an inhalation exposure assessment was performed for occupational/commercial handlers. Handler exposure resulting from application of pesticides outdoors is likely to result in higher exposure than post-application inhalation exposure. Therefore, it is expected that these handler inhalation exposure estimates would be protective of most occupational post-application inhalation exposure scenarios.

9.3 Restricted Entry Interval

The REI specified on the proposed label is based on the acute toxicity of saflufenacil. Saflufenacil is classified as Toxicity Category III for acute oral, acute dermal toxicity, and acute eye irritation. It is classified as Toxicity Category IV for acute inhalation toxicity and acute dermal irritation. It is not a dermal sensitizer. Short- and intermediate-term post-application risk estimates were not a concern on day 0 (12 hours following application) for all post-application activities. Under 40 CFR §156.208 (c) (2) (iii), ais classified as Acute III or IV for acute dermal, eye irritation and primary skin irrigation are assigned a 12-hour REI. Therefore, the [156 subpart K] Worker Protection Statement interim REI of 12 hours is adequate to protect agricultural workers from post-application exposures to saflufenacil.

10.0 References

Previous Risk Assessments: L. Austin, *et al.*, 22-JUL-2009; D367317. G. Kramer, *et al.*; 19-APR-2011; D380636. G. Kramer, *et al.*; 23-JAN-2014; D405506

HASPOC Memo: A. Dunbar, 02-AUG-2013; TXR #0056720

Chemistry Memo: G. Kramer, 24-JUN-2014; D414003

Drinking Water Memo: M. Ruhman, 12-MAR-2014; D414485

Dietary Memo: G. Kramer, 24-JUN-2014; D418585

Occupational and Residential Exposure Assessment Memo: K. Lowe, 24-JUN-2014; D418586

List of Appendices:
Appendix A. Toxicology Profile
Appendix B. Physical/Chemical Properties
Appendix C. Review of Human Research

cc: G. Kramer (RAB1)
RDI: RAB1 (4/2/14)
G.F. Kramer:S10957:PY-S:(703)305-5079:7509P:RAB1

Appendix A. Toxicology Assessment

A.1 Toxicology Data Requirements for Saflufenacil

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-Day Dermal	yes	yes
870.3250 90-Day Dermal	no	-
870.3465 90-Day Inhalation	no	yes[1]
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
870.5xxx Mutagenicity—Structural Chromosomal Aberrations	yes	yes
870.5xxx 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)	yes	yes
870.6200b 90-Day Neurotox. Screening Battery (rat)	yes	yes
870.6300 Develop. Neuro	no	no
870.7485 General Metabolism	yes	yes
870.7600 Dermal Penetration	yes	yes
870.7800 Immunotoxicity	yes	yes

[1] Waived by the HASPOC (A. Dunbar, 02-AUG-2013; TXR #0056720).

A.2 Toxicity Profiles

Table A.2.1. Acute Toxicity Profile – Saflufenacil.

Guideline No.	Study Type	MRID(s)	Results	Toxicity Category	Purity
870.1100	Acute oral [rat]	47128101	LD_{50} >2000 mg/kg bw	III	93.8%
870.1200	Acute dermal [rat]	47128102	LD_{50} >2000 mg/kg	III	93.8%
870.1300	Acute inhalation [rat]	47128103	LC_{50} >5.3 mg/L	IV	93.8%
870.2400	Acute eye irritation [White New Zealand rabbit]	47128105	minimal irritation	III	93.8%
870.2400	Acute eye irritation [White New Zealand rabbit]	47128104	minimal irritation	III	93.8%
870.2500	Acute dermal irritation [rabbit]	47128106	slightly irritating	IV	93.8%
870.2600	Skin sensitization [Guinea Pig]	47128107	not a sensitizer	N/A	93.8%

