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Saflufenacil: Tolerance Petition to Establish Field Pennycress Seed, May 2024

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PP4E9140

EPA has received a pesticide petition (PP4E9140) from the Interregional Research Project #4 (IR-4), NC State University, 1730 Varsity Drive, Venture IV, Suite 210, Raleigh, NC 27606 proposing, pursuant to section 408(d) of the Federal Food, Drug, and Cosmetic Act (FFDCA), 21 U.S.C. 346a(d), to amend 40 CFR part 180.649 by establishing a new tolerance for residues of the herbicide saflufenacil, including its metabolites and degradates. 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(2H)-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(2H)-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 following raw agricultural plant commodities: establishing a tolerance in or on Pennycress, seed at 0.45 parts per million (ppm).

EPA has determined that the petition contains data or information regarding the elements set forth in section 408 (d)(2) of FDDCA; however, EPA has not fully evaluated the sufficiency of the submitted data at this time or whether the data supports granting of the petition. Additional data may be needed before EPA rules on the petition.

A. Residue Chemistry

1. *Plant metabolism.* 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 preplant/preemergence application, a postemergence-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 postemergence application in rice as a representative monocot (grass) species showed metabolism similar to the metabolism of saflufenacil in plants following a preplant/preemergence application. Therefore, the residues of concern for the tolerance expression and risk assessment consist of saflufenacil, M800H11, and M800H35.

2. *Analytical method.* Adequate enforcement methodology (liquid chromatography/mass spectrometry/mass spectrometry (LC/MS/MS) methods for plant and livestock commodities are available to enforce the tolerance expression.

3. *Magnitude of residues.* No magnitude of residue data was submitted specifically for (field) pennycress, as data on this crop is bridged from previously submitted magnitude of residue data on rapeseed (canola) subgroup 20A. Detected combined residues of saflufenacil plus metabolites in the crop commodities support the proposed establishing of tolerances.

B. Toxicological Profile

1. *Acute toxicity.* Saflufenacil has low acute toxicity via the oral, dermal, and inhalation routes of exposure. It is slightly irritating to the eye but is neither a dermal irritant nor sensitizer.

2. *Genotoxicity.* Saflufenacil is 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 is neither mutagenic in bacterial cells nor clastogenic in rodents *in vivo*.

3. *Reproductive and developmental toxicity.* Increased fetal and offspring susceptibility to saflufenacil were observed in the developmental toxicity studies in the rat and rabbit and in the 2-generation reproduction study in the rat. Developmental effects such as decreased fetal body weights and increased skeletal variations occurred at doses that were not maternally toxic in the developmental study in rats, indicating increased quantitative susceptibility. In rabbits, developmental effects such as increased liver porphyrins were observed at doses that were not maternally toxic, indicating increased quantitative susceptibility. In the 2-generation reproduction study in rats, offspring effects such as increased number of stillborn pups, decreased viability and lactation indices, decreased pre-weaning body weight and/or body-weight gain and changes in hematological parameters were observed at a dose resulting in less severe maternal toxicity (decreased food intake, body weight/weight gain and changes in hematological parameters and organ weights indicative of anemia), indicating increased qualitative susceptibility.

4. *Sub-chronic toxicity.* Short-term, sub-chronic, and chronic toxicity studies in rats, mice, and dogs identified the hematopoietic system as the target organ of saflufenacil. Protoporphyrinogen oxidase inhibition in the mammalian species may result in disruption of heme synthesis which in turn causes anemia. In these studies, decreased hematological parameters (red blood cells (RBC), hematocrit (Ht), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC)) were seen at about the same dose level 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 the short-term through long-term exposures without increasing in severity. Effects were also seen in the liver (increased weight, centrilobular fatty change, and lymphoid infiltrate) in mice, the spleen (increased spleen weight and extramedullary hematopoiesis) in rats, and in both 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 the short-term through long-term exposures without increasing in severity. No dermal toxicity was seen at the limit dose in a 28–day

