OFFICE OF CHEMICAL SAFETY AND POLLUTION PREVENTION

WASHINGTON, D.C. 20460

April 11, 2024

MEMORANDUM

SUBJECT: **Flonicamid.** Human Health Risk Assessment for the Petition for Amendment of Tolerances in/on Low Growing Berry Subgroup 13-07G.

PC Code: 128016
CAS No.: 158062-67-0
Decision No.: 591545
Petition No.: 3F9050
Risk Assessment Type: Single Chemical/Aggregate
TXR No.: NA
MRID No.: NA

DP Barcode: D467665
Task Group No.: 00484486
Parent Case No.: 00475300
Registration No.: NA
Regulatory Action: Section 3 – Tolerance amendment
Case No.: NA
40 CFR: §180.613

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The Registration Division (RD) of the Office of Pesticide Programs (OPP) has requested that the Health Effects Division (HED) conduct a risk assessment to estimate the risks to human health that may result from the amended tolerance on low growing berry subgroup 13-07G. The most recent quantitative human health risk assessment was performed in 2023 (J. Smith, *et al*., D465992, 09/12/2023). Flonicamid also recently completed registration review and the interim decision (ID) was made public on March 18, 2021 (Case No. 7436, EPA-HQ-OPP-2014-0777, 86 FR 14748).

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: EPA's Scientific Integrity Policy. The full text of the EPA Scientific Integrity Program's *Approaches for Expressing and Resolving Differing Scientific Opinions* can be found here: Approaches for Expressing and Resolving Differing Scientific Opinions | US EPA

1.0 Executive Summary

The active ingredient (ai) flonicamid, *N*-(cyanomethyl)-4-(trifluoromethyl)-3-pyridinecarboxamide, is a systemic insecticide that immediately suppresses the feeding of sucking insects on plants. Based on its chemical structure (a nicotinic acid derivative), flonicamid would be expected to exhibit the same mode of action as similarly structured neonicotinoid pesticides; however, flonicamid has not been found to inhibit acetylcholine esterase (like organophosphates and carbamates) or nicotinic acetylcholine receptors (like neonicotinoids).

Flonicamid is currently registered for use on a variety of agricultural crops, commercial ornamentals, interiorscapes, and nurseries; and in residential settings on roses, flowers, shrubs, and small (non-fruit bearing) trees. Tolerances are established for residues of flonicamid and its metabolites in 40 CFR 180.613 and range from 0.15 ppm for tree nuts except pistachio, group 14-12 to 40 ppm for tea. Livestock tolerances are established for poultry, cattle, goats, hogs, horses, and sheep fat at 0.03 ppm, egg at 0.04 ppm, milk at 0.05 ppm, meat & meat byproducts of goats, horses, and sheep at 0.08 ppm, meat and meat byproducts of hogs and poultry at 0.03 ppm. A regional registration for clover forage and hay is established at 0.90 and 5.0 ppm, respectively.

The petitioner, ISK Biosciences Corporation (ISK), is requesting to amend tolerances for residues of the insecticide flonicamid and its metabolites and degradates determined by measuring flonicamid and its metabolites TFNA (4-trifluoromethylnicotinic acid), TFNA-AM (4-trifluoromethyl-nicotinamide), and TFNG [*N*-(4-trifluoromethylnicotinoyl)glycine], calculated as the stoichiometric equivalent of flonicamid in or on the raw agricultural commodity low growing berry subgroup 13-07G in order to harmonize the U.S. EPA-established 1.5 ppm tolerance to the current 2 ppm tolerance in Japan and minimize trade barriers.

Use Profile

The use pattern associated with flonicamid remains unchanged since the previous assessments. Flonicamid end-use products (EPs) are currently registered as water-dispersible granular (WDG) and solid granular (SG) formulations containing 50% ai by weight. Applications can be made with ground, aerial, airblast, chemigation, and handheld equipment. The labels require that applicators and other handlers wear long-sleeved shirts, long pants, shoes, socks, and personal protection equipment (PPE) consisting of chemical-resistant gloves. The Beleaf® 50SG Insecticide, EPA Reg. No. 71512-10, label requires applicators using mechanically pressurized handgun equipment in greenhouses must wear a NIOSH approved respirator; all other product labels do not require handlers to wear respiratory protection. The restricted-entry interval (REI) on the registered labels is 12 hours.

Exposure Profile

Humans may be exposed to flonicamid in food and drinking water since flonicamid may be applied directly to growing crops, and applications may result in flonicamid reaching surface and ground sources of drinking water. Based on the registered use patterns, occupational handler short- (1 to 30 days) and intermediate-term (1 to 6 months) dermal and inhalation exposures to flonicamid are expected. There is also potential for short- and intermediate term occupational post-application dermal exposures to occur for workers entering fields previously treated with flonicamid. There are no residential exposures expected from the submitted petition; however, there are registered residential

uses that have been included in this assessment for purposes of aggregate assessment. Short-term non-occupational spray drift exposures may also occur and are assessed as part of Registration Review.

Residue Chemistry & Tolerance Considerations

The residue chemistry database is considered complete, including adequate analytical methods; storage stability; residues from field trials; and residues in processed commodities. The nature of the residues in plants, rotational crops, and livestock is adequately understood. Adequate analytical methods are available for enforcing tolerances in plant and livestock commodities. Adequate storage stability data are available to support the storage durations and conditions of samples of the registered uses. Adequate crop field trial data are available to support the petition. HED notes: ISK Biosciences has submitted data for residues of flonicamid in/on strawberry from trials performed in Japan (MRID 52081601).

Dietary Exposure and Risk Assessment

Based upon the hazard profile of flonicamid, no acute dietary assessment is warranted. The chronic dietary exposure estimates for food and drinking water are below HED's level of concern (LOC), <100% of the chronic population-adjusted dose (cPAD), for the general U.S. population and all population subgroups and are therefore not of concern. Flonicamid dietary exposures account for 30% of the cPAD for the general U.S. population and 91% of the cPAD for children 1-2 years old, the most highly exposed population subgroup.

Flonicamid has been determined to have suggestive evidence of carcinogenicity, but not sufficient to assess human carcinogenic potential. The Agency has determined that quantification of risk using a non-linear approach (*i.e*., using a chronic reference dose) adequately accounts for all chronic toxicity, including carcinogenicity that could result from exposure to flonicamid. Therefore, the chronic reference dose (cRfD) is considered protective for carcinogenic effects. As a result, a separate cancer risk assessment was not conducted.

Aggregate Exposure and Risk Assessment

In accordance with the Food Quality Protection Act (FQPA), HED must consider and aggregate (add) pesticide exposures and risks from three major sources: food, drinking water, and residential exposures. For the current action, HED has determined that there is likely potential dietary exposure but do not expect residential handler or post-application exposures; however, there are existing registered residential handler uses that were previously assessed which have been included for purposes of aggregate assessment (S. Garred, D452374, 10/14/2020). Therefore, for short-term aggregate risk, adult residential exposure estimates have been aggregated with adult dietary exposure estimates, considered background. The estimated short-term aggregate MOE for adults is 1,100 (level of concern (LOC) = 100) and is not of concern.

Residential and Occupational Exposure and Risk Assessment

The use pattern associated with flonicamid remains unchanged since the previous assessments. Therefore, HED has previously assessed residential and occupational exposures and risk estimates (S. Garred, D452374, 10/14/2020) and has not identified any risks of concern. The conclusions of those assessments remain unchanged.