Table A.2.2. Subchronic, Chronic, and Other Toxicity Profile for Saflufenacil.		
Guideline No./Study Type	MRID No. (year)/Classification/Doses	Results
870.3100 28-Day Oral Toxicity feeding-mice	47128110 (2007) Acceptable/non-guideline 0, 50, 150, 450, 1350, or 4050 ppm M\F: 0, 12.8/17.9, 36.6/63.4, 112/153.1, 335/446, 882/1630 mg/kg bw/day	LOAEL = 36.6 mg/kg bw/day (males) based on increased alanine aminotransferase, aspartate aminotransferase, urea and total bilirubin, decreased hemoglobin (Hb) and Ht, and increased liver weight and centrilobular fatty change. NOAEL = 12.8 mg/kg bw/day. LOAEL = 153.1 mg/kg bw/day (females) based on moderate centrilobular fatty change in the liver. NOAEL = 63.4 mg/kg bw/day.
870.3100 28-Day Oral Toxicity feeding-rat	47128108 (2007) Acceptable/non-guideline 0, 50, 150, 450, 1350, or 4050 ppm M = 0, 4.5, 13.4, 39.2, 117, 357 F = 0, 5.0, 15.9, 43.6, 130.4, 376 mg/kg bw/day	LOAEL = 39.2 mg/kg bw/day (males) based on decreased Hb, MCV, and MCH. NOAEL =13.4 mg/kg bw/day. LOAEL = 130.4 mg/kg bw/day (females) based on decreased Hb, Ht, MCV, and MCH. NOAEL = 43.6 mg/kg bw/day.
870.3100 90-Day Oral Toxicity feeding-mice	47128111 (2007) Acceptable/guideline 0, 15 (males only), 50, 150, 450, and 1350 (females only) ppm M = 0, 3.6, 12.4, 36.7, 109.1 F = 0, 17.6, 51.8, 156.6, 471.2 mg/kg bw/day	LOAEL = 36.7 mg/kg bw/day (males) based on multiple hematological changes, liver-weight increases with centrilobular fatty change and lymphoid infiltrate in males. NOAEL = 12.4 mg/kg bw/day. LOAEL = 156.6 mg/kg/day (females) based on increased liver weight with centrilobular fatty change and lymphoid infiltrate. NOAEL = 51.8 mg/kg/day.
870.3100 90-Day Oral Toxicity feeding-rat	47128109 (2007) Acceptable/guideline 0, 50, 150, 450 (males), 1350, or 4050 (females) ppm M =0, 3.5, 10.5, 32.3, 94.7 F = 0, 4.3, 12.6, 110.5, 344.7 mg/kg bw/day	LOAEL = 32.3 mg/kg bw/day (M) and 110.5 mg/kg bw/day (F) based on multiple hematological effects and increased spleen weight and extramedullary hematopoiesis. NOAEL = 10.5 (M), 12.6 mg/kg bw/day (F).
870.3150 28-Day Oral Toxicity feeding-dog	47128112 (2005) Acceptable/non-guideline 0, 30, 100, or 300 mg/kg bw/day	LOAEL = 100 mg/kg bw/day based decreased mean corpuscular volume, MCH, and MCHC, bone marrow hyperplasia, increased iron storage in the liver and extramedullary hematopoiesis in the spleen. NOAEL = 30 mg/kg bw/day.
870.3150 90-Day Oral Toxicity feeding-dog	47128113 (2006) Acceptable/guideline 0, 10, 50, or 150 mg/kg bw/day	LOAEL = 50 mg/kg bw/day based on lower MCV and MCH values in both sexes. NOAEL = 10 mg/kg bw/day.
870.3200 21/28-Day dermal toxicity (rat)	47128114 (2006) Acceptable/guideline 0, 100, 300, or 1000 mg/kg	LOAEL was not established. NOAEL = 1000 mg/kg bw/day.
870.3700a Prenatal developmental in (rat)	47128115 (2007) Acceptable/guideline 0, 5, 20, or 60 mg/kg/day	**Maternal** NOAEL = 20 mg/kg/day. LOAEL = 60 mg/kg/day based on decreased Hb, Ht, MCV, and MCH. **Developmental** NOAEL = 5 mg/kg/day. LOAEL = 20 mg/kg/day based on decreased fetal body weights and increase in skeletal variations.