dermal toxicity study in rats. There was no evidence of neurotoxicity or neuropathology in the toxicity database for saflufenacil. In the acute neurotoxicity study, a decrease in motor activity was observed on the first day of dosing at the limit dose in males only. The finding was not accompanied by any other neuropathological changes and was considered a reflection of a mild and transient general systemic toxicity and not a substance-specific neurotoxic effect. In the sub-chronic neurotoxicity study, systemic toxicity (anemia), but no evidence of neurotoxicity, was seen in males and females. There was no evidence of immunotoxity in the toxicity database for saflufenacil. In the immunotoxicity study conducted in male mice, systemic toxicity (signs of anemia and liver effects) was seen, but the effects were not indicative of immunotoxicity. There were no effects on sheep red blood cell (SRBC) IgM antibody titers or immune system organ weights (spleen and thymus) in the treated mice. In the 90-day oral toxicity study in rats, the increase in spleen weight seen only in rats is attributable to an increased clearance of defective RBCs (i.e., defective hemoglobin synthesis) and is thus an indication of toxicity to the hematopoietic system rather than to the immune system.

5. *Chronic toxicity.* Carcinogenicity studies in rats and mice showed no evidence of increased incidence of tumors at the tested doses. Saflufenacil is classified as not likely to be carcinogenic to humans.

6. *Animal metabolism.* Rat metabolism data indicate that saflufenacil is well absorbed and rapidly excreted. The maximum concentration of saflufenacil in blood and plasma was reached within 1 hour (h) of dosing and declined rapidly after 24 h. Excretion of orally dosed saflufenacil was essentially complete within 96 h, with the majority eliminated within the first 24 to 48 h. There was a sex-dependent difference in the excretion of orally administered saflufenacil. The main route of elimination in male rats was via the feces, while urinary excretion was the major route of elimination in females. The sex-dependent excretion was more pronounced at the low-dose level than at the high-dose level. Also, males had significantly higher biliary excretion of saflufenacil residues than 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. The parent molecule and 3 major metabolites were identified and isolated from urine and feces. There were no significant gender differences in metabolic profiles. Saflufenacil was metabolized by three major transformation steps, which were 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 sulfonylamide group. The metabolism of saflufenacil in the animals is well understood.

7. *Metabolite toxicology*. No metabolites of toxicological concern are identified.

8. *Endocrine disruption*. No specific tests have been conducted with saflufenacil to determine whether the chemical may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen or other endocrine effects. However, there were no significant findings in other relevant toxicity studies (e.g., sub-chronic and chronic toxicity, developmental toxicity and multi-generation reproductive studies) which would suggest that saflufenacil produces any endocrine disruption.

C. Aggregate Exposure

1. *Dietary exposure.* Exposure assessments were conducted to evaluate the potential risk due to acute and chronic dietary exposure of the U.S. population to combined residues of saflufenacil and metabolites M800H11 and M800H35. The current established tolerance values are listed as of May 1, 2024, in the U.S. 40 CFR § 180.649. This analysis includes all the crops with established tolerances, and also includes the proposed amended tolerances (submitted to EPA in April 2024) on forage (popcorn and sweet corn) and stover (popcorn and sweet corn) and the proposed established tolerances on soybean forage and soybean hay that do not impact the livestock feeding burden nor the established tolerances for meat and dairy commodities, and the proposed established tolerance on pennycress, seed. Therefore, there is no increase in the estimated dietary exposure for the US populations.

i. *Food.*

Acute Dietary Exposure Assessment

Acute dietary exposure estimates were conducted using the currently established tolerances for saflufenacil (40 CFR 180.649). The unrefined assessment was conducted using tolerance values, default process factors, and 100% crop treatment factors. The consumption data was from the 2003-2008 USDA National Nutrition Examination survey (What We Eat in America). The drinking water estimated concentrations were included directly into the acute dietary exposure analysis. The assessments were performed with DEEM-FCID version 4.02. No food item tolerance values were changed as the result of this petition, but the dietary assessments have been updated using DEEM-FCID version 4.02 with consumption data from the 2005-2010 NHANES surveys and as requested by EPA, a comparison of DEEM with CARES NG Dietary Model 1.2.4. The resulting exposure estimates were compared against the saflufenacil acute Population Adjusted Dose (aPAD) of 5 mg/kg b.w./day for all populations. This endpoint is based on the NOAEL of 500 mg/kg/day with the standard inter- and intra-species uncertainty factors of 100X and an FQPA safety factor of 1. The exposure for all sub-population was less than 1.0% utilization of the aPAD. The results of the acute dietary assessment are presented in **Table 1** with exposure estimates using DEEM-FCID version 4.02 compared to CARES NG Dietary Model 1.2.4.