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.[1]"

Human Studies

This risk assessment relies in part on data from studies in which adult human subjects were intentionally exposed to a pesticide to determine their exposure. Appendix C provides additional information on the review of human research used to complete the risk assessment. There is no regulatory barrier to continued reliance on these studies, and all applicable requirements of EPA's Rule for the Protection of Human Subjects of Research (40 CFR Part 26) have been satisfied (see Appendix C).

2.0 HED Recommendations

There are no residue chemistry, toxicology, or risk issues that would preclude granting the tolerance for residues of flonicamid in/on low growing berry subgroup 13-07G. Tolerance recommendations are included in Section 2.2.2.

2.1 Data Deficiencies

None.

2.2 Tolerance Considerations

2.2.1 Enforcement Analytical Method

Plants: FMC Method No. P-3561M, a liquid chromatography with tandem mass spectroscopy (LC/MS/MS) method, is an acceptable enforcement method for flonicamid and its metabolites in plant commodities. The method determines residues of flonicamid and its metabolites TFNA, TFNA-AM, and TFNG. The method has been sufficiently validated in five diverse crops. Depending on the matrix, the limit of quantification (LOQ) is 0.01 or 0.02 ppm. The limit of detection (LOD) can be estimated as one-third the LOQ.

Livestock: Three enforcement methods are used for livestock commodities: an LC/MS/MS method RCC No. 844743 for determination of residues in/on eggs, poultry tissues, and fat of cattle, goat, hog, horse, and sheep; LC/MS method RCC No. 842993 for determination of residues in milk; and LC/MS/MS method FMC No. P-3580, for determination of residues in/on meat and meat byproducts (kidney and liver) of cattle, goat, hog, horse, and sheep. All three methods determine flonicamid and the metabolites TFNA and TFNA-AM. The LOQs for each analyte in each matrix (based on the lowest level of method validation) are 0.01 ppm for Methods RCC No. 844743 and RCC No. 842993, and 0.025 for FMC No. P-3580. The LODs are all 0.005 ppm.

2.2.2 Recommended Tolerances

[1] https://www.epa.gov/laws-regulations/summary-executive-order-12898-federal-actions-address-environmental-justice

The residue definition (40 CFR §180.613) complies with current HED's guidance on tolerance expression. ISK proposed and HED recommended revised tolerances for residues of flonicamid including its metabolites and degradates, in or on the raw agricultural commodities (RACs) as shown in Table 2.2.2.1. below.

Table 2.2.2.1. Tolerance Summary for Flonicamid (40 CFR §180.613).

Commodity/ Correct Commodity Definition	Proposed New/Revised Tolerance (ppm)	Established Tolerance (ppm)	Recommended Tolerance (ppm)	Comments
Berry, low growing, subgroup 13-07G	2	1.5	2	Harmonization with Japan.

2.2.3 Revisions to Petitioned-For Tolerances

There are no revisions to the petitioned-for tolerances.

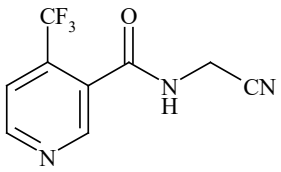
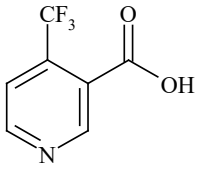
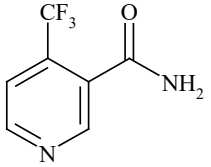
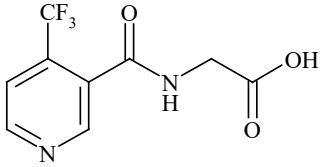
2.2.4 International Harmonization

The tolerance expression for plant and livestock commodities are harmonized between the U.S. and Canada, but not Codex and Japan. Codex and Japanese residues of concern (ROC) are expressed as flonicamid only. Canada has tolerances for residues of flonicamid in/on bearberry; bilberry; blueberry, lowbush; cloudberry; cranberry; and lingonberry at 1.5 ppm. The U.S. is currently harmonized with Canada, but once the U.S. sets the tolerance at 2 ppm, the U.S. will no longer be harmonized with Canada. Codex has a maximum residue limit (MRL) for flonicamid in/on low growing berries at 1.5 ppm. The U.S. is currently harmonized with Codex, but once the U.S. sets the tolerance at 2 ppm, the U.S. will no longer be harmonized with Codex. Japan has MRLs established for residues of flonicamid in/on strawberry, cranberry and other berries at 2 ppm. In making its tolerance decisions, EPA seeks to harmonize U.S. tolerances with international standards whenever possible, consistent with U.S. food safety standards and agricultural practices. The registrant requested that the low growing berry, subgroup 13-07G be harmonized with the Japan tolerance of 2 ppm to minimize barriers to the export of strawberries to the U.S. The U.S. is currently not harmonized with Japan, but once the tolerance for residues in/on low growing berry, subgroup 13-07G is set at 2 ppm then the U.S. will be harmonized with Japan.

3.0 Introduction

3.1 Chemical Identity

The chemical structure and nomenclature of flonicamid and its metabolites TFNA, TFNA-AM, and TFNG are presented in Table 3.1.1.

Table 3.1.1. Flonicamid Nomenclature.	
Compound	
Common name	Flonicamid
Company experimental name	IKI-220
IUPAC name	*N*-cyanomethyl-4-(trifluoromethyl)nicotinamide
CAS name	*N*-(cyanomethyl)-4-(trifluoromethyl)-3-pyridinecarboxamide
CAS #	158062-67-0
End-use product (EP)	Beleaf™ 50 SG (EPA Reg. No. 71512-10) and Flonicamid 50 WG (EPA Reg. No. 71512-9)
Compound	
Common name	TFNA
Chemical name	4-trifluoromethylnicotinic acid
Compound	
Common name	TFNA-AM
Chemical name	4-trifluoromethylnicotinamide
Compound	
Common name	TFNG
Chemical name	*N*-(4-trifluoromethylnicotinoyl)glycine

3.2 Physical/Chemical Characteristics

Flonicamid has a log octanol/water partition coefficient (log P_{ow}) of 0.3 and is considered very soluble in water (5 g/L at 20°C) and is therefore highly mobile with a very low persistence in soil. Flonicamid is considered to be not very volatile, with a vapor pressure of 1.91×10^{-8} mm Hg at 25°C and a Henry's Law Constant of 4.2×10^{-8} Pa-m^3/mol at 25°C. With a molecular weight of 229.2 g/mol, the potential to cross biological barriers is somewhat limited. The physicochemical properties of the technical grade of flonicamid are presented in Appendix B, Table B.1.

3.3 Pesticide Use Pattern

The use pattern associated with flonicamid remains unchanged since the previous assessments. Flonicamid EPs are currently registered as a WDG and SG formulations containing 50% ai by weight.

Applications can be made with ground, aerial, airblast, chemigation, and handheld equipment. The labels require that applicators and other handlers wear long-sleeved shirts, long pants, shoes, socks, and PPE consisting of chemical-resistant gloves. The Beleaf® 50SG Insecticide, EPA Reg. No. 71512-10, label requires applicators using mechanically pressurized handgun equipment in greenhouses must wear a NIOSH approved respirator; all other product labels do not require handlers to wear respiratory protection. Flonicamid may be applied to low growing berries 3 times per season at a single maximum application rate of 0.089 lb ai/A. The retreatment interval (RTI) is 7 days between applications. The seasonal maximum application rate is 0.267 lb ai/A. The REI on the registered labels is 12 hours.