Table A.2.2. Subchronic, Chronic, and Other Toxicity Profile for Saflufenacil.		
Guideline No./Study Type	MRID No. (year)/Classification/Doses	Results
870.3700b Prenatal developmental in (rabbit)	47128116 (2006) Acceptable/guideline 0, 50, 200, or 600 mg/kg/day	**Maternal** NOAEL = 200 mg/kg bw/day. LOAEL = 600 mg/kg bw/d based on mortality and increased necropsy findings. **Developmental** NOAEL = 50 mg/kg/day LOAEL = 200 mg/kg/day based on increased liver porphyrins.
870.3800 Reproduction and fertility effects (rat)	47128117 (2007) acceptable/guideline 0, 5, 15, or 50 mg/kg bw/day	**Parental Systemic** NOAEL = 15 mg/kg/day. **Parental Systemic** LOAEL = 50 mg/kg/day based on decreased food intake, body weight, and changes in hematological parameters and organ weights indicative of anemia. **Reproduction** NOAEL = M/F 50 mg/kg/day. **Reproduction** LOAEL was not established. **Offspring** NOAEL = 15 mg/kg/day. **Offspring** LOAEL = 50 mg/kg/day based on decreased number of live born pups, increased number of stillborn pups, decreased viability and lactation indices, decreased pre-weaning body weight, and changes in hematological parameters.
870.4300b Chronic Toxicity (dog)	47128118 (2007) Acceptable/guideline 0, 5, 20, or 80 mg/kg bw/day	LOAEL = 80 mg/kg bw/day based on decreased albumin, MVH, and MCH. NOAEL = 20 mg/kg bw/day.
870.4300 Chronic/Carcinogenicity (rat)	47128120 (2007) Acceptable/guideline 0, 20, 100, 250 (males), 500 or 1000 (females) ppm M = 0, 0.9, 4.8, 12.0, 24.2 F = 0, 1.3, 6.2, 31.4, 63.0 mg/kg bw/day	LOAEL = 31.4 mg/kg bw/day (females) based on decreased Hb, Ht, MCV, and MCH. NOAEL = 6.2 mg/kg bw/day (females). LOAEL was not established in males. NOAEL = 24.2 mg/kg bw/day. **No evidence of carcinogenicity.**
870.4300 Chronic/Carcinogenicity (mouse)	47128119 (2007) Acceptable/guideline 0, 1 (males), 5, 25, 75, or 150 (females) ppm M = 0, 0.2, 0.9, 4.6, 13.8 F = 0, 1.2, 6.4, 18.9, 38.1 mg/kg bw/day satellite groups: M = 0, 14.2 F = 0, 39.0 mg/kg bw/d	NOAEL = 4.6 mg/kg bw/day (males) and 18.9 mg/kg bw/day (females). LOAELs = 13.8 mg/kg bw/day (males) and 38.1 mg/kg bw/day (females) based on decreased red blood cells, Hb, and Ht and porphyria observed in the satellite group. **No evidence of carcinogenicity.**
Gene Mutation 870.5100 *In vitro* Bacterial Gene Mutation	47128121 (2005) Acceptable/guideline 0, 20, 100, 500, 2500, or 5000 µg/plate (saflufenacil hydrate)	There was no evidence of induced mutant colonies over background.
Gene Mutation 870.5100 *In vitro* Bacterial Gene Mutation	47128122 (2005) Acceptable/guideline 0, 20, 100, 500, 2500, or 5000 µg/plate (saflufenacil anhydrate)	There was no evidence of induced mutant colonies over background.
Gene Mutation 870.5300 *In vitro* Mammalian Cells Gene Mutation (Chinese Hamster Ovary Cells)	47128123 (2005) Acceptable/guideline 0, 312.5, 625, 1250, 2500, or 5000 µg/mL	There was no evidence of induced mutant colonies over background.
Cytogenetics	47128124 (2005)	Saflufenacil was considered clastogenic in