Table 1. Saflufenacil Acute Dietary Exposure Analysis Considering all Tolerances at the 95th Percentile per Capita

Population Subgroups	Exposure Estimate (mg/kg b.w./day)		%aPAD (all models)
	DEEM 4.02	CARES 1.2.4	
General U.S. Population	0.010600	0.010242	< 1
All Infants (< 1 year old)	0.028718	0.028718	< 1
Children (1-2 years old)	0.018312	0.017625	< 1
Children (3-5 years old)	0.014595	0.013925	< 1

Children (6-12 years old)	0.011222	0.010763	< 1
Youth (13-19 years old)	0.008555	0.008221	< 1
Adults (20-49 years old)	0.009329	0.009149	< 1
Adults (50+ years old)	0.007846	0.007714	< 1
Females (13 – 49 years old)	0.009081	0.008893	< 1

The results of the analysis show that for all populations, the estimated exposures are well below the Agency's level of concern (< 100% aPAD). Additional refinements in the dietary risk assessment (i.e. utilizing anticipated residue values, percent crop treated values) would further reduce the estimated exposure values.

Chronic Dietary Exposure Assessment

Chronic dietary exposure estimates were conducted using the currently established tolerances for saflufenacil (40 CFR 180.649). The unrefined assessment was conducted using tolerance values, default process factors, and 100% crop treatment factors. The consumption data was from the USDA Continuing Survey of Food Intake by Individuals (CSFII 1994 - 1996, 1998) and the EPA Food Commodity Ingredient Database (FCID) using Exponent's Dietary Exposure Evaluation Module (DEEM-FCID) software. The drinking water estimated concentrations were included directly into the chronic dietary exposure analysis. No food item tolerance values were changed as the result of this petition, but the dietary assessments have been updated using DEEM-FCID version 4.02 with consumption data from the 2005-2010 NHANES surveys and as requested by EPA, a comparison of DEEM with CARES NG Dietary Model 1.2.4. The chronic Population Adjusted Dose (cPAD) used for U.S. population and all sub-populations is 0.046 mg/kg bw/day. This endpoint is based on the NOAEL value of 4.6 using the standard inter- and intra-species uncertainty factors of 100X and with a FQPA safety factor of 1. The most highly exposed population sub-group was infants (< 1 year old) which utilized 26 % cPAD (from DEEM 4.02 and CARES 1.2.4 assessment). The results of the chronic dietary assessment are presented in **Table 2**.

Table 2. Saflufenacil Chronic Dietary Exposure Analysis Considering all Tolerances

Population Subgroups	Exposure Estimate (mg/kg b.w./day)		%cPAD	
	DEEM 4.02	CARES 1.2.4	DEEM 4.02	CARES 1.2.4
General U.S. Population	0.004490	0.004292	9.8%	9.33
All Infants (< 1 year old)	0.012074	0.011976	26.2%	26.04
Children (1-2 years old)	0.009161	0.008656	19.9%	18.82
Children (3-5 years old)	0.007587	0.007083	16.5%	15.4
Children (6-12 years old)	0.005176	0.004819	11.3%	10.48

Youth (13-19 years old)	0.003611	0.003393	7.8%	7.38
Adults (20-49 years old)	0.004149	0.003991	9.0%	8.68
Adults (50+ years old)	0.003807	0.003673	8.3%	7.99
Females (13-49 years old)	0.003954	0.003795	8.6%	8.25