3.4 Anticipated Exposure Pathways

Humans may be exposed to flonicamid in food and drinking water since flonicamid may be applied directly to growing crops, and applications may result in flonicamid reaching surface and ground sources of drinking water. Based on the registered use patterns, occupational handler short- (1 to 30 days) and intermediate-term (1 to 6 months) dermal and inhalation exposures to flonicamid are expected. There is also potential for short- and intermediate term occupational post-application dermal exposures to occur for workers entering fields previously treated with flonicamid. There are no residential exposures expected from the submitted petition; however, there are registered residential uses that have been included in this assessment for purposes of aggregate assessment. Short-term non-occupational spray drift exposures may also occur and are assessed as part of Registration Review.

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 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.

4.0 Hazard Characterization and Dose-Response Assessment

Flonicamid is a pyridinecarboxamide insecticide used to control aphids and other sucking insects. Despite being a nicotinic acid derivative, flonicamid does not activate acetylcholine esterase nor

nicotinic acetylcholine receptors. The toxic mode of action for flonicamid is not fully elucidated in mammals.

The hazard characterization of flonicamid was summarized in the latest registration review draft risk assessment (DRA) (J. Smith, *et al*., 09/11/2019, D451646). This document should be consulted for the complete hazard characterization of flonicamid. Briefly, the available toxicity database of guideline studies for flonicamid indicates that the kidney and liver were considered target organs. In repeat-dose (i.e., subchronic and chronic) oral toxicity studies, the consistently observed adverse effect in rats were kidney toxicity (i.e., hyaline deposition and nephritis in males and females); in mice, extramedullary hematopoiesis of the spleen was observed, and in dogs, vomiting and increased percentage of reticulocytes and decreased red blood cells was evident. There was no evidence of increased susceptibility following pre-/post-natal exposure in pre-natal developmental toxicity studies or the reproduction and fertility effects study, or clear evidence of neurotoxicity in the database. Therefore, FQPA Safety Factor[2] can be reduced to 1X for all assessment scenarios. Lastly, the determination of carcinogenicity potential for flonicamid was based on the weight of the evidence approach and resulted in the classification of "suggestive evidence of carcinogenicity, but not sufficient to assess human carcinogenic potential" (J. Kidwell, 02/24/2005, TXR 0052013). The Agency determined that quantification of risk using a non-linear approach (i.e., using a chronic reference dose) adequately accounts for all chronic toxicity, including carcinogenicity that could result from exposure to flonicamid. Therefore, the chronic risk assessment is considered protective for carcinogenic effects. As a result, a separate cancer risk assessment was not conducted.

Since the last published risk assessment, there have been no changes to the dose-response assessment. There have also been no changes to the prior recommendations regarding the cancer classification or in combining routes of exposures. Please refer to Tables 4.0.1 and 4.0.2 for detailed information regarding the toxicity endpoints and the PODs selections.

Table 4.0.1. Summary of Toxicological Doses and Endpoints for use in Dietary and Non-Occupational Human Health Risk Assessments.

Exposure Scenario	Point of Departure (POD)	Uncertainty / FQPA SF	RfD, PAD, LOC for Risk Assessment	Study and Toxicological Effects
Acute Dietary General population (including infants and children) Females (13-49 years old)	No endpoint was identified since there is no indication of an adverse effect attributable to a single dose and susceptibility, neurotoxicity, and immunotoxicity were not observed in the database.			
Chronic Dietary	NOAEL = 3.7 mg/kg/day	UF_A = 10X UF_H = 10X FQPA SF = 1X	cRfD = 0.04 mg/kg/day cPAD = 0.04 mg/kg/day	<u>Reproduction and Fertility Effects Study in Rats</u> Parental LOAEL = 22 mg/kg/day Based on increased kidney weights, kidney hyaline deposition in the proximal tubules of the kidneys in males, increased blood serum LH (F_1 females).

[2] HED's standard toxicological, exposure, and risk assessment approaches are consistent with the requirements of EPA's children's environmental health policy (https://www.epa.gov/children/epas-policy-evaluating-risk-children).

Table 4.0.1. Summary of Toxicological Doses and Endpoints for use in Dietary and Non-Occupational Human Health Risk Assessments.				
Exposure Scenario	**Point of Departure (POD)**	**Uncertainty / FQPA SF**	**RfD, PAD, LOC for Risk Assessment**	**Study and Toxicological Effects**
Incidental Oral/Adult Oral Short- and Intermediate-Term	NOAEL = 12 mg/kg/day	UF_A = 10X UF_H = 10X FQPA SF = 1X	Residential LOC for MOE = 100	90-Day Oral Toxicity – Rat LOAEL = 60 mg/kg/day Based on an increased incidence of microscopic pathology (i.e., hyaline deposition) in males and females.
Dermal (All Durations)	No endpoint was identified for this risk assessment since systemic toxicity was not observed in the 28-day dermal toxicity study at the limit dose (1,000 mg/kg/day) and no quantitative or qualitative susceptibility was observed in the database.			
Inhalation Short-Term (1-30 days) Intermediate-Term (1-6 months)	Oral NOAEL = 12 mg/kg/day	UF_A = 10X UF_H = 10X FQPA SF = 1X	Residential LOC for MOE = 100	90-Day Oral Toxicity – Rat LOAEL = 60 mg/kg/day Based on an increased incidence of microscopic pathology (i.e., hyaline deposition).
Cancer (oral, dermal, and inhalation)	Classification: "Suggestive evidence of carcinogenicity, but not sufficient to assess human carcinogenic potential" based on the results of carcinogenicity studies in rats and mice (02/24/2005, J. Kidwell, TXR 0052013). For cancer risk, RfD approach was recommended.			

Point of Departure (POD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no-observed adverse-effect level. LOAEL = lowest-observed adverse-effect level. UF = uncertainty factor. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). FQPA SF = FQPA Safety Factor. PAD = population-adjusted dose (a = acute, c = chronic). RfD = reference dose. MOE = margin of exposure. LOC = level of concern.

Table 4.0.2. Summary of Toxicological Doses and Endpoints for use in Occupational Human Health Risk Assessments.				
Exposure Scenario	**Point of Departure (POD)**	**Uncertainty / FQPA SF**	**LOC for Risk Assessment**	**Study and Toxicological Effects**
Dermal Short-Term (1-30 Days) Intermediate-Term (1-6 Months)	No endpoint was identified for this risk assessment since systemic toxicity was not observed in the 28-day dermal toxicity study at the limit dose (1,000 mg/kg/day) and no quantitative or qualitative susceptibility was observed in the database.			
Inhalation All Durations	Oral NOAEL = 12 mg/kg/day	UF_A = 10X UF_H = 10X	Occupational LOC for MOE = 100	90-Day Oral Toxicity – Rat LOAEL = 60 mg/kg/day Based on an increased incidence of microscopic pathology (i.e., hyaline deposition) in males and females.
Cancer (dermal and inhalation)	Classification: "Suggestive evidence of carcinogenicity, but not sufficient to assess human carcinogenic potential" based on the results of carcinogenicity studies in rats and mice (02/24/2005, J. Kidwell, TXR 0052013). For cancer risk, RfD approach was recommended.			

Point of Departure (POD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no-observed adverse-effect level. LOAEL = lowest-observed adverse-effect level. UF = uncertainty factor. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). FQPA SF = FQPA Safety Factor. MOE = margin of exposure. LOC = level of concern.