Table A.2.2. Subchronic, Chronic, and Other Toxicity Profile for Saflufenacil.		
Guideline No./Study Type	MRID No. (year)/Classification/Doses	Results
870.5375 *In vitro* Mammalian Cytogenetics chromosomal aberration assay- V79 cells	Acceptable/guideline 0, 5, 10, and 20 ug/ml without S9 activation 0, 10, 20, and 40 ug/ml with S9 activation	vitro in V79 cells in the presence of S9 metabolic activation. Saflufenacil was not clastogenic in the absence of metabolic activation.
Cytogenetics-other 870.5395 *In Vivo* Mammalian Cytogenetics - Erythrocyte Micronucleus assay in mice	47128125 (2005) Acceptable/guideline 0, 500, 1000, or 2000 mg/kg bw	There was no increase in the frequency of micronucleated immature erythrocytes in mouse bone marrow.
870.5550 Other Genotoxicity-*In vivo* unscheduled DNA synthesis (rat)	47128126 (2005) Acceptable/guideline single oral dose of 1000, or 2000 mg/kg bw	Negative
870.6200a Acute neurotoxicity battery (rat)	47128127 (2007) Acceptable/Guideline 0, 125, 500, or 2000 mg/kg bw	Systemic LOAEL was 2000 mg/kg bw (males) based on the decreased motor activity representing mild and transient systemic toxicity. Systemic LOAEL was not established for females. Systemic NOAEL = 500 (M) and 2000 (F) mg/kg bw. There was no evidence of neurotoxicity.
870.6200b Subchronic neurotoxicity (rat)	47128128 (2007) Acceptable/Guideline 0, 50, 250, 1000 (males), or 1350 (females) ppm M = 0, 3.3, 16.6, 66.2 F = 0, 3.9, 19.4, 101.0 mg/kg bw/d	Systemic NOAEL = 16.6 (males), 19.4 (females) mg/kg bw/day. Systemic LOAEL = 66.2 (males) and 101 (females) mg/kg bw/day based on decreased Hb, Ht, MCV, and MCH. There was no evidence of neurotoxicity.
870.7485 Metabolism and pharmacokinetics (rat)	47128130, 47128129 (2007) 4, 20, or 100 mg/kg bw (single oral dose) 5 or 100 mg/kg bw (single dose) 100 mg/kg for 14 days	Saflufenacil was rapidly absorbed, distributed, and excreted. Regardless of the dose administered, maximum concentration of saflufenacil in blood and plasma was reached within 1 h of dosing and declined rapidly after 24 h. Excretion of orally dosed saflufenacil was essentially complete within 96 h; the majority was eliminated within the first 24 to 48 h. Demonstrating that the majority of the saflufenacil residues occurred in the plasma and were not bound to cellular elements of the blood. There was a sex-dependent difference in the excretion of orally administered saflufenacil. Following single low- and high-dose administration or a repeat high-dose administration, the main route of elimination in male rats was via the feces, while urinary excretion was the major route of elimination in females. There was significantly higher biliary excretion of saflufenacil residues in males than in females. Exhalation was not a relevant excretion pathway of saflufenacil. At 168 h after dosing, saflufenacil residues remaining in tissues were very low, and occurred mainly in carcass, liver, skin, and gut contents. Saflufenacil was metabolized by three major transformation steps: demethylation of the uracil ring system, degradation of the *N*-methyl-*N*-isopropyl

