OFFICE OF CHEMICAL SAFETY AND POLLUTION PREVENTION

WASHINGTON, D.C. 20460

MEMORANDUM

DATE: June 17, 2024

SUBJECT: **SAFLUFENACIL.** Section 3 Human Health Risk Assessment for Proposed New Uses on Mint (Peppermint and Spearmint) and Crop Group Conversions and Expansions.

PC Code: 118203
CAS No.: 372137-35-4
Decision No.: 591247
Petition No.: 2E9045
Risk Assessment Type: Single Chemical/Aggregate
TXR No.: NA
MRID No.: NA

DP Barcode: D467481
Task Group No.: 00484712
Parent Case No.: 00478596
Registration No.: 7969-275, 7969-276, 7969-278
Regulatory Action: Section 3 Registration
Reg. Review Case No.: 7277
40 CFR: §180.649

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The conclusions conveyed in this assessment were developed in full compliance with *EPA Scientific Integrity Policy for Transparent and Objective Science*, and EPA Scientific Integrity Program's *Approaches for Expressing and Resolving Differing Scientific Opinions.* The full text of *EPA Scientific Integrity Policy for Transparent and Objective Science*, as updated and approved by the Scientific Integrity Committee and EPA Science Advisor can be found here: https://www.epa.gov/system/files/documents/2023-12/scientific_integrity_policy_2012_accessible.pdf. The full text of the EPA Scientific Integrity Program's *Approaches for Expressing and Resolving Differing Scientific Opinions* can be found here: https://www.epa.gov/scientific-integrity/approaches-expressing-and-resolving-differing-scientific-opinions.

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 mint (fresh leaves and mint, dried leaves) (peppermint and spearmint); and crop group conversions for citrus fruit (crop group 10-10), pome fruit (crop group 11-10), stone fruit (crop group 12-12), and tree nuts (crop group 14-12).

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 HED team members contributing to this risk assessment include Anwar Dunbar (hazard evaluation), Oluwaseun Gbemigun (dietary assessment, and residue chemistry), Lata Venkateshwara (occupational/residential assessments), 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 in mode-of-action Group 14 (cell membrane disruptors). It acts through the inhibition of protoporphyrinogen oxidase (PPO), resulting in cell membrane damage and subsequent plant death. Saflufenacil is currently registered in the U.S. for use on legume vegetables, citrus fruit, pome fruit, stone fruit, tree nuts, cereal grains, cotton, oilseeds, grapes, grass forage/hay/grass grown for seed, olives, soybean, pomegranate, caneberry, fig, chia, field corn commodities, post-harvest, and fallow. The previous toxicological, occupational, and residential profiles for saflufenacil in the most recent risk assessment document remain relevant for this petition. The most recent risk assessment was conducted for a Section 3 registration for uses on field corn commodities, post-harvest, and fallow (O. Gbemigun *et al.*, D466353, 05-DEC-2023).

Use Profile: Interregional Research Project No. 4 (IR-4), in cooperation with the registrant, BASF has petitioned for the establishment of permanent tolerances under 40 CFR §180.649(a)(1) for residues of saflufenacil, including its metabolites and degradates in/on mint, fresh leaves and mint, dried leaves (peppermint and spearmint); and crop group conversions for citrus fruit (crop group 10-10), pome fruit (crop group 11-10), stone fruit (crop group 12-12), and tree nuts (crop group 14-12). The labels require applicators and handlers to wear long-sleeved shirt, long pants, shoes, and socks, protective eyewear, and chemical resistant gloves. Under the proposed uses, the label required occupational personal-protective equipment (PPE) is sufficient. The 12-hour restricted entry interval (REI) listed on the proposed label is considered protective of post-application exposure.

Exposure Profile: 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; however, there is potential for exposure to saflufenacil in non-occupational settings due to spray drift. 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 use of saflufenacil and considers the existing registered uses as well for the dietary exposure assessments.

Hazard Characterization: No new data have been submitted for Saflufenacil. 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 were seen at about the same dose level (≥ 20-30 mg/kg/day) across species, except in the case of the dog, where the effects were seen at a slightly higher dose. 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 in mice, the spleen in rats, and in both organs in dogs. These effects also occurred around the same dose level from short- through long-term exposures without increasing in severity. There was increased susceptibility in the developmental studies; however, in the reproductive toxicity study, effects were observed at the same dose in pups as parents.

Carcinogenicity studies in rats and mice showed no evidence of increased incidence of tumors at the

tested doses, therefore, saflufenacil was classified as being "Not Likely to be Carcinogenic to Humans." No new data have been submitted for saflufenacil. 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 an immunotoxicity study. 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 IV) but was not a dermal irritant or a dermal sensitizer. To see the detailed hazard characterization, see the 2020 risk assessment (G. Kramer *et al.*, D456093, 07-AUG-2020). RAB1 risk assessment team for saflufenacil previously determined that the FQPA Safety Factor (SF) should be reduced to 1X for all exposure scenarios for the following reasons: the toxicological database is adequate for FQPA assessment, there is no evidence of neurotoxicity, the points of departure used for risk assessment are protective of the fetal and offspring effects, 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 previously determined acute reference dose (aRfD, 5.0 mg/kg) and chronic RfD (cRfD, 0.046 mg/kg/day). Since the FQPA SF has been reduced to 1X, the acute population-adjusted dose (aPAD) and the chronic population-adjusted dose (cPAD) are equal to the acute and chronic RfDs, respectively. The endpoint used for deriving the acute population-adjusted dose (aPAD) was selected from the acute neurotoxicity (ACN) study in rats with a no-observed adverse-effect level (NOAEL) of 500 mg/kg/day. The lowest-observed adverse-effect level (LOAEL) is 2000 mg/kg bw, based on decreased motor activity representing mild and transient systemic toxicity in male rats. The endpoint used for deriving the chronic population-adjusted dose (cPAD) was selected from the carcinogenicity study in mice with a NOAEL of 4.6 mg/kg/day. The LOAEL is 13.8 mg/kg/day 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). The short- and intermediate-term incidental oral PODs were selected from the two-generation reproductive study. The offspring NOAEL is 15 mg/kg/day and the LOAEL is 50 mg/kg/day, based on decreased viability and lactation indices, decreased pre-weaning body weight, and changes in hematological parameters. The adult short-term oral, dermal, and inhalation PODs were selected from the developmental rat study. The developmental NOAEL is 5 mg/kg/day and the developmental LOAEL is 20 mg/kg/day based upon decreased fetal weights and increased skeletal variations were observed in the rat. Saflufenacil is classified as "Not Likely Carcinogenic to Humans"; therefore, cancer risk assessments are not required. In estimating margins of exposure (MOEs), the level of concern (LOC) is for MOEs <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.