5.0 Dietary Exposure and Risk Assessment

5.1 Residues of Concern Summary and Rationale

The nature of the residue in plants and livestock is adequately understood for the purposes of risk assessment and tolerance evaluation. The residues of concern in plants for tolerances and risk assessment are flonicamid and its metabolites TFNA, TFNA-AM, and TFNG. In livestock commodities, HED has determined that the residues of concern for the tolerances and risk assessment are flonicamid, TFNA and TFNA-AM.

The rationale for inclusion of metabolites and degradates was discussed in (J. Arthur, 5/25/05, D289592).

Table 5.1.1. Summary of Metabolites and Degradates to be Included in the Risk Assessment and Tolerance Expression.			
Matrix		**Residues Included in Risk Assessment**	**Residues Included in Tolerance Expression**
Plants	Primary Crop	Flonicamid, TFNA, TFNA-AM, and TFNG	Flonicamid, TFNA, TFNA-AM, and TFNG
	Rotational Crop	Flonicamid, TFNA, TFNA-AM, and TFNG	Flonicamid, TFNA, TFNA-AM, and TFNG
Livestock	Ruminant	Flonicamid, TFNA and TFNA-AM	Flonicamid, TFNA and TFNA-AM
	Poultry	Flonicamid, TFNA and TFNA-AM	Flonicamid, TFNA and TFNA-AM
Drinking Water		Flonicamid, TFNA, TFNG-AM, TFNG, TFNA-OH, TFNA-AM	Not Applicable

5.2 Food Residue Profile

The nature of the residues in plants, rotational crops, and livestock is adequately understood. Adequate analytical methods are available for enforcing tolerances in plant and livestock commodities. Adequate storage stability data are available to support the storage durations and conditions of samples of the proposed uses. Adequate crop field trial data have been submitted to support the proposed uses. The residue chemistry database is sufficient to support the revised tolerance petition for the low growing berry, subgroup 13-07G.

ISK Biosciences has submitted data for residues of flonicamid in/on strawberry from trials performed in Japan (MRID 52081601). The Japanese residue data utilized an application rate of 0.16 to 0.18 lb ai/A (2 applications of 0.080 to 0.091 lb ai/A); however, the U.S. domestic application rate for flonicamid on low growing berries is 0.263 lb ai/A (based on 3 applications of 0.088 lb ai/A/application). Thus, the application rate utilized for the Japanese data is 68% of the U.S. domestic application rate. These data (Japanese field trials) are not adequate to determine the tolerance level for low growing berries, subgroup 13-07G.

5.3 Water Residue Profile

Based on the petition, impacts to the drinking water assessment are not expected as there are no proposed new uses. Therefore, the previous assessment remains the most current and conservative estimate of drinking water exposure. Maximum estimated drinking water concentrations (EDWCs) for flonicamid ROC in surface water do not exceed maximum surface water EDWCs modeled for flonicamid on legumes (U.S. EPA, 2016) or groundwater EDWCs for flonicamid on fruiting vegetables (U.S. EPA, 2013). No new groundwater modeling was performed as no there are no proposed new uses compared to what was previously assessed; thus, the previous groundwater exposure modeling remains relevant and unchanged. EDWCs in surface source water are not expected to exceed 12.29 µg/L for the 1-in-10 year daily average, 2.78 µg/L for the 1-in-10 year annual average, and 1.46 µg/L for the 30-year annual average (U.S. EPA, 2016). **EDWCs in ground water are not expected to exceed 15.9 µg/L for acute concentrations or 9.92 µg/L for chronic concentrations** (G. Dykes, D465993, D466239, D466243, 12/05/2022). Water residues were incorporated directly in the Dietary Exposure Evaluation Model

software with the Food Commodity Intake Database (DEEM-FCID) into the food categories "water, direct, all sources" and "water, indirect, all sources."

The drinking water models and their descriptions are available at the EPA internet site: https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/models-pesticide-risk-assessment.

Table 5.3.1. Estimated Drinking Water Concentrations Based on Flonicamid Uses.[1]		
Source of Drinking Water	**Acute (µg/L)**	**30-Year Annual Average (µg/L)**
Ground water (PRZM-GW)	15.9	**9.92**

1. These are the highest EDWCs for the proposed and previously evaluated use scenarios. The Tier 1 rice model for cranberry is not used in this risk assessment because it is considered to be overly conservative.

5.4 Dietary Risk Assessment

5.4.1 Description of Residue Data Used in Dietary Assessment

An unrefined exposure assessment was conducted for all proposed and registered uses of flonicamid. The assumptions of the analysis were 100% crop treated (% CT) and tolerance level residues for all commodities. Separate tolerances have been established for potato granules/flakes, tomato paste, and tomato puree based on processing studies. The processing factors were set to 1.0 for these commodities. HED's default processing factors were used for the other processed commodities for which default processing factors are available.

5.4.2 Percent Crop Treated Used in Dietary Assessment

The assessment used 100% CT for all established and proposed agricultural crops.

5.4.3 Acute Dietary Risk Assessment

No appropriate endpoint attributable to a single dose (exposure) was identified in oral toxicity studies. Therefore, an acute dietary assessment was not conducted.

5.4.4 Chronic Dietary Risk Assessment

The results of the chronic dietary (food and drinking water) exposure analysis are reported in Table 5.4.6.1. and show that exposure to flonicamid is below HED's LOC for the general U.S. population and all population subgroups. The chronic dietary exposure estimates are 30% cPAD for the general U.S. population and 91% cPAD for children 1-2 years old, the most highly exposed population subgroup.

5.4.5 Cancer Dietary Risk Assessment

Flonicamid has been determined to have "suggestive evidence of carcinogenicity, but not sufficient to assess human carcinogenic potential." The Agency has determined that quantification of risk using a non-linear approach (*i.e.*, using a chronic RfD) adequately accounts for all chronic toxicity, including carcinogenicity that could result from exposure to flonicamid. Therefore, the cRfD is considered

protective for carcinogenic effects. As a result, a separate cancer risk assessment was not conducted. The chronic dietary exposure is considered protective of any cancer dietary risks.

5.4.6 Summary Table

Table 5.4.6.1. Summary of Dietary (Food and Drinking Water) Exposure and Risk for Flonicamid.[1]			
Population Subgroup	**cPAD (mg/kg/day)**	**Exposure (mg/kg/day)**	**% cPAD**
General U.S. Population	0.04	0.012145	30
All Infants (< 1 year old)		0.017118	43
Children 1-2 years old		**0.036532**	**91**
Children 3-5 years old		0.026840	67
Children 6-12 years old		0.013908	35
Youth 13-19 years old		0.008446	21
Adults 20-49 years old		0.010147	25
Adults 50-99 years old		0.011093	28
Females 13-49 years old		0.010302	26

[1] The population with the highest exposure is in bold.

6.0 Residential Exposure/Risk Characterization

There are no proposed residential uses at this time, therefore neither a residential handler nor a post-application risk assessment have been conducted. However, there are existing registered residential handler uses that were previously assessed and which resulted in no risks of concern (S. Garred, D452374, 10/14/2020).

6.1 Residential Risk Estimates for Use in Aggregate Assessment

Table 6.1.1. reflects the residential risk estimates that are recommended for use in the aggregate assessment for flonicamid.

