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Proposed Registration Decision PRD2022-14

Florylpicoxamid, GF-3840 Fungicide and GF-4017 Fungicide

(*publié aussi en français*)

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Overview

Proposed registration decision for florylpicoxamid

Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act*, is proposing registration for the sale and use of XDE-659 Technical Fungicide, GF-3840 Fungicide and GF-4017 Fungicide, containing the technical grade active ingredient florylpicoxamid, to manage certain diseases of wheat, sugar beet, canola, lentil, and turfgrass.

The proposed end-use product GF-4017 Fungicide is a coformulation of florylpicoxamid with the registered active ingredient pyraclostrobin, and does not represent any expansion of use of pyraclostrobin. For details regarding the registration of pyraclostrobin, see Proposed Registration Decisions PRD2008-04, *Pyraclostrobin, Insignia EG Fungicide, Headline EC* and PRD2011-15, *Pyraclostrobin Seed Treatment*, and Registration Decision RD2012-07 *Pyraclostrobin Seed Treatment*.

An evaluation of available scientific information found that, under the approved conditions of use, the health and environmental risks and the value of the pest control products are acceptable.

This Overview describes the key points of the evaluation, while the Science evaluation provides detailed technical information on the human health, environmental and value assessments of florylpicoxamid, GF-3840 Fungicide and GF-4017 Fungicide.

What does Health Canada consider when making a registration decision?

The key objective of the *Pest Control Products Act* is to prevent unacceptable risks to people and the environment from the use of pest control products. Health or environmental risk is considered acceptable[1] if there is reasonable certainty that no harm to human health, future generations or the environment will result from use or exposure to the product under its proposed conditions of registration. The Act also requires that products have value[2] when used according to the label directions. Conditions of registration may include special precautionary measures on the product label to further reduce risk.

To reach its decisions, the PMRA applies modern, rigorous risk-assessment methods and policies. These methods consider the unique characteristics of sensitive subpopulations in humans (for example, children) as well as organisms in the environment. These methods and policies also consider the nature of the effects observed and the uncertainties when predicting the

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1 "Acceptable risks" as defined by subsection 2(2) of the *Pest Control Products Act.*

2 "Value" as defined by subsection 2(1) of the *Pest Control Products Act*: "the product's actual or potential contribution to pest management, taking into account its conditions or proposed conditions of registration, and includes the product's (*a*) efficacy; (*b*) effect on host organisms in connection with which it is intended to be used; and (*c*) health, safety and environmental benefits and social and economic impact."

impact of pesticides. For more information on how the Health Canada regulates pesticides, the assessment process and risk-reduction programs, please visit the Pesticides section of the Canada.ca website.

Before making a final registration decision on florylpicoxamid, GF-3840 Fungicide and GF-4017 Fungicide, Health Canada's PMRA will consider any comments received from the public in response to this consultation document.[3] Health Canada will then publish a Registration Decision[4] on florylpicoxamid, GF-3840 Fungicide and GF-4017 Fungicide, which will include the decision, the reasons for it, a summary of comments received on the proposed registration decision and Health Canada's response to these comments.

For more details on the information presented in this Overview, please refer to the Science evaluation of this consultation document.

What is florylpicoxamid?

Florylpicoxamid is a conventional fungicide active ingredient that can be used to manage certain diseases of wheat, sugar beet, canola, lentil, and turfgrass. This product provides growers with a unique mode of action fungicide for disease management.

Health considerations

Can approved uses of florylpicoxamid affect human health?

GF-3840 Fungicide and GF-4017 Fungicide, containing florylpicoxamid, are unlikely to affect your health when used according to proposed label directions.

Potential exposure to florylpicoxamid may occur through the diet (food and drinking water), when handling and applying the end-use products, or when entering an area that has been treated with the products. When assessing health risks, two key factors are considered: the levels at which no health effects occur and the levels to which people may be exposed. The dose levels used to assess risks are selected to protect the most sensitive human population (for example, children and nursing mothers). As such, sex and gender are taken into account in the risk assessment. Only uses for which the exposure is well below levels that cause no effects in animal testing are considered acceptable for registration.