Dietary Exposure/Risk Assessment Characterization: Acute and chronic dietary exposure assessments were conducted using the Dietary Exposure Evaluation Model - Food Consumption Intake Database (DEEM-FCID, ver. 4.02) 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; 2005-2010). The acute and chronic analyses assumed 100% crop treated (PCT), HED's default processing factors, and 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 26% of the cPAD.

Residential Exposure and Risk Assessment: There are no residential uses proposed or currently registered for saflufenacil. Therefore, a residential risk assessment was not conducted.

Aggregate-Risk Estimates: 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.

Non-Occupational Spray Drift Exposure and Risk Estimates: The potential for spray drift from saflufenacil uses will be evaluated during the ongoing Registration Review process to ensure that all uses for that pesticide will be considered concurrently.

Occupational Exposure and Risk Assessment: Short- and intermediate-term occupational handler inhalation and dermal risk estimates are not of concern. Combined dermal and MOEs range from 2,600 to 50,000 (LOC = 100) with baseline attire and label-required baseline attire and PPE (i.e., protective gloves, protective eyewear, and no respirator).

A quantitative post-application dermal exposure assessment was not conducted for the proposed use on mint since the proposed use (see label Sharpen® (EPA Reg. No. 7969-278)), is a broadcast burndown spray to emerged broadleaf weeds in the dormant season (i.e., when mint is not actively growing in the fall (postharvest) or during winter dormancy). The fruit and nut tree crop conversions and expansion uses proposed on the label Treevix® (EPA Reg. #: 7969-276) indicate the application should be directed at the base of the tree trunks; therefore, HED does not expect that post-application dermal exposure will occur. The proposed labels indicate that crop injury will result if the products are applied post-emergent (over the top) to any crop.

The REI is based on the acute toxicity of saflufenacil technical material. Saflufenacil is classified as Toxicity Category III for acute oral and acute dermal toxicity. It is classified as Toxicity Category IV for acute inhalation toxicity, acute eye irritation and primary skin 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.

Environmental Justice Considerations: Potential areas of environmental justice concerns, to the extent possible, were considered in this human health risk assessment, in accordance with U.S. Executive Order 12898, “Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations.”

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. Please refer to Appendix C for a discussion of the human study data used in this risk assessment.

2.0 HED Recommendations

There are no residue chemistry, occupational, or toxicology data deficiencies that would preclude the establishment of permanent tolerances for residues of saflufenacil and its metabolites and degradates as outlined in Table 2.2.2.

2.1 Data Deficiencies

None.

2.2 Tolerance Considerations

2.2.1 Enforcement Analytical Method

Samples were analyzed for residues of saflufenacil, M800H11, M800H35, and M800H02 using Method D0603/04, a high-performance liquid chromatography method with tandem mass spectrometry detection (LC-MS/MS). Method D0603/04 is an updated version of the enforcement method (Method D0603/02) for determination of residues of saflufenacil and its metabolites in plant matrices that has been revised to add instructions for determination of M800H02.

Briefly, samples were extracted with methanol:water (70:30, v:v) by shaking for 10 minutes and then isolated by two consecutive centrifugation steps. An aliquot of the supernatant was concentrated under nitrogen to remove methanol, then acidified with 0.1% trifluoroacetic acid, and partitioned with ethyl acetate:cyclohexane (70:30, v:v) and centrifuged. An aliquot of the organic phase was evaporated to dryness under nitrogen and reconstituted in methanol:water (50:50, v:v) for LC/MS/MS analysis.

The limit of quantitation (LOQ), based on lowest level of method validation (LLMV), was 0.01 ppm. The limit of detection (LOD) is defined as 10% below the smallest concentration within the standard curve were 0.1 ppm. Residues of the metabolites M800H11 and M800H35 were converted to parent equivalents by using MWCFs of 1.06 and 1.42, respectively; residues of M800H02 were not converted to parent equivalents.

2.2.2 Recommended Tolerances

HED reviewed the submitted residue data and determined the appropriate tolerance levels for residues of mint and crop group expansions (Table 2.2.2). A summary of proposed and recommended tolerances for saflufenacil are summarized below.

Table 2.2.2. Tolerance Summary for Saflufenacil (40 CFR §180.649).				
Commodity/ Correct Commodity Definition	**Established Tolerance (ppm)**	**Proposed Tolerance (ppm)**	**HED-Recommended Tolerance (ppm)**	**Comments**
40 CFR 180.649 (a) General. (1) Tolerances are established for residues of saflufenacil, including its metabolites and degradates, in or on the commodities in the table below. Compliance with the tolerance levels specified below is to be determined by measuring only the sum of saflufenacil, 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, and its metabolites *N*-[2-chloro-5-(2,6-dioxo-4-(trifluoromethyl)-3,6-dihydro-1(2*H*)-pyrimidinyl)-4-fluorobenzoyl]-*N'*-isopropylsulfamide and *N*-[4-chloro-2-fluoro-5-({[(isopropylamino)sulfonyl]amino}carbonyl)phenyl]urea, calculated as the stoichiometric equivalent of saflufenacil, in or on the plant commodities.				
Fruit, citrus, group 10-10	-	0.03	0.03	Tolerance based on Fruit, citrus, group 10 tolerance at 0.03 ppm.
Fruit, citrus, group 10	0.03	-	remove	
Fruit, pome, group 11-10	-	0.03	0.03	Tolerance based on Fruit, pome, group 11 tolerance at 0.03 ppm.
Fruit, pome, group 11	0.03	-	remove	
Fruit, stone, group 12-12	-	0.03	0.03	Tolerance based on Fruit, stone, group 12 tolerance at 0.03 ppm.
Fruit, stone, group 12	0.03	-	remove	
Mint, dried leaves*	-	0.04	0.03	Tolerance based on mint, dried leaves residue data.
Mint, fresh leaves*	-	0.04	0.03	Tolerance based on mint, fresh leaves residue data.
Nut, tree, group 14-12	-	0.03	0.03	Tolerance based on Nut, tree, group 14 tolerance at 0.03 ppm.
Nut, tree, group 14	0.03	-	remove	
Pistachio	0.03	-	remove	

*** The term "mint" is an umbrella term for the *Mentha* plant family that includes spearmint, peppermint, orange mint, apple mint, etc. See 40 CFR 180.1(g). As spearmint and peppermint are the main varieties utilized in commercial production, HED considers the residue data to cover all *Mentha* species.**

2.2.3 Revisions to Petitioned-For Tolerances

A revised Section F is requested with the revised tolerance levels and/or commodity definitions as recommended by HED. For mint, fresh and dried leaves, the proposed and recommended tolerance values differ due to combined residues being expressed in terms of saflufenacil and metabolites, M800H02, M800H11, and M800H35 by the study author versus HED excluded residues of M800H02 as the Residues of Concern Knowledgebase Subcommittee (ROCKS) determined that the residues of concern for the tolerance expression and risk assessment consist of saflufenacil, M800H11, and M800H35.