- The recommended residential exposure for use in the adult aggregate assessment is inhalation exposure from applications to roses, flowers, shrubs, and small (non-fruit bearing) trees via backpack spray equipment.

Table 6.1.1. Recommendations for the Residential Exposures Used in the Flonicamid Aggregate Assessment.									
Lifestage	**Exposure Scenario**	**Dose (mg/kg/day)[1]**				**MOE[2] (LOC = 100)**			
		Dermal	**Inhalation**	**Oral**	**Total**	**Dermal**	**Inhalation**	**Oral**	**Total**
Adult	Handler – Backpack on Roses, Flowers, Shrubs, and Small (Non-Fruit Bearing) Trees	N/A	6.7E-06	N/A	6.7E-06	N/A	1,800,000	N/A	1,800,000

1. Dose = the highest inhalation dose for each applicable life stage of all residential scenarios assessed.
2. MOE = the MOEs associated with the highest residential doses. Total = (inhalation MOE).

7.0 Aggregate Exposure/Risk Characterization

In accordance with the FQPA, HED must consider and aggregate (add) 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. Registered residential use patterns are expected to result in only short-term exposures to flonicamid and, as a dermal endpoint was not selected, residential risk estimates were calculated for the inhalation route only.

7.1 Acute Aggregate Risk

Acute exposure is not expected for adults or children via residential exposure pathways. Therefore, the acute aggregate risk estimates would be equivalent to the acute dietary risk estimates. However, an acute dietary assessment was not conducted as no appropriate endpoint attributable to a single dose (exposure) was identified in oral toxicity studies.

7.2 Short- and Intermediate-Term Aggregate Risk

For short-term aggregate risk, adult residential handler exposure estimates are aggregated with adult dietary exposure estimates, considered background. The estimated aggregate MOE for adult handlers is 1,100 (LOC = 100) and is not of concern. Risk estimates for children are expected to be equivalent to the dietary.

Table 7.2.1. Short-and Intermediate-Term Aggregate Risk Calculations.

Short- and Intermediate-Term Scenario							
Pop.	**NOAEL (mg/kg/day)**	**LOC[1]**	**Max Allowable Exposure[2] (mg/kg/day)**	**Average Food & Water Exposure (mg/kg/day)**	**Residential Inhalation Exposure (mg/kg/day)[3]**	**Total Exposure (mg/kg/day)[4]**	**Aggregate MOE (food, water, & residential)[5]**
Adults	12	100	0.12	0.011093	6.7E-06	0.011	1,100

1. LOC of 100 includes the standard inter- and intra- species uncertainty factors totaling 100 and SF = 1X.
2. Maximum Allowable Exposure (mg/kg/day) = NOAEL/LOC.
3. Residential Exposure = [Inhalation Exposure]. See Table 6.1.1.
4. Total Exposure = (Avg Food & Water Exposure + Residential Exposure).
5. Aggregate MOE = [NOAEL / (Avg Food & Water Exposure + Residential Exposure)].

7.3 Chronic Aggregate Risk

Long-term exposure is not expected for adults or children via residential exposure pathways. Therefore, the chronic aggregate risk estimates would be equivalent to the chronic dietary risk estimates (refer to Table 5.4.6.1.).

7.4 Cancer Aggregate Risk

Flonicamid has been determined to have “suggestive evidence of carcinogenicity, but not sufficient to assess human carcinogenic potential.” The Agency has determined that quantification of risk using a non-linear approach (*i.e.*, using a chronic reference dose) adequately accounts for all chronic toxicity, including carcinogenicity that could result from exposure to flonicamid. Therefore, a cancer aggregate exposure assessment was not conducted.

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[3], 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).[4] 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 flonicamid 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 FIFRA Scientific Advisory Panel (SAP) in December 2009, and received the SAP's final report on March 2, 2010[5]. 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*[6]).

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 flonicamid.

10.0 Cumulative Exposure/Risk Characterization

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 flonicamid and any other substances, and flonicamid does not appear to produce a toxic metabolite produced by other substances. For the purposes of this action, therefore, EPA has not assumed that flonicamid has a common mechanism of toxicity with other substances.

[3] 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

[4] 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.

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

[6] Available online: Regulations.gov

In 2016, EPA's Office of Pesticide Programs released a guidance document entitled, Pesticide Cumulative Risk Assessment: Framework for Screening Analysis.[7] 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)[8] and conducting cumulative risk assessments (CRA)[9].

Flonicamid has not been classified in a group. At this time, EPA does not expect any exposures from other pesticides or substances that would warrant screening with the framework. As a result, EPA concludes that flonicamid does not have a common mechanism of toxicity with other substances that contribute to the risk assessment. If other pesticides are registered that have the potential to be grouped with flonicamid, EPA will use the framework to examine the potential for a common mechanism of toxicity and the potential for cumulative risk as part of the ongoing registration review process.

11.0 Occupational Exposure/Risk Characterization

HED uses the term handlers to describe those individuals who are involved in the pesticide application process. HED believes that there are distinct job functions or tasks related to applications and exposures can vary depending on the specifics of each task. Job requirements (amount of chemical used in each application), the kinds of equipment used, the target being treated, and the level of protection used by a handler can cause exposure levels to differ in a manner specific to each application event.

The use pattern associated with flonicamid remains unchanged since the previous assessments. Therefore, HED has previously assessed occupational exposures and risk estimates (J. Smith, *et al.*, D451646, 09/11/2019) and has not identified any risks of concern. The conclusion of the assessment remains unchanged.

12.0 References

W.D Wassell, TG00484486, 04/11/2024. Flonicamid (128016); Petition to Amend the Tolerance for Berry, Low Growing, Subgroup 13-07G.

W.D Wassell, TG00484486, 04/11/2024. Flonicamid (128016); Chronic Aggregate Dietary (Food and Drinking Water) Exposure and Risk Assessment for the Petition to Amend the Tolerance for Berry, Low Growing, Subgroup 13-07G.

J. Smith, *et al.,* D465992, 09/12/2023. Flonicamid. Human Health Risk Assessment for the Proposed New Uses and Tolerance Establishment in/on Bushberry Subgroup 13-07B, Caneberry Subgroup 13-07A, Cherry Subgroup 12A, Peach Subgroup 12-12B, Plum Subgroup 12C, Pomegranate, Prickly Pear Cactus, Sweet Corn, and Crop Group Conversions/Expansions for Legume Vegetables New Crop Group 6-22A-F.

[7] https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/pesticide-cumulative-risk-assessment-framework
[8] Guidance For Identifying Pesticide Chemicals and Other Substances that have a Common Mechanism of Toxicity (USEPA, 1999)
[9] Guidance on Cumulative Risk Assessment of Pesticide Chemicals That Have a Common Mechanism of Toxicity (USEPA, 2002)

Dykes G., D465993, D466239, D466243, 12/05/2022. *Drinking Water Assessment for the Proposed New Use of Flonicamid on Bushberry Subgroup 13-07B, Caneberry Subgroup 13-07A, Sweet Corn, Pomegranate, and Prickly Pear Cactus.*

S. Garred, D452374, 10/14/2020. Flonicamid. Human Health Aggregate Risk Assessment for Proposed New Residential Outdoor Use on Roses, Flowers, Shrubs, and Small (Non-Fruit Bearing) Trees.

J. Smith, D451646, 09/11/2019. Flonicamid**:** Human Health Draft Risk Assessment for Registration Review.

Appendix A. Toxicology Profile and Executive Summaries

A.1 Toxicology Data Requirements

The requirements (40 CFR 158.340) for food-use for flonicamid are in Table A.1. Use of the new guideline numbers does not imply that the new (1998) guideline protocols were used.