Toxicology studies in laboratory animals describe potential health effects from varying levels of exposure to a chemical and identify the dose level at which no effects are observed. The health effects noted in animals occur at dose levels more than 100-times higher (and often much higher) than levels to which humans are normally exposed when pesticide products are used according to label directions.

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[3] "Consultation statement" as required by subsection 28(2) of the *Pest Control Products Act*.

[4] "Decision statement" as required by subsection 28(5) of the *Pest Control Products Act*.

In laboratory animals, the technical grade active ingredient florylpicoxamid was of low acute toxicity by the oral, dermal and inhalation routes. It was non-irritating to the eyes and skin, and did not cause an allergic skin reaction.

The acute toxicity of the end-use product GF-3840 containing florylpicoxamid was low via the oral, dermal and inhalation routes of exposure. It was minimally irritating to the skin and did not cause an allergic skin reaction. GF-3840 was mildly irritating to the eyes; consequently, the signal word and hazard statement "CAUTION – EYE IRRITANT" are required on the label.

The end-use product GF-4017 containing florylpicoxamid and pyraclostrobin was of low acute toxicity via the dermal and inhalation routes of exposure, and did not cause an allergic skin reaction. It was moderately toxic via the oral route and mildly irritating to the eyes and skin. Consequently, the signal word "WARNING" and hazard statements "POISON" and – "EYE AND SKIN IRRITANT" are required on the label.

Registrant-supplied short- and long-term (lifetime) animal toxicity tests were assessed for the potential of florylpicoxamid to cause neurotoxicity, immunotoxicity, chronic toxicity, cancer, reproductive and developmental toxicity, and various other effects. There was no evidence of tumourigenicity. The most sensitive endpoints for risk assessment were abortions and delayed puberty. Although there were serious effects observed in the young (delayed puberty and abortions), there was no evidence of increased sensitivity of the young compared to adult animals. The risk assessment protects against the effects noted above and other potential effects by ensuring that the level of exposure to humans is well below the lowest dose level at which these effects occurred in animal tests.

Occupational risks from handling GF-3840 and GF-4017 Fungicides

Occupational risks are not of health concern when GF-3840 and GF-4017 Fungicides are used according to the proposed label directions, which include protective measures.

Workers mixing, loading or applying GF-3840 or GF-4017 Fungicides, and workers entering recently treated fields of wheat, canola, lentils, sugar beets and turf can be exposed to florylpicoxamid residues through direct skin contact or through inhalation. Therefore, the label specifies that anyone mixing, loading and applying GF-3840 or GF-4017 Fungicides must wear a long-sleeved shirt, long pants, chemical-resistant gloves, socks and shoes, and protective eyewear. The labels also requires that workers do not enter or be allowed into treated fields and sod farms during the restricted-entry interval (REI) of 12 hours, and for golf course entry is permitted once sprays have dried. Taking into consideration the label statements, the number of applications and the duration of exposure for handlers and postapplication workers, the risks to these individuals from exposure to GF-3840 and GF-4017 Fungicides are not of health concern when the end-use product is used according to the proposed label directions.

GF-4017 Fungicide is formulated with pyraclostrobin. Pyraclostrobin is already registered for the proposed use in Canada.

Health risks in residential and other non-occupational environments

Risks in residential and other non-occupational environments are not of health concern when GF-3840 Fungicide is used according to the proposed label directions and REIs are observed.

Adults, youth and children golfing can come into direct contact with florylpicoxamid residues from treated turf. Therefore, the label requires that individuals do not enter treated golf courses until sprays have dried. Taking into consideration the label statements, the number of applications and the duration of exposure, the risks to individuals golfing from exposure to GF-3840 Fungicide are not of health concern when the end-use product is used according to the proposed label directions.

Health risks to bystanders

Bystander risks are not of health concern when GF-3840 and GF-4017 Fungicides are used according to the proposed label directions and spray drift restrictions are observed.

A standard label statement to protect against drift during application is on the label. Therefore, health risks to bystanders are not of concern when the end-use product is used according to the proposed label directions.

Residues in water and food

Dietary risks from food and drinking water are not of health concern.

Studies in laboratory animals showed no acute health effects. Consequently, a single dose of florylpicoxamid is not likely to cause acute health effects in the general population (including infants and children).