2.2.4 International Harmonization

The Codex has established MRLs for saflufenacil in or on Fruit, citrus, group 10-10 at 0.01 ppm; Fruit, pome, group 11-10 at 0.01 ppm; Fruit, stone, group 12-12 at 0.01 ppm; and Nut, tree, group 14-12 at 0.01 ppm. These MRLs are different than the HED-recommended tolerance levels (all 0.03 ppm) for saflufenacil. Based on available residue data, use by U.S. growers consistent with approved label instructions would result in residues that exceed the Codex MRL. Harmonizing with these Codex MRLs could put U.S. growers at risk of potentially violative residues despite legal use of saflufenacil according to the label. Refer to Appendix D for the international residue limit table.

2.3 Label Recommendations

Note on mixing/loading liquid formulation scenarios: A 2019 study by the Agricultural Handler Exposure Task Force (AHETF), a consortium of pesticide manufacturing companies, measured dermal and inhalation exposure for workers who loaded liquid pesticides using closed loading systems such as gravity feed, container breach, and suction/extraction systems. As a result of the review and acceptance of that data, labels for liquid pesticide products for which suction/extraction systems are applicable should instruct users to rinse extraction probes within the pesticide container prior to removal of the probes. These instructions will ensure that users of suction/extraction systems do not remove and handle chemical extraction probes still coated with the concentrated liquid formulation.

3.0 Introduction

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.

3.1 Chemical Identity

Table 3.1 is a summary of the nomenclature and chemical structure for saflufenacil and its metabolites.

Table 3.1. Saflufenacil and Metabolite Nomenclature.

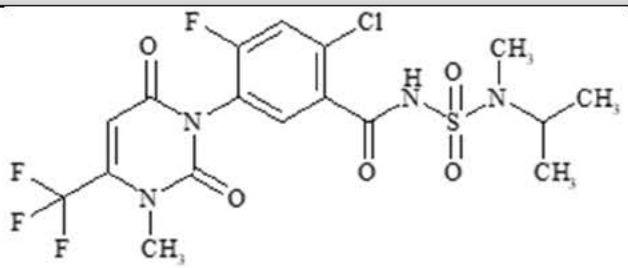
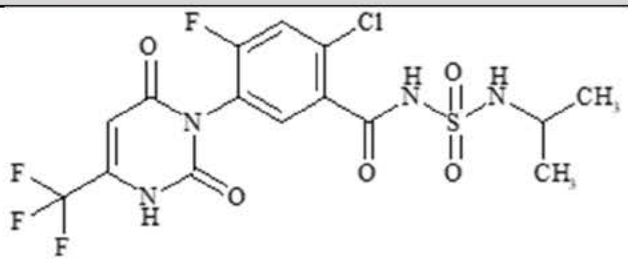
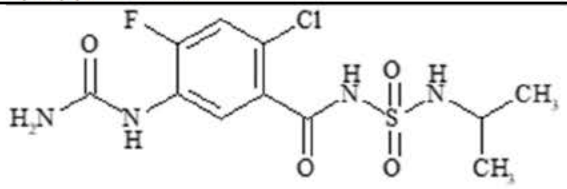
Chemical Structure	
Common name	Saflufenacil
Company experimental name	BAS 800 H (synonyms: AC 433 379, BASF Reg. No. 4054449)
IUPAC name	*N*'-[2-chloro-4-fluoro-5-(3-methyl-2,6-dioxo-4-(trifluoromethyl)-3,6-dihydro-1(2*H*)-pyrimidinyl)benzoyl]-*N*-isopropyl-*N*-methylsulfamide
CAS name	2-chloro-5-[3,6-dihydro-3-methyl-2,6-dioxo-4-(trifluoromethyl)-1(2*H*)-pyrimidinyl]-4-fluoro-*N*-[[methyl(1-methylethyl)amino]sulfonyl]benzamide
CAS registry number	372137-35-4
End-use product (EP)	Sharpen® Powered by Kixor® Herbicide (EPA Reg. No. 7969-278) (2.85 lb ai/gal SC formulation) Treevix 7969-276

Table 3.1. Saflufenacil and Metabolite Nomenclature.	
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 an uracil-based PPO 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 is expected to 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/Directions for Use

Saflufenacil is currently registered for use on legume vegetables, citrus fruit, pome fruit, stone fruit, tree nuts, cereal grains, corn, cotton, grapes, grass forage/hay/grass grown for seed, olives, soybean, pomegranate, caneberry, fig, and chia. IR-4 is proposing new use on mint and crop group expansions for citrus fruit (crop group 10-10), pome fruit (crop group 11-10), stone fruit (crop group 12-12), and tree nuts (crop group 14-12). For the crops associated with the crop group expansions, no amendments to the use patterns [i.e., maximum use rates, retreatment intervals (RTIs), preharvest intervals (PHIs), use of adjuvants, etc.] have been proposed. Therefore, an updated occupational exposure assessment for these uses was not needed.

The maximum single application rate is 0.044 lb ai/A, and a summary of directions for the proposed mint use is detailed below in Table 3.3.2.

Table 3.3.1. Summary of Proposed End-Use Product.						
Trade Name	**Reg. No.**	**ai (% of formulation)**	**Formulation Type**	**Target Site**	**Target Pests**	**Label Date**
Sharpen® Powered by Kixor® Herbicide	7969-278	29.74	SC	Soil	Broadleaf weeds	-
Treevix by Kixor Herbicide	7969-276	70	WG	Soil	Post-emergence broadleaf weeds	Not specified

WG = water-dispersible granule.
SC = suspension Concentrate.