Table A.1. Toxicology Data Requirements

Study	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 Acute Eye Irritation	yes	yes
870.2500 Acute Dermal Irritation	yes	yes
870.2600 Skin Sensitization	yes	yes
870.3100 90-Day Oral Toxicity in Rodents	yes	yes
870.3150 90-Day Oral Toxicity in Nonrodents	yes	yes
870.3200 21/28-Day Dermal Toxicity	yes	yes
870.3250 90-Day Dermal Toxicity	yes	yes
870.3465 90-Day Inhalation Toxicity	no[1]	no[1]
870.3700a Prenatal Developmental Toxicity (rodent)	yes	yes
870.3700b Prenatal Developmental Toxicity (nonrodent)	yes	yes
870.3800 Reproduction and Fertility Effects	yes	yes
870.4100a Chronic Toxicity (rodent)	yes	yes
870.4100b Chronic Toxicity (nonrodent)	no	no
870.4200a Carcinogenicity (rat)	yes	yes
870.4200b Carcinogenicity (mouse)	yes	yes
870.4300 Combined Chronic Toxicity/Carcinogenicity	yes	yes
870.5100 Mutagenicity—Bacterial Reverse Mutation Test	yes	yes
870.5300 Mutagenicity—Mammalian Cell Gene Mutation Test	yes	yes
870.5xxx Mutagenicity—Structural Chromosomal Aberrations	yes	yes
870.5xxx Mutagenicity—Other Genotoxic Effects	yes	yes
870.6200a Acute Neurotoxicity Screening Battery (rat)	yes	yes
870.6200b 90-Day Neurotoxicity Screening Battery (rat)	yes	yes
870.6300 Developmental Neurotoxicity	no	no
870.7485 Metabolism and Pharmacokinetics	yes	yes
870.7600 Dermal Penetration	no	no
870.7800 Immunotoxicity	yes	yes

[1] Recommended to be waived by HASPOC (R. Louden, 08/23/2019, TXR 0057924).

A.2 Toxicity Profiles

Table A.2.1 Acute Toxicity Profile for Flonicamid				
Guideline	**Study Type**	**MRID (year)**	**Results**	**Toxicity Category**
870.1100	Acute Oral (Rat)	45656707 (2001)	LD_{50} (mg/kg): M = 884 F = 1768	III
870.1200	Acute Dermal (Rat)	45656708 (2000)	LD_{50} (mg/kg): M > 5000 F > 5000	IV
870.1300	Acute Inhalation (Rat)	45656709 (2000)	LC_{50} (mg/L): M > 4.90 F > 4.90	IV
870.2400	Acute Eye Irritation (Rabbit)	45656710 (2000)	No irritation observed in this study.	IV
870.2500	Acute Dermal Irritation (Rabbit)	45656711 (2000)	Minimally irritating.	IV
870.2600	Skin Sensitization (Guinea Pig)	45656712 (2000)	No evidence of dermal sensitization	NA

Table A.2.2 Acute Toxicity Profile for Select Flonicamid Metabolites				
Guideline	**Study Type**	**MRID (year)**	**Results**	**Toxicity Category**
870.1100	Acute Oral (Rat) – TFNA	45854605 (2002)	LD_{50} (mg/kg): M ≥ 2000 F ≥ 2000	III
870.1100	Acute Oral (Rat) – TFNA-AM	45854606 (2002)	LD_{50} (mg/kg): M ≥ 2000 F ≥ 2000	III
870.1100	Acute Oral (Rat) – TFNA-OH	45854609 (2002)	LD_{50} (mg/kg): M ≥ 2000 F ≥ 2000	III
870.1100	Acute Oral (Rat) – TFNG	45854607 (2002)	LD_{50} (mg/kg): M ≥ 2000 F ≥ 2000	III
870.1100	Acute Oral (Rat) – TFNG-AM	45854608 (2002)	LD_{50} (mg/kg): M ≥ 2000 F ≥ 2000	III

The Agency reassessed the toxicity databases for flonicamid in accordance with current policies and determined that many of the effects previously noted are no longer considered to be adverse. It should be noted that many of the no observed adverse effect levels (NOAELs) and lowest observed affect levels (LOAELs) presented in the toxicology profile table have not been updated to comply with current policy since they did not impact points of departure for risk assessment.

Table A.2.3 Subchronic, Chronic, and Additional Toxicity Profile for Flonicamid			
Guideline	**Study Type**	**MRID (year) / Doses / Classification**	**Results**
870.3050	Repeated Dose 28-Day Oral Toxicity Study in Rodents (Rat)	45656720 (2002) Dietary Concentration (ppm): M: 0, 50, 100, 500, 1000, 5000 F: 0, 100, 500, 1000, 5000, 10000 Dietary Dose (mg/kg/day): M: 0, 3.61, 7.47, 36.45, 73.8, 353.4 F: 0, 8.36, 41.24, 81.9, 372.6, 642 Acceptable / Non-Guideline	NOAEL (mg/kg/day): M = 7.47 F = 81.9 LOAEL (mg/kg/day): M = 36.45 F = 372.6 M: Based on changes in the kidney (i.e., hyaline deposition). F: Based on changes in the kidney (i.e., hyaline deposition), liver changes (i.e., centrilobular hypertrophy), hematological effects (i.e., anemia), and clinical chemistry (i.e., increased cholesterol).
870.3100	90-Day Oral Toxicity in Rodents (Rat)	45656721 (2002) Dietary Concentration (ppm): M: 0, 50, 200, 1000, 2000 F: 0, 200, 1000, 5000 Dietary Dose (mg/kg/day): M: 0, 3.08, 12.11, 60.0, 119.4 F: 0, 14.52, 72.3, 340.1 Acceptable / Guideline	NOAEL (mg/kg/day): M = 12.11 F = 72.3 LOAEL (mg/kg/day): M = 60.0 F = 340 M: Based on changes in the kidney (i.e., hyaline deposition). F: Based on kidney (i.e., hyaline deposition) and liver changes (i.e., centrilobular hypertrophy).
	90-Day Oral Toxicity in Rodents (Mouse)	45656719 (2001) Dietary Concentration (ppm): 0, 100, 1000, 7000 Dietary Dose (mg/kg/day): M: 0, 15.25, 153.9, 1069 F: 0, 20.10, 191.5, 1248 Unacceptable / Guideline	NOAEL (mg/kg/day): M = 15.25 F = 20.10 LOAEL (mg/kg/day): M = 153.9 F = 191.5 Based on extramedullary hematopoiesis of the spleen.