Aggregate chronic dietary (food plus drinking water) intake estimates indicated that the general population and all population subgroups are exposed to less than 74% of the acceptable daily intake, and therefore are not of health concern.

The *Food and Drugs Act* prohibits the sale of adulterated food, that is, food containing a pesticide residue that exceeds the established maximum residue limit (MRL). Pesticide MRLs are established for *Food and Drugs Act* purposes through the evaluation of scientific data under the *Pest Control Products Act.* Given that dietary risks from the consumption of foods are shown to be acceptable when florylpicoxamid is used according to the supported label directions, MRLs are being proposed as a result of this assessment (refer to PMRL2022-19, *Florylpicoxamid*).

MRLs for florylpicoxamid determined from the acceptable residue trials conducted throughout Canada and the United States on canola, dry beans and peas, sugar beets, and wheat can be found in the Science evaluation section of this document.

One of the proposed end-use products, GF-4170 Fungicide, is also formulated with the active ingredient pyraclostrobin. This co-active ingredient is already registered for these uses in Canada, and residues in treated commodities will be covered under the existing pyraclostrobin MRLs.

Aggregate health risks

When golf courses are treated with GF-3840 Fungicide, there is potential for individuals to be exposed to florylpicoxamid concurrently via the dermal route while golfing and the oral route while eating treated food commodities. As such, aggregation of dermal and dietary exposure was assessed and no health risks of concern were identified.

Environmental considerations

What happens when florylpicoxamid is introduced into the environment?

When used according to label directions, environmental risks associated with florylpicoxamid and its associated end-use products are acceptable.

Florylpicoxamid enters the environment when GF-3840 Fungicide and GF-4017 Fungicide are used to control diseases in labelled crops. Florylpicoxamid is quickly broken down into several transformation products, one of which is X12485649. X12485649 has a similar structure to florylpicoxamid but takes much longer to break down in the environment.

Transformation products of florylpicoxamid may move through soil to reach groundwater. They may also move off the treatment area in runoff to reach surface water. Florylpicoxamid and its transformation products are not expected to be found in the air, travel long distances in the atmosphere or accumulate in the tissue of animals.

Florylpicoxamid and X12485649 may cause adverse effects to aquatic organisms, beneficial arthropods and non-target terrestrial plants if they are exposed to high enough concentrations. Risk mitigation measures (described below) are required to reduce these risks. After a scientific review of the available information, the PMRA has concluded that the environmental risks from the proposed uses of florylpicoxamid are acceptable when used according to the label directions.

Value considerations

What is the value of GF-3840 Fungicide and GF-4017 Fungicide?

GF-3840 Fungicide contains florylpicoxamid as the active ingredient while GF-4017 Fungicide contains both florylpicoxamid and the registered active ingredient, pyraclostrobin. The registration of these products will provide Canadian growers and turf managers with a unique mode of action fungicide to manage important fungal diseases in wheat, sugar beet, canola, lentil, and turfgrass, while reducing the risk of resistance development by causal pathogens.

GF-3840 Fungicide is applied to foliage of wheat to control septoria leaf spot, to sugar beet to control cercospora leaf spot, to canola to suppress black leg and sclerotinia stem rot, and to turf grass on sod farms and golf courses to control dollar spot. GF-4017 Fungicide is applied to canola to suppress blackleg and to lentil to control anthracnose.

Measures to minimize risk

Labels of registered pesticide products include specific instructions for use. Directions include risk-reduction measures to protect human and environmental health. These directions must be followed by law.

The key risk-reduction measures being proposed on the labels of XDE-659 Technical Fungicide, GF-3840 Fungicide and GF-4017 Fungicide to address the potential risks identified in this assessment are as follows.

Key risk-reduction measures - Human health

- To reduce the potential exposure of workers to florylpicoxamid through direct skin contact or inhalation of sprays, workers mixing, loading and applying GF-3840 and GF-4017 Fungicides and performing cleaning and repair activities must wear a long-sleeved shirt, long pants, chemical-resistant gloves, socks and shoes, and protective eyewear. Additionally, standard label statements to protect against drift during application are on the label. The label also requires that workers do not enter or be allowed entry into treated fields and sod farms during the REI of 12 hours and not to enter into treated golf courses until the sprays have dried.
- The following label statement is required for GF-3840 Fungicide:
    - An 8-day restriction for foraging and cutting of hay for wheat is required.