Table 3.3.2. Summary of Directions for Use of Saflufenacil.								
Formulation	**Applic. Timing, Type, and Equip.**	**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**	**PPE**
Mint (New Use – Post-emergence)								
Sharpen® powered by Kixor® Herbicide. (7969-278) SC	Broadcast spray Groundboom sprayer, Fixed wing, Helicopter	0.044	2	0.044	-	No required (PHI)	• Broadcast burndown spray to emerged broadleaf weeds in the dormant season (i.e., when mint is not actively growing in the fall (postharvest) or during winter dormancy). • Separate sequential applications may be made within the dormant season if the maximum cumulative amount does not exceed 2.0 fl ozs/A. Separate sequential dormant season burndown applications by at least 14 days. • Do not apply to mint that has broken dormancy. Do apply to mint in the first year of growth and establishment. Do not apply to mint stands that have been weakened by age, disease, cold weather, excessive moisture, or other factors that reduce crop vigor. • Do not apply by chemigation. • For use in Idaho, Indiana, Michigan, Montana, Oregon, Utah, Washington, and Wisconsin.	• Long-sleeved shirt, long pants • Shoes plus socks • Waterproof glove • Protective eyewear.

PHI = preharvest interval; RTI = retreatment interval; SC = Suspension Concentrate.

Conclusion: The submitted use directions for Sharpen® Powered by Kixor® Herbicide and Saflufenacil CS Herbicide are adequate to allow evaluation of the residue data relative to the proposed use.

3.4 Anticipated Exposure Pathways

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; however, there is potential for exposure to saflufenacil in non-occupational settings due to spray drift. 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 exposure pathways based on the registered uses of saflufenacil and updated dietary exposure assessment to DEEM Version 4.02.

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," (https://www.archives.gov/files/federal-register/executive-orders/pdf/12898.pdf). As a part of every pesticide risk assessment, OPP considers a large variety of consumer subgroups according to well-established procedures. In line with OPP policy, HED estimates risks to population subgroups from pesticide exposures that are based on patterns of that subgroup's food and water consumption, and activities in and around the home that involve pesticide use in a residential setting. Extensive data on food consumption patterns are compiled by the USDA's U.S. Department of Agriculture's National Health and Nutrition Examination Survey, What We Eat in America, (NHANES/WWEIA) and are used in pesticide risk assessments for all registered food uses of a pesticide. These data are analyzed and categorized by subgroups based on age and ethnic group. Additionally, OPP is able to assess dietary exposure to smaller, specialized subgroups and exposure assessments are performed when conditions or circumstances warrant. Whenever appropriate, non-dietary exposures based on home use of pesticide products and associated risks for adult applicators and for toddlers, youths, and adults entering or playing on treated areas post-application are evaluated. Spray drift can also potentially result in post-application exposure, and it is also being considered whenever appropriate. Further considerations are also currently in development as OPP has committed resources and expertise to the development of specialized software and models that consider exposure to other types of possible bystander exposures 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. There are no new data or changes to the endpoints or point of departures since the last human health risk assessment (O. Gbemigun *et al.*, D466353, 05-DEC-2023).

4.2 Toxicity Endpoint and Point of Departure Selections

An incidental oral endpoint was selected to account for exposure of neonates (infants) due to spray drift. Adult oral, residential dermal, and inhalation endpoints were also selected because there is an increased quantitative susceptibility in utero in rats and rabbits resulting from maternal exposure to saflufenacil. Because the two-generation reproduction study shows toxicity to parents and offspring at similar doses, dermal and inhalation endpoints were not selected for offspring (protecting for parents, protects for offspring).

4.2.1 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 POD is protective of the developmental and offspring effects.

Incidental Oral (Short- and Intermediate-Term): The point of departure for the short-term incidental oral exposure scenarios is based upon the offspring NOAEL from the two-generation reproductive study of 15 mg/kg/day. The LOAEL is 50 mg/kg/day based upon a 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. This study is protective of young children in residential settings and is appropriate for short- and intermediate- durations. It is further protective of the effects in saflufenacil's other studies of similar duration. The LOC is for MOEs less than 100 based on a combined UF of 100 applied to account for interspecies (10X), intraspecies (10X) extrapolation and the 1X FQPA SF.

Adult Oral (Short-Term): The point of departure for the short-term adult oral exposure scenario is derived from the prenatal developmental toxicity study in rats. The developmental NOAEL is 5 mg/kg/day and the LOAEL is 20 mg/kg/day based upon the decreased fetal weights and increased skeletal variations were observed in the rat oral prenatal developmental toxicity study at a lower dose than maternal toxicity. Increased quantitative susceptibility was also observed in the rabbit developmental toxicity study at higher doses. These effects are protective of pregnant mothers in scenarios where there may be saflufenacil exposure due to spray drift. The residential LOC is for MOEs less than 100 based on a combined UF of 100 applied to account for interspecies (10X), intraspecies (10X) extrapolation, and the 1X FQPA SF.

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 increased quantitative susceptibility following exposure to saflufenacil. Decreased fetal weights and increased skeletal variations were observed in the rat oral prenatal developmental toxicity study at a lower dose than maternal toxicity (LOAEL of 20 mg/kg/day; NOAEL of 5 mg/kg/day). Increased quantitative susceptibility was also observed in the rabbit developmental toxicity study at a higher dose. A DAF of 6% was estimated based on a dermal penetration study in rats (see Section 4.2.1). Thus, the equivalent dermal NOAEL based on the rat prenatal developmental toxicity study can be estimated at 83.3 mg/kg/day (5 mg/kg/day ÷ 0.06 = 83.3 mg/kg/day). The occupational LOC is for MOEs less than 100 based on a combined UF of 100 applied to account for interspecies (10X), intraspecies (10X) extrapolation, and the 1X FQPA SF in residential settings.

Inhalation (Short- and Intermediate-Term): The inhalation risk for saflufenacil is being assessed using the rat prenatal developmental toxicity study assuming toxicity via the inhalation route is equivalent to oral route. The HASPOC recommended, based on a weight-of-evidence approach, that a subchronic inhalation toxicity study is not required at this time (A. Dunbar, TXR 0056720, 02-AUG-2013). 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 occupational LOC is for MOEs less than 100 based on a combined UF of 100 applied to account for interspecies (10X), intraspecies (10X) extrapolation, and the 1X FQPA SF in residential settings.

The toxicological doses and endpoints selected for acute and chronic dietary risk assessments of saflufenacil are summarized in Table 4.1.

Table 4.2.1. Summary of Toxicological Doses and Endpoints for Saflufenacil for Use in Dietary Human Health Risk Assessments.