Table A.2.2. Subchronic, Chronic, and Other Toxicity Profile for Saflufenacil.		
Guideline No./Study Type	MRID No. (year)/Classification/Doses	Results
		group to NH_2, and cleavage of the uracil ring, forming a sulfonylamide group. The predominant metabolites were M800H01, M800H03, M800H07, and the parent compound. Other minor metabolites were M800H05, M800H16, M800H17, M800H18, M800M19, and M800M20. There were no significant sex differences in metabolic profiles.
870.7600 Dermal penetration (rat)	47128214 (2007) Acceptable/guideline 1.1723 mg/cm^2, 0,1172 mg/cm^2 and 0.0117 mg/cm^2 11.723, 1.172 and 0.117 mg/rat	Dermal absorption is 6%.
870.7800 Immunotoxicity (mice)	48233701 (2010) Acceptable/guideline 0, 50, 125, and 250 ppm (0, 10, 27, and 52 mg/kg/day)	LOAEL for systemic toxicity was 125 ppm (or 27 mg/kg bw/day) based on significant changes in pathological and clinical pathology parameters. The NOAEL for systemic toxicity was 50 ppm (10 mg/kg bw/day). The LOAEL for immunotoxicity was not identified. The NOAEL for immunotoxicity is the highest dose tested of 250 ppm (52 mg/kg bw/day).
Comparative Bioavailability/Toxicity Study (rat)	47128133 (2005) Acceptable/non-guideline 0 or 1350 ppm	The bioavailability and toxicity potential of the hydrated and anhydrated forms of saflufenacil were similar.
Mechanistic study – total porphyrin analysis in rat	47128132 (2006) Acceptable/non-guideline 0, 10, 50, or 1000 ppm (♂ = 0, 0.8, 4.1, 80.6; ♀ = 0, 0.9, 4.6, 89.5 mg/kg bw/day, respectively)	Total porphyrins in feces and liver provided the most reliable and sensitive data. Statistically significant effects on porphyrin metabolism could be detected at exposure concentrations well below those associated with adverse hematological effects. NOAEL= 4.1 mg/kg/day. LOAEL = 80.6 mg/kg/day based on decreased Hb, Ht, MCV, MCH, and MCHC.
Mechanistic study-porphyrin analysis supplementary (rat)	47128131 (2005) Acceptable/non-guideline 0, 1, 5, or 25 ppm (♂ = 0, 0.1, 0.4, 2.0; ♀ = 0, 0.1, 0.5, 2.3 mg/kg bw/day	Dietary administration of saflufenacil at 25 ppm caused an increase in porphyrin in feces of male (237%) and female (61%) rats, while saflufenacil at 5 ppm caused an increase in fecal porphyrin only in males. There were no effects on hematology parameters.

Appendix B. Physical/Chemical Properties

Table B.1. Physicochemical Properties of Technical Grade Saflufenacil.	
Parameter	Value
Melting point	Average = 189.9 °C, peak max = 193.4 °C
pH	4.43 of 1% solution at 25 °C
Bulk Density (ambient temp.)	0.661 kg/L (free fall), 0.736 kg/L (packed)
Water solubility (20 °C)	in g/100 mL: 0.0025 in water (pH = 5); 0.0014 in pH 4 buffer; 0.21 in pH 7 buffer; not determined due to degradation in pH 9 buffer
Solvent solubility (20 °C)	in g/100 mL: 19.4 acetonitrile; 24.4 dichloromethane; 55.4 *N*,*N*-dimethylformamide; 27.5 acetone; 6.55 ethyl acetate; 36.2 tetrahydrofuran; 35.0 butyrolactone; 2.98 methanol; 0.25 isopropyl alcohol; 0.23 toluene; <0.01 1-octanol; <0.005 n-heptane
Vapor pressure at 20/25 °C	20 °C = 4.5×10^{-15} Pa 25 °C = 2.0×10^{-15} Pa
Dissociation constant (pK_a)	4.41
Octanol/water partition coefficient	Mean Log P_{ow} = 2.6 (P_{ow} = 368.3)
UV/visible absorption spectrum	wavelength maximum: λ_{max} = 271.6 nm extinction coefficient: ε = 9709 L/mol-cm

Reference: BASF Registration Document Number (DocID) 2005/1026464.

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, which include studies from the Pesticide Handlers Exposure Database (PHED) 1.1, the Agricultural Handler Exposure Task Force (AHETF) database, and the ARTF database are (1) subject to ethics review pursuant to 40 CFR §26, (2) have received that review, and (3) are compliant with applicable ethics requirements. For certain studies, the ethics 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 the Agency website[5].

[5] http://www.epa.gov/pesticides/science/handler-exposure-data.html and http://www.epa.gov/pesticides/science/post-app-exposure-data.html