The results of the analysis show that for all populations, the exposures are far below a level of concern (< 100% cPAD). Additional refinements in the chronic dietary risk assessment (i.e. utilizing anticipated residue values and percent crop treated values) would further reduce the estimated exposure values.

ii. *Drinking water*. The drinking water values used in this assessment were from the most recent human health risk assessment conducted by US EPA on December 5, 2023, "Saflufenacil. Human-Health Risk Assessment for Proposed New and Amended Uses on Field Corn Commodities, Post-harvest, and Fallow Land". The highest Estimated Drinking Water Concentrations (EDWC's) for saflufenacil occurred with the rice use. The EDWCs used in the dietary exposure analysis were 133 µg/L (ppb) for acute risk assessment and 120 µg/L (ppb) for the chronic risk assessment.

Acute Aggregate Exposure and Risk (food and water)
The aggregate acute risk includes exposure of saflufenacil from food and water (**Table 1**). The results demonstrate that the use of saflufenacil does not result in an unacceptable acute risk.

Short- and Intermediate-Term Aggregate Exposure and Risk (food, water, and residential)
Short- and intermediate-term aggregate risk assessments include exposure from food, water, and residential uses. There are no registered or proposed residential uses for saflufenacil therefore a short- and intermediate-term aggregate risk assessment is not required.

Chronic Aggregate Exposure and Risk (food and water)
The aggregate chronic risk includes exposure of saflufenacil from food and water (**Table 2**). The results demonstrate that the use of saflufenacil does not result in an unacceptable chronic risk.

2. *Non-dietary exposure*. The term ''residential exposure'' is used to refer to non-occupational, non-dietary exposure (e.g., for lawn and garden pest control, indoor pest control, termiticides, and flea and tick control on pets). Saflufenacil is not registered for any specific use patterns that would result in residential exposure. Therefore, a non-dietary exposure and risk evaluation was not conducted.

D. Cumulative Effects

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

common mechanism of toxicity." EPA has not found saflufenacil to share a common mechanism of toxicity with any other substances, and saflufenacil does not appear to produce a toxic metabolite produced by other substances. For the purposes of this tolerance petition, therefore, EPA will assume that saflufenacil does not have a common mechanism of toxicity with other substances.

E. Safety Determination

1. *U.S. population.* Based on this risk assessment, BASF concludes that there is a reasonable certainty that no harm will result to the general population from the aggregate exposure to saflufenacil from the proposed uses.

2. *Infants and children*. Based on this risk assessment, BASF concludes that there is a reasonable certainty that no harm will result to infants or children from the aggregate exposure to saflufenacil from the proposed uses.

F. International Tolerances

National maximum residue limits (MRLs) for saflufenacil are available in a number of countries as referenced below.

Codex CXLs for saflufenacil are available for numerous plant and animal commodities (website reference: http://www.codexalimentarius.net/pestres/data/pesticides/details.html?id=251);

Canadian MRLs for saflufenacil (including its metabolites) are established and harmonized with US Tolerances for various crops and livestock commodities (website reference: http://pr-rp.hc-sc.gc.ca/mrl-lrm/results-eng.php)

Japanese MRLs for saflufenacil are established for numerous plant and animal commodities (website reference: http://www.m5.ws001.squarestart.ne.jp/foundation/agrdtl.php?a_inq=24250)

South Korean MRLs for saflufenacil are established for numerous plant commodities (website reference: http://fse.foodnara.go.kr/residue/pesticides/pesticides_mrl_korea_view.jsp?pesticideCode=P01627)

Australian MRLs for saflufenacil are established for numerous plant and animal commodities (website reference: http://www.apvma.gov.au/residues/docs/mrl_table1_december_2012.pdf)

Brazilian MRLs for Saflufenacil are established for a few plant commodities (website reference: http://portal.anvisa.gov.br/wps/wcm/connect/db5a2c804b9a7f57afa2bfaf8fded4db/S16+-+Saflufenacil.pdf?MOD=AJPERES)

European Union MRLs for saflufenacil are established for numerous plant and animal commodities (website reference: http://ec.europa.eu/sanco_pesticides/public/?event=homepage)