Exposure/ Scenario	Point of Departure	Uncertainty/ FQPA SFs	RfD, PAD, LOC for Risk Assessment	Study and Toxicological Effects
Acute Dietary (General Population, including Infants and Children)	NOAEL = 500 mg/kg/day	UF_A = 10X UF_H = 10X FQPA SF = 1X	Acute RfD = 5.0 mg/kg aPAD = 5.0 mg/kg	Acute Neurotoxicity Study (rat) (MRID 47128127) LOAEL was 2000 mg/kg/day (males) based on the decreased motor activity representing mild and transient systemic toxicity. LOAEL was not established for females.
Chronic Dietary (All Populations)	NOAEL = 4.6 mg/kg/day	UF_A = 10X UF_H = 10X FQPA SF = 1X	Chronic RfD = 0.046 mg/kg/day cPAD = 0.046 mg/kg/day	Chronic/Carcinogenicity (mouse) (MRID 47128119) LOAELs = 13.8 mg/kg bw/day (males) and 38.1 mg/kg bw/day (females) based on decreased red blood cells, hemoglobin, and hematocrit and porphyria observed in the satellite group.
Incidental Oral Short-and Intermediate-Term (1-30 days and 1-6 months, respectively)	NOAEL = 15 mg/kg/day	UF_A = 10X UF_H = 10X FQPA SF = 1X	Non-Occupational LOC for MOE = 100	Reproduction and fertility effects (rat) (MRID 47128117) Offspring LOAEL = 50 mg/kg/day based on decreased viability and lactation indices, decreased pre-weaning body weight, and changes in hematological parameters.
Adult Oral Short-Term (1-30 days)	NOAEL = 5 mg/kg/day	UF_A = 10X UF_H = 10X FQPA SF = 1X	Non-Occupational LOC for MOE = 100	Developmental study (rat) LOAEL = 20 mg/kg bw/day based on decreased fetal bodyweight and increased skeletal variations.
Dermal Short- and Intermediate-Term (1-30 days and 1-6 months, respectively)	NOAEL = 5 mg/kg/day Dermal-absorption factor = 6%[1]	UF_A = 10X UF_H = 10X FQPA SF = 1X	Non-Occupational LOC for MOE <100	Developmental study (rat) (MRID 47128115) 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 assumed to be equivalent with oral	UF_A = 10X UF_H = 10X FQPA SF = 1X	Non-Occupational LOC for MOE <100	Developmental study (rat) (MRID 47128115) LOAEL = 20 mg/kg bw/day based on decreased fetal bodyweight and increased skeletal variations.
Cancer (oral, dermal, inhalation)	Classification: "Not likely to be carcinogenic to humans" based on the lack of tumors in the mouse and rat carcinogenicity studies and lack of mutagenicity.			

[1] 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 (MRID 47128214). NOAEL = no-observed adverse-effect level. LOAEL = lowest-observed adverse-effect level. UF = uncertainty factor. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). FQPA SF = FQPA Safety Factor. PAD = population-adjusted dose (a = acute, c = chronic). RfD = reference dose. LOC = level of concern.

Table 4.2.2. 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%[1]	UF_A = 10X UF_H = 10X FQPA SF = 1X	Occupational LOC for MOE < 100	Developmental study (rat) (MRID 47128115) 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 assumed to be equivalent with oral	UF_A = 10X UF_H = 10X FQPA SF = 1X	Occupational LOC for MOE < 100	Developmental study (rat) (MRID 47128115) LOAEL = 20 mg/kg bw/day based on decreased fetal bodyweight and increased skeletal variations.
Cancer (oral, dermal, inhalation)	Classification: "Not Likely to be Carcinogenic to Humans" based on the lack of tumors in the mouse and rat carcinogenicity studies and lack of mutagenicity.			

[1] 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 (MRID 47128214). 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

O. Gbemigun; 118203_TG00484712_CHEMD_2024-04-17

An overview of the dietary exposure and risk assessment is discussed in Section 5.4.1 and summarized in Table 5.4.6 of this document. Since the completion of the previous review of this petition, the applicant withdrew their initial request to support certain crop group expansions for 6-22A through 6-22F, 7-22, 15-22A through 15-22F, and 16-22. As there were no dietary exposure estimates that exceed the level of concern, the dietary risk assessment was not revised at this time. These changes to the dietary exposure assessment will be incorporated in the next risk assessment.

5.1 Residues of Concern Summary and Rationale

Plants (Primary Crops): The previously submitted metabolism data for corn, soybean, and tomato; and a confined rotational crop study are adequate to elucidate the nature of the residue in plants resulting from pre-plant/pre-emergence application, a post-emergence-directed at the base of plants underneath the leaf canopy application, and a pre-harvest/desiccant application. An additional nature of residue study with a post-emergence application in rice as a representative monocot (grass) species showed metabolism similar to the metabolism of saflufenacil in plants following a pre-plant/pre-emergence application. The HED ROCKS determined that residues of concern for the tolerance expression and risk assessment consist of saflufenacil, M800H11, and M800H35 (Memo, B. Daiss, 06-JAN-2009; D359645).

Livestock: The nature of the residue in livestock is adequately understood based on acceptable metabolism studies conducted on lactating goats and laying hens. Mint is not a livestock feeding item.

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 (1,1,1-trifluoro-2-propanol). 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 (L. Austin, *et al.*, D367317, 22-JUL-2009).

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	Primary Crops (pre-plant application)*	Saflufenacil + M800H11, M800H35	Saflufenacil + M800H11, M800H35
	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 and to weeds in fruit/nut orchards/groves.

5.2 Food Residue Profile

The nature of the residue is adequately understood in the subject petition (O. Gbemigun; 118203_TG00484712_CHEMR_2024-06-17). There are no residue chemistry issues that would preclude establishing tolerances for residues of saflufenacil, as outlined in Table 2.2.2.

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 18-FEB-2020 (Memo, M. Ruhman, D453029). We received a confirmation from EFED that the previous EDWC remain unchanged. (Email correspondence with M. Ruhman, 22-DEC-2022). Water residues were incorporated directly into the DEEM-FCID in the food categories "water, direct, all sources" and "water, indirect, all sources."

The highest 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. Values from the Tier I rice modeling were recommended for use in dietary assessments.

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

Acute and chronic dietary exposure assessments were conducted using DEEM-FCID, ver. 4.02 which incorporates consumption data from the USDA (NHANES/WWEIA; 2005-2010. The acute and chronic analyses assumed 100 PCT, HED's default processing factors, and 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 (O. Gbemigun; 118203_TG00484712_CHEMD_2024-04-17)

5.4.2 Percent Crop Treated Used in Dietary Assessment

The acute and chronic analyses assumed 100 PCT.