Table A.2.3 Subchronic, Chronic, and Additional Toxicity Profile for Flonicamid			
Guideline	**Study Type**	**MRID (year) / Doses / Classification**	**Results**
870.3150	90-Day Oral Toxicity in Non-Rodents (Dog)	45656722 (2001) Capsule Dose (mg/kg/day): M: 0, 3, 8, 20 F: 0, 3, 8, 20, 50 Acceptable / Guideline	NOAEL (mg/kg/day): M = 8 F = 20 LOAEL (mg/kg/day): M = 20 F = 50 M: Based on clinical signs (i.e., vomiting), clinical chemistry at 7 weeks (i.e., increased total protein levels), increased adrenal weight, and decreased thymus gland weight. F: Based on clinical signs (i.e., vomiting), hematology at 7 weeks (i.e., decreased RBC and increased reticulocyte counts), and increased incidences of kidney tubular vacuolation.
870.3200	28-Day Dermal Toxicity (Rat)	45656723 (2001) Dermal Dose (mg/kg/day): M: 0, 20, 150, 1000 F: 0, 20, 150, 1000 Acceptable / Guideline	Dermal Irritation NOAEL (mg/kg/day): M = 1000 F = 1000 LOAEL (mg/kg/day): M > 1000 F > 1000 Systemic NOAEL (mg/kg/day): M = 1000 F = 1000 LOAEL (mg/kg/day): M > 1000 F > 1000
870.3465	90-Day Inhalation Toxicity Study	TXR 0057924 (2019)	A subchronic inhalation study is not required.
870.3700	Prenatal Developmental Toxicity Study (Rat)	45656724 (2002) Gavage Dose (mg/kg/day): F: 0, 20, 100, 500 Acceptable / Guideline	Maternal NOAEL (mg/kg/day) = 100 LOAEL (mg/kg/day) = 500 Based on increased liver weight and increased incidences of gross pathology in the liver (i.e., hepato-diaphragmatic nodule) and kidneys (i.e., nephritis). Developmental NOAEL (mg/kg/day) = 100 LOAEL (mg/kg/day) = 500 Based on increased incidences of cervical ribs.
	Prenatal Developmental Toxicity Study (Rabbit)	45854611 (2002) Gavage Dose (mg/kg/day): F: 0, 2.5, 7.5, 25 Acceptable / Guideline	Maternal NOAEL (mg/kg/day) = 7.5 LOAEL (mg/kg/day) = 25 Based on decreased body weight gains and food consumption. Developmental NOAEL (mg/kg/day) = 25 LOAEL (mg/kg/day) > 25
		45854610 (2002) – Range Finding Gavage Dose (mg/kg/day): F: 0, 3, 10, 30, 100, 300, 1000 Acceptable / Non-Guideline	Maternal NOAEL (mg/kg/day) = 10 LOAEL (mg/kg/day) = 30 Based on decreased body weight gain and food consumption. Developmental NOAEL (mg/kg/day) = 10 LOAEL (mg/kg/day) = 30 Based on decreased gravid uterine weights.

Table A.2.3 Subchronic, Chronic, and Additional Toxicity Profile for Flonicamid			
Guideline	**Study Type**	**MRID (year) / Doses / Classification**	**Results**
870.3800	Reproduction and Fertility Effects (Rat)	45854613 (2002) 45851612 (2002) Dietary Concentration (ppm): 0, 50, 300, 1800 Dietary Dose (mg/kg/day): M: 0, 3.7, 22.3, 132.9 F: 0, 4.4, 26.5, 153.4 Acceptable / Guideline	<u>Parental</u> NOAEL (mg/kg/day): M = 3.7 F = 4.4 LOAEL (mg/kg/day): M = 22.3 F = 26.5 Based on increased relative kidney weight and hyaline droplet deposition in the proximal tubules of the kidneys in the males and increased blood serum LH levels in the F1 females. <u>Reproductive</u> NOAEL (mg/kg/day): M = 132.9 F = 153.4 LOAEL (mg/kg/day): M > 132.9 F > 153.4 <u>Offspring</u> NOAEL (mg/kg/day): M = 22.3 F = 26.5 LOAEL (mg/kg/day): M = 132.9 F = 153.4 Based on decreased absolute and relative to body uterus weights and delayed sexual maturation in the F1 females.
870.4100	Chronic Toxicity (Dog)	45854614 (2002) Capsule Dose (mg/kg/day): M: 0, 3, 8, 20 F: 0, 3, 8, 20 Acceptable / Guideline	NOAEL (mg/kg/day): M = 8 F = 8 LOAEL (mg/kg/day): M = 20 F = 20 Based on increased reticulocytes and vomiting (within the first week of dosing) in males and females.
870.4200	Carcinogenicity (Mouse)	46205801 (2004) 46242201 (2004) 46242202 (2004) Dietary Concentration (ppm): 0, 10, 25, 80, 250 Dietary Dose (mg/kg/day): M: 0, 1.2, 3.1, 10.0, 30.3 F: 0, 1.4, 3.7, 11.8, 36.3 Acceptable / Guideline	NOAEL (mg/kg/day): M = 10 F = 12 LOAEL (mg/kg/day): M = 30 F = 36 Based on lung masses and terminal bronchiole epithelial cell hyperplasia/hypertrophy in both sexes. The alveolar/bronchiolar tumors were considered to be treatment related.
		45854615 (2003) 45854616 (2003) Dietary Concentration (ppm): 0, 250, 750, 2250 Dietary Dose (mg/kg/day): M: 0, 29, 88, 261 F: 0, 38, 112, 334 Acceptable / Guideline	NOAEL (mg/kg/day): M < 29 F < 38 LOAEL (mg/kg/day): M = 29 F = 38 Based on minimal to moderate centrilobular hepatocellular hypertrophy, minimal to severe extra medullary hematopoiesis, minimal to moderate pigment deposition in the sternal bone marrow, and increased incidence of tissue masses/ nodules in the lungs, and minimal to moderate decreased cellularity in the femoral bone marrow and hyperplasia/hypertrophy of the epithelial cells of the terminal bronchioles of the female. The alveolar/bronchiolar tumors were considered to be treatment-related.
870.4300	Combined Chronic Toxicity / Carcinogenicity (Rat)	45863801 (2002) Dietary Concentration (ppm): M: 0, 50, 100, 200, 1000 F: 0, 200, 1000, 5000 Dietary Dose (mg/kg/day): M: 0, 1.84, 3.68, 7.32, 36.5 F: 0, 8.92, 44.1, 219 Acceptable / Guideline	NOAEL (mg/kg/day): M = 7.32 F = 8.92 LOAEL (mg/kg/day): M = 36.5 F = 44.1 Based on decreased body weights and body weight gains, and increased incidences of keratitis in males and striated muscle fiber atrophy in females. There was no evidence of treatment-related carcinogenicity.
870.5100	Bacterial Reverse Mutation Test (*S. typhimurium* & *E. coli*)	45656725 (2002) Applied Dose (µg/plate): ±S9: 61.7 – 5000 Acceptable / Guideline	IKI-220 (Flonicamid) is concluded to be non-mutagenic to *S. typhimurium* & *E. coli* tested up to the limit dose.
		45854617 (2002) Applied Dose (µg/plate): ±S9: 33 – 5000 Acceptable / Guideline	TFNA (Flonicamid metabolite) is considered non-mutagenic in this standard battery of bacterial strains.