5.4.3 Acute Dietary Risk Assessment

The unrefined acute dietary (food and drinking water) exposures were not of concern (<100% of the aPAD)) for the general U.S. population and all population subgroups. 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 empirical processing factors, incorporation of PCT data, or monitoring data.

5.4.4 Chronic Dietary Risk Assessment

The unrefined chronic dietary (food and drinking water) exposures were not of concern (<100% of the cPAD) for the general U.S. population and all population subgroups. The general U.S. population used 9.3% of the cPAD. The most highly exposed population subgroup was all infants <1 year old which used 26% 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, empirical processing factors, incorporation of PCT data, or monitoring data.

5.4.5 Cancer Dietary Risk Assessment

Saflufenacil is classified as "Not Likely to be Carcinogenic to Humans." Therefore, a cancer risk assessment is not required.

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	0.010215	<1	0.004296	9.3
All Infants (<1-year old)	**0.029126**	**<1**	**0.011983**	**26**
Children 1-2 years old	0.017401	<1	0.008557	19
Children 3-5 years old	0.013946	<1	0.007414	16
Children 6-12 years old	0.010698	<1	0.004839	11
Youth 13-19 years old	0.008265	<1	0.003377	7.3
Adults 20-49 years old	0.009148	<1	0.003982	8.7
Adults 50-99 years old	0.007698	<1	0.003663	8.0
Females 13-49 years old	0.008880	<1	0.003784	8.2

* The subpopulation(s) with the highest risk estimates are bolded.

6.0 Residential Exposure/Risk Characterization

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

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.

7.1 Acute Aggregate Risk

As there are no registered or proposed uses that result in residential exposures, the acute aggregate risk assessment consists of exposure estimates from dietary consumption of saflufenacil (food and drinking water) only. The acute aggregate exposure estimates are therefore equivalent to the exposures in Table 5.4.6 and are not of concern to HED (<100% aPAD) for the general U.S. population or any population subgroups.

7.2 Chronic Aggregate Risk

As there are no registered or proposed uses that result in residential exposures, the chronic aggregate risk assessment consists of average exposure estimates from dietary consumption of saflufenacil (food and drinking water) only. The chronic aggregate exposure estimates are therefore equivalent to the exposures in Table 5.4.6 and are not of concern to HED (<100% cPAD) for the general U.S. population or any population subgroups.

8.0 Non-Occupational Spray Drift Exposure and Risk Estimates

Spray drift is a potential source of exposure to individuals who are located in close proximity to pesticide applications. This is particularly the case with aerial application, which tends to have the highest amount of drift as evaluated, but spray drift can also be a potential source of exposure from the ground application methods. The Agency has developed best spray drift management practices with input from the Spray Drift Task Force[1], EPA Regional Offices, and State Lead Agencies for pesticide regulation as well as other parties (see the Agency's Spray Drift website for more information).[2] The Agency has also prepared a draft document on how to appropriately consider spray drift as a potential source of exposure in risk assessments for pesticides. The approach is outlined in the revised 2013 *Residential Exposure Assessment Standard Operating Procedures Addenda 1: Consideration of Spray Drift*, which can be found at Regulations.gov in docket identification number EPA-HQ-OPP-2013-0676. The potential for spray drift from saflufenacil uses will be evaluated during the ongoing Registration Review process to ensure that all uses for that pesticide will be considered concurrently.

9.0 Non-Occupational Bystander Post-Application Inhalation Exposure and Risk Estimates

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 Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) Scientific

[1] This task force was organized in 1990, pursuant to the provisions of FIFRA section 3(c)(2)(B)(ii). It was comprised of pesticide registrants and those applying for registration of pesticide products to give them the option of fulfilling spray drift data requirements by participating in the task force, which would share the cost of developing a generic spray drift database expected to be capable of satisfying spray drift data requirements for virtually all pesticide product registrations in the United States and Canada. Available online: PRN 90-3: Announcing the Formation of an Industry-Wide Spray Drift Task Force | US EPA

[2] EPA's webpage is available online: Reducing Pesticide Drift | US EPA. It contains extensive information about EPA's efforts to reduce spray drift as well as additional materials and links to educational materials that provide information about practices for reducing spray drift.

Advisory Panel (SAP) in December 2009, and received the SAP's final report on March 2, 2010[3]. The Agency has evaluated the SAP report and has developed a Volatilization Screening Tool and a subsequent Volatilization Screening Analysis (*Human Health Bystander Screening Level Analysis: Volatilization of Conventional Pesticides*[4]).

During Registration Review, the Agency will utilize this analysis to determine if data (i.e., flux studies, route-specific inhalation toxicological studies) or further analysis is required for saflufenacil.

10.0 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. For the purposes of this action, therefore, EPA has not assumed that saflufenacil has a common mechanism of toxicity with other substances. In 2016, EPA's Office of Pesticide Programs released a guidance document entitled, Pesticide Cumulative Risk Assessment: Framework for Screening Analysis.[5] This document provides guidance on how to screen groups of pesticides for cumulative evaluation using a two-step approach beginning with the evaluation of available toxicological information and if necessary, followed by a risk-based screening approach. This framework supplements the existing guidance documents for establishing common mechanism groups (CMGs)[6] and conducting cumulative risk assessments (CRA)[7]. Saflufenacil is a broad-spectrum herbicide in mode-of-action Group 14 (cell membrane disruptors). As part of the ongoing process to review registered pesticides, the Agency intends to apply this framework to determine if the available toxicological data for saflufenacil suggests a candidate CMG may be established with other pesticides. If a CMG is established, a screening-level toxicology and exposure analysis may be conducted to provide an initial screen for multiple pesticide exposure.

11.0 Occupational Exposure/Risk Characterization

L. Venkateshwara, 06-11-2024; 118203_TG00484712_ORE_2024-06-17

Based on the use patterns and current labeling, types of equipment and techniques that can be used, dermal and inhalation occupational handler exposure is expected. The following use sites were assessed, for both ground and aerial applications:

- Mint (pre-plant, pre-emergence and early post-emergence) at an application rate of 0.044 lb ai/A.

  The combined dermal and inhalation occupational risk estimate MOEs range from 2,600 to 50,000 with label PPE (long-sleeved shirt, long pants, shoes and socks, protective eyewear, and chemical-resistant gloves). All MOEs are ≥ LOC of 100 and are not of concern. A summary of

[3] Available online: A Set of Scientific Issues Being Considered by the Environmental Protection Agency Regarding Field Volatilization of Conventional Pesticides | US EPA ARCHIVE DOCUMENT

[4] Available online: Regulations.gov

[5] https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/pesticide-cumulative-risk-assessment-framework

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

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

occupational handler exposure risk estimates can be found in Table 11.1. Note, an occupational exposure assessment for the crop group/subgroups associated with the newly proposed crop group conversions was conducted previously (Nowotarski, A., D379647, 7/27/2010 and C. Severini, D456302, 8/7/2020). No amendments to the use patterns [i.e., maximum use rates, RTIs, or PHIs] have been proposed.

Table 11.1. Occupational Handler Non-Cancer Exposure and Risk Estimates for Saflufenacil.

Exposure Scenario	Crop or Target	Dermal Unit Exposure[1] (µg/lb ai)	Level of PPE or Engineering control	Inhalation Unit Exposure[1] (µg/lb ai)	Level of PPE or Engineering control	Maximum Application Rate[2]	Area Treated or Amount Handled Daily[3]	Dermal		Inhalation		Total
								Dose[4] (mg/kg/day)	MOE[5] (LOC=100)	Dose[6] (mg/kg/day)	MOE[7] (LOC=100)	MOE[8] (LOC=100)
Mixer/Loader												
Liquid, Aerial, Broadcast	Field crop, high-acreage	37.6	SL/G	0.219	No-R	0.044 lb ai/acre	1200 acres	0.00173	2900	0.000168	30000	2600
Liquid, Groundboom, Broadcast	Field crop, high-acreage	37.6	SL/G	0.219	No-R	0.044 lb ai/acre	200 acres	0.000288	17000	0.000028	180000	16000
Applicator												
Spray (all starting formulations), Aerial, Broadcast	Field crop, high-acreage	2.08	EC/G	0.0049	EC/No-R	0.044 lb ai/acre	1200 acres	0.0000957	52000	0.00000375	1300000	50000
Spray (all starting formulations), Groundboom, Broadcast	Field crop, high-acreage	16.1	SL/G	0.34	No-R	0.044 lb ai/acre	200 acres	0.000123	41000	0.0000433	120000	31000
Flagger												
Spray (all starting formulations), Aerial, Broadcast	Field crop, high-acreage	12	SL/G	0.202	No-R	0.044 lb ai/acre	350 acres	0.000161	31000	0.0000451	110000	24000

1 Based on the "Occupational Pesticide Handler Unit Exposure Surrogate Reference Table" (https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticide-handler-exposure-data); Level of PPE: SL/G = single layer, gloves; EC = engineering controls; No-R = no respirator.

2 Based on proposed label (Reg. No. 7969-278).

3 Exposure Science Advisory Council Policy #9.2.

4 Dermal Dose = Dermal Unit Exposure (µg/lb ai) × Conversion Factor (0.001 mg/µg) × Application Rate (lb ai/acre or gal) × Area Treated or Amount Handled (A or gal/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 or gal) × Area Treated or Amount Handled (A or gal/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.

11.2 Occupational Post-application Exposure/Risk Estimates

HED uses the term post-application to describe exposures that occur when individuals are present in an environment that has been previously treated with a pesticide (also referred to as re-entry exposure). Such exposures may occur when workers enter previously treated areas to perform job functions, including activities related to crop production, such as scouting for pests or harvesting. Post-application exposure levels vary over time and depend on such things as the type of activity, the nature of the crop or target that was treated, the type of pesticide application, and the chemical's degradation properties. In addition, the timing of pesticide applications, relative to harvest activities, can greatly reduce the potential for post-application exposure.

11.2.1 Occupational Post-application Inhalation Exposure/Risk Estimates

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 FIFRA SAP in December 2009, and received the SAP's final report on March 2, 2010[8]. The Agency has evaluated the SAP report and has developed a Volatilization Screening Tool and a subsequent Volatilization Screening Analysis (*Human Health Bystander Screening Level Analysis: Volatilization of Conventional Pesticides*[9]). During Registration Review, the Agency will utilize this analysis to determine if data (i.e., flux studies, route-specific inhalation toxicological studies) or further analysis is required 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 exposure, and all of the occupational handler scenarios resulted in inhalation risk estimates that were not of concern at baseline (i.e., all inhalation MOEs without a respirator ≥ the LOC). Therefore, it is expected that these handler inhalation exposure estimates would be protective of most occupational post-application inhalation exposure scenarios (see Table 11.1).

11.2.2 Occupational Post-application Dermal Exposure/Risk Estimates

The end-use product, Sharpen® supplemental label (EPA Reg. No. 7969-278) states for mint, saflufenacil can only be applied to dormant established stands (defined as at least one year after planting) mint, up to two applications can be made per crop season and as a broadcast burndown spray to emerged broadleaf weeks in the dormant season (i.e., when mint is not actively growing in fall (post-harvest) or during winter dormancy. Note, for the proposed uses for saflufenacil on mint, there is no required PHI interval between a dormant application and the harvest of mint. HED does not expect post-application dermal exposure will occur.

[8] Available online: A Set of Scientific Issues Being Considered by the Environmental Protection Agency Regarding Field Volatilization of Conventional Pesticides | US EPA ARCHIVE DOCUMENT

[9] Available online: Regulations.gov

The EP, Treevix® (EPA Reg. No. 7969-276) is proposed for several crop group expansions: citrus fruit (crop group 10-10), pome fruit (crop group 11-10), stone fruit (crop group 12-12), tree nuts (crop group 14-12). The label states the application should be directed at the base of the tree trunks; therefore, HED does not expect that post-application dermal exposure will occur. The label also indicates that crop injury will result if the products are applied post-emergent (over the top) to any crop.

Restricted Entry Interval

Saflufenacil is classified as Toxicity Category III via the dermal route and Toxicity Category IV for skin irritation potential. It is not a skin 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), is classified as Acute III or IV for acute dermal, eye irritation and primary skin irritation 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. HED would recommend a REI of 12 hours. This is the REI listed on the proposed labels and is considered protective of post-application exposure.

12.0 References

G. Kramer *et al.*, D456093, 07-AUG-2020
HASPOC Memo: A. Dunbar, TXR 0056720, 02-AUG-2013
Chemistry Memo: O. Gbemigun, 118203_TG00484712_CHEMR_2024-06-17
Drinking Water Memo: M. Ruhman, D453029, 18-FEB-2020
Dietary Memo: O. Gbemigun, 118203_TG00484712_CHEMD_2024-04-17
ORE Memo: L. Venkateshwara, 118203_TG00484712_ORE_2024-06-17

List of Appendices:

Appendix A. Toxicology Profile
Appendix B. Physical/Chemical Properties
Appendix C. Review of Human Research
Appendix D: International Residue Limits

Appendix A. Toxicology Assessment

A.1 Toxicology Data Requirements for Saflufenacil

The requirements (40 CFR 158.500) for a food use for saflufenacil are in Table A.1. Use of the new guideline numbers does not imply that the new (1998) guideline protocols were used.