Table A.2.3 Subchronic, Chronic, and Additional Toxicity Profile for Flonicamid			
Guideline	**Study Type**	**MRID (year) / Doses / Classification**	**Results**
870.5300	*in vitro* Mammalian Cell Gene Mutation Test (mouse lymphoma L5178Y $TK^{+/-}$ cells)	45656726 (2002) Applied Dose (mg/mL): ±S9: 28.3 – 2290 Acceptable / Guideline	The test material was declared not to be mutagenic in either the presence or absence of S9 activation in this mammalian test system.
870.5375	*in vitro* Mammalian Chromosome Aberration Test (Chinese Hamster Lung (CHL) Cells)	45656727 (2002) Applied Dose (µg/mL): ±S9: 573 – 2290 Acceptable / Guideline	Minimal cytotoxicity was shown at the highest dose tested (HDT), 2290 µg/mL (10 mM, the limit concentration) with no precipitation at any dose or time exposure. Also, no increases in mutant frequency (TK^{-1}) were reported at any dose up to the HDT.
870.5395	*Mammalian Erythrocyte Micronucleus Test (Mouse)*	45656728 (2002) Gavage Dose (mg/kg): M: 0, 250, 500, 1000 F: 0, 125, 250, 500 Acceptable / Guideline	No significant increases in the frequencies of micronuclei were observed at any treatment dose.
870.6200	Acute Neurotoxicity Screening Battery (Rat)	45854624 (2002) Gavage Dose (mg/kg): M: 0, 100, 300, 600, 1000 F: 0, 100, 300, 1000 Unacceptable / Guideline	NOAEL (mg/kg/day): M = 600 F = 300 LOAEL (mg/kg/day): M = 1000 F = 1000 Based on mortality and signs of overt toxicity (i.e., decreased motor activity, tremors, impaired respiration, and impaired gait) in males.
	90-Day Neurotoxicity Screening Battery (Rat)	45854702 (2003) 45854701 (2003) Dietary Concentration (ppm): 0, 200, 1000, 10000 Dietary Dose (mg/kg/day): M: 0, 13, 67, 625 F: 0, 16, 81, 722 Acceptable / Guideline	NOAEL (mg/kg/day): M = 13 F = 81 LOAEL (mg/kg/day): M = 67 F = 722 Based on decreased motor activity, rearing, and foot splay in males; decreased body weights, body weight gains, and food consumption in males and females.

Table A.2.3 Subchronic, Chronic, and Additional Toxicity Profile for Flonicamid			
Guideline	**Study Type**	**MRID (year) / Doses / Classification**	**Results**
870.7485	Metabolism and Pharmacokinetics (Rat)	45863802 (2001) 45863803 (2002) 45863804 (2002) 45863805 (2002) 45854703 (2002) Gavage Dose (mg/kg): Single: 2, 400 Repeated: 2 Acceptable / Guideline	Overall recovery of the radioactive dose from all groups were 94-99% by 168 hours post-dose. Absorption was rapid as radioactivity was detected in the plasma within 10 minutes of dosing, with maximum plasma concentrations being achieved within 24-54 minutes. Furthermore, absorption was extensive as only 4-5% of the dose was isolated in the feces of the bile duct-cannulated rats; absorption also did not appear to be dose limited based on the proportional increase in area under the curve (AUC) values from the low to high dose groups. By 168 hours post-dose, total urinary excretion accounted for 72-78% of the dose, cage rinse accounted for 10-21% of the dose, and fecal excretion accounted for 4-7% of the dose. Concentrations of radioactivity in each tissue decreased with time, and only 1-6% of the dose remained in the blood and tissues by 168 hours post-dose. The time-related concentration of radioactivity in plasma in the 400 mg/kg dose males showed a pattern indicating saturation of absorption when compared to the female high dose and the male and female low dose groups. The excretion profile was not affected by sex nor by increasing the dose concentration or the number of doses. A similar excretion profile was observed in the bile duct-cannulated rat study. Tissue distribution was generally similar between sexes of each dose group, the single dose 2 mg/kg group and the repeated-dose 2 mg/kg group, and the 2 mg/kg and 400 mg/kg groups. Initially, the highest concentrations of radioactivity in all groups and both sexes were found in the adrenals and thyroid (2.40-6.52 µg equiv./g at 2 mg/kg and 652-782 µg equiv./g at 400 mg/kg) and in the liver, kidney, spleen and ovaries of the 2 mg/kg groups (2.08-3.77 µg equiv./g). HPLC and LC-MS analyses of excreta identified parent and 9 metabolites accounting for 80-94% of the dose in all groups, and all metabolites accounting for at least 5% dose were identified. Parent, which was detected primarily in urine, accounted for 46-73% of the dose in excreta in all groups. The primary metabolite was 4-trifluoromethylnicotinamide (TFNA-AM), which accounted for 18-27% dose in all dose groups, along with minor amounts of TFNA-AM N-oxide (1-4% dose). Other metabolites identified in urine and feces were detected at ≤2.5% of the dose. Parent was also the major component identified in bile at 2.5-3.3% of the dose, along with TFNA-AM (0.6-1.1% dose). Analyses of liver, sampled when total radioactive residues (TRR) were highest, identified parent (33-51% TRR), TFNA-AM (10-28% TRR) and *N*-(4-trifluoromethyl nicotinoyl) glycine (TFNG, 8-15% TRR). Although IKI-220 was excreted primarily unchanged in the urine, biotransformation of IKI-220 in rats included nitrile hydrolysis, *N*-oxidation, hydroxylation of the pyridine ring, and amide hydrolysis.
870.7800	Immunotoxicity (Mouse)	48870201 (2012) Dietary Concentration (ppm): 0, 100, 600, 6000 Dietary Dose (mg/kg/day): F: 0, 23.2, 141.8, 1540.2 Acceptable / Guideline	<u>Immunotoxicity</u> NOAEL (mg/kg/day): M = N/A F = 1540 LOAEL (mg/kg/day): M = N/A F > 1540 <u>Systemic</u> NOAEL (mg/kg/day): M = N/A F = 1540 LOAEL (mg/kg/day): M = N/A F > 1540

Appendix B. Physical/Chemical Properties

Table B.1. Physicochemical properties of technical grade flonicamid.		
Parameter	**Value**	**Reference**
Molecular weight (g/mole)	229.16	
Melting point	157.5 °C	MRID 45854601
pH	4.5 (25 °C)	
Relative Density	1.531 (20 °C)	
Water solubility	5.2 g/L (20 °C)	
Solvent solubility	Solvent — g/100 mL (20 °C) acetone — 17.32 acetonitrile — 12.04 dichloromethane — 0.40 ethyl acetate — 3.57 hexane — 0.00003 isopropyl alcohol — 1.46 methanol — 9.76 n-octanol — 0.26 toluene — 0.03	MRID 45656705
Vapor pressure	9.43×10^{-7} Pa (20 °C) 2.55×10^{-6} Pa (25 °C)	MRID 45854601
Dissociation constant, pK_a	11.60 ± 0.03 (20 ± 1 °C)	MRID 45656705
Octanol/water partition coefficient, Log(K_{OW})	1.9 (Log P_{OW} = 0.3) (29.8 °C)	MRID 45854601
UV/visible absorption spectrum	Acidic and neutral aqueous solutions exhibited similar spectra with an absorption maximum near 265 nm and a molar absorptivity of 3,900 L/cm mol. A basic solution exhibited two absorption peaks. The peak observed in acidic and neutral solutions was present at a slightly longer wavelength, 270 nm, with an absorptivity of 4,200 L/cm mol. The second peak had an absorption maxima at 204 nm with an absorptivity of 13,200 L/cm mol.	

Appendix C. Review of Human Research

This risk assessment relies in part on data from studies in which adult human subjects were intentionally exposed to a pesticide or other chemical. These data are (1) subject to ethics review pursuant to 40 CFR §26, (2) have received that review, and (3) are compliant with applicable ethics requirements. For certain studies, the ethics review may have included review by the Human Studies Review Board. Descriptions of data sources, as well as guidance on their use, can be found at the Agency website[10].

[10] https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticide-handler-exposure-data and https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticide-post-application-exposure