Test	Technical	
	Required	Satisfied
870.1100 Acute Oral Toxicity	yes	yes
870.1200 Acute Dermal Toxicity	yes	yes
870.1300 Acute Inhalation Toxicity	yes	yes
870.2400 Primary Eye Irritation	yes	yes
870.2500 Primary Dermal Irritation	yes	yes
870.2600 Dermal Sensitization	yes	yes
870.3100 Oral Subchronic (rodent)	yes	yes
870.3150 Oral Subchronic (nonrodent)	yes	yes
870.3200 21-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	-
870.7485 General Metabolism	yes	yes
870.7600 Dermal Penetration	yes	yes
870.7800 Immunotoxicity	yes	yes

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

A.2 Toxicity Profiles

Table A.2.1. Acute Toxicity Profile – Saflufenacil.[1]

Guideline No.	Study Type	MRID(s)	Results	Toxicity Category
870.1100	Acute Oral (rat)	47128101 (93.8% ai)	LD_{50} > 2000 mg/kg (F)	III
870.1200	Acute Dermal (rat)	47128102 (93.8% ai)	LD_{50} > 2000 mg/kg (M & F)	III
870.1300	Acute Inhalation (rat)	47128103 (93.8% ai)	LC_{50} > 5.3 mg/L (M & F)	IV
870.2400	Primary Eye Irritation (rabbit)	47128104 (93.9% ai)	Minimally irritating	IV
		47128105 (93.8% ai)	Minimally irritating	IV
870.2500	Primary Skin Irritation (rabbit)	47128106 (93.9% ai)	Non-irritating	IV
870.2600	Dermal Sensitization (guinea pig)	47128107 (93.8% ai)	Not a dermal sensitizer (Maximization)	N/A

[1] TXR 5010659, D349940, R. Whiting, 21-JUL-2009

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.

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

Table A.2.2. Subchronic, Chronic, and Other Toxicity Profile for Saflufenacil.		
Guideline No./Study Type	**MRID No. (year)/Classification/Doses**	**Results**
		*Note: This study was not updated; however, some of the offspring effects (e.g., decreased live born pups, increased number of stillborn pups, and decreased viability) would also be considered parental effects under current practices in hazard evaluation.
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. **There was 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. **There was 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 870.5375 *In vitro* Mammalian Cytogenetics chromosomal aberration assay-V79 cells	47128124 (2005) Acceptable/guideline 0, 5, 10, and 20 ug/ml without S9 activation 0, 10, 20, and 40 ug/ml with S9 activation	Saflufenacil was considered clastogenic in 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.

Table A.2.2. Subchronic, Chronic, and Other Toxicity Profile for Saflufenacil.		
Guideline No./Study Type	**MRID No. (year)/Classification/Doses**	**Results**
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 mg/kg bw/d F = 0, 3.9, 19.4, 101.0 mg/kg bw/d	Systemic NOAEL = 16.6 (males) and 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 group to NH_2, and cleavage of the uracil ring, forming a

Table A.2.2. Subchronic, Chronic, and Other Toxicity Profile for Saflufenacil.		
Guideline No./Study Type	**MRID No. (year)/Classification/Doses**	**Results**
		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-related 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	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 (MRID 47128214). Immediately after a 10-hour exposure, the estimated DAF was 3.4% calculated as the sum of the excreta, carcass, and blood. 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.
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 anhydrate forms of saflufenacil were similar.
Mechanistic study – total porphyrin analysis in rat	47128132 (2006) Acceptable/non-guideline 0, 10, 50, or 1000 ppm (M = 0, 0.8, 4.1, 80.6; F = 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.

Table A.2.2. Subchronic, Chronic, and Other Toxicity Profile for Saflufenacil.		
Guideline No./Study Type	**MRID No. (year)/Classification/Doses**	**Results**
Mechanistic study-porphyrin analysis supplementary (rat)	47128131 (2005) Acceptable/non-guideline 0, 1, 5, or 25 ppm (M = 0, 0.1, 0.4, 2.0; F = 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 Version 1.1 (PHED 1.1), the Agricultural Handler Exposure Task Force (AHETF) database, the Agricultural Reentry Task Force (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 websites: http://www2.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticide-handler-exposure-data and http://www2.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticide-post-application-exposure.

Appendix D: International Residue Limits Table

Saflufenacil (118203)

Summary of U.S. and International Tolerances and Maximum Residue Limits				
Residue Definition:				
U.S.	Canada		Mexico[2]	Codex
40 CFR 180.649: Plant: saflufenacil, including its metabolites and degradates, sum of saflufenacil, 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, and its metabolites *N*-[2-chloro-5-(2,6-dioxo-4-(trifluoromethyl)-3,6-dihydro-1(2*H*)-pyrimidinyl)-4-fluorobenzoyl]-*N*'-isopropylsulfamide and *N*-[4-chloro-2-fluoro-5-({[(isopropylamino)sulfonyl]amino}carbonyl)phenyl]urea, calculated as the stoichiometric equivalent of saflufenacil	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, including the metabolites *N*'-{2-chloro-4-fluoro-5-[1,2,3,6-tetrahydro-2,6-dioxo-4-(trifluoromethyl)pyrimidin-1-yl]benzoyl}-*N*-isopropyl sulfamide and *N*-[4-chloro-2-fluoro-5-({[(isopropylamino)sulfonyl]amino}carbonyl)phenyl]urea Livestock: 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		Saflufenacil The residue is not fat soluble. Residue definition does not include metabolites.
Commodity[1]	*Tolerance (ppm)/Maximum Residue Limit (mg/kg)*			
	U.S.	Canada	Mexico[2]	Codex
Fruit, citrus, group 10-10	0.03	0.03	0.03	0.01
Fruit, pome, group 11-10	0.03	0.03	0.03	0.01
Fruit, stone, group 12-12	0.03	0.03	0.03	0.01
Mint, dried leaves	0.03	-	-	-
Mint, fresh leaves	0.03	-	-	-
Nut, tree, group 14-12	0.03	0.03	0.03	0.01
From the Global MRL Database. Completed: O. Gbemigun (July 25, 2023)				

[1] Includes only commodities of interest for this action. Tolerance values should be the HED recommendations and not those proposed by the applicant. [2] Mexico adopts U.S. tolerances and/or Codex MRLs for its export purposes.