Key risk-reduction measures - Environment

- Precautionary label statements to inform users of:
    - Toxicity to aquatic organisms.
    - Toxicity to non-target terrestrial plants and beneficial arthropods (for GF-3840 Fungicide only).
    - The potential for leaching of florylpicoxamid residues to groundwater.
- Spray buffer zones of up to 50 metres to protect sensitive non-target aquatic and terrestrial habitats.
- Standard runoff label statements to reduce risk to aquatic organisms from runoff.

Next steps

Before making a final registration decision on florylpicoxamid, GF-3840 Fungicide and GF-4017 Fungicide, Health Canada's PMRA will consider any comments received from the public in response to this consultation document. Health Canada will accept written comments on this proposal up to 45 days from the date of publication of this document. Please note that, to comply with Canada's international trade obligations, consultation on the proposed MRLs will also be

conducted internationally via a notification to the World Trade Organization. Please forward all comments to Publications (contact information on the cover page of this document). Health Canada will then publish a Registration Decision, which will include its decision, the reasons for it, a summary of comments received on the proposed decision and Health Canada's response to these comments.

Other information

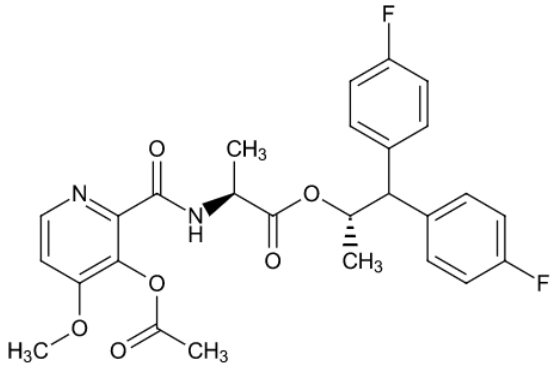
When Health Canada makes its registration decision, it will publish a Registration Decision on florylpicoxamid, GF-3840 Fungicide and GF-4017 Fungicide (based on the Science evaluation of this consultation document). In addition, the test data referenced in this consultation document will be available for public inspection, upon application, in the PMRA's Reading Room. For more information, please contact the PMRA's Pest Management Information Service.

Science evaluation

Florylpicoxamid, GF-3840 Fungicide and GF-4017 Fungicide

1.0 The active ingredient, Its properties and uses

1.1 Identity of the active ingredient

Active substance	Florylpicoxamid
Function	Picolinamide
Chemical name	
1. International Union of Pure and Applied Chemistry (IUPAC)	(1*S*)-2,2-bis(4-fluorophenyl)-1-methylethyl *N*-[(3-acetoxy-4-methoxy-2-pyridyl)carbonyl]-L-alaninate
2. Chemical Abstracts Service (CAS)	(1*S*)-2,2-bis(4-fluorophenyl)-1-methylethyl *N*-[[3-(acetyloxy)-4-methoxy-2-pyridinyl]carbonyl]-L-alaninate
CAS number	1961312-55-9
Molecular formula	$C_{27}H_{26}F_2N_2O_6$
Molecular weight	512.5
Structural formula	
Purity of the active ingredient	95%

1.2 Physical and chemical properties of the active ingredient and end-use product

Technical product – XDE-659 Technical Fungicide

Property	Result
Colour and physical state	Light tan solid
Odour	Yeast-like
Melting range	91.0°C to 95.5°C
Boiling point or range	Decomposes without boiling at ~ 150°C
Density	0.56 g/mL
Vapour pressure at 20°C	$<5 \times 10^{-6}$ Pa at 20°C
Ultraviolet (UV)-visible spectrum	Solution: Acidic; Wavelength λMax, nm: 244, 265, 271; Molar absorption coefficient ε, L/(mol*cm): 7810, 6370, 5300 Solution: Neutral; Wavelength λMax, nm: 265, 271, 220; Molar absorption coefficient ε, L/(mol*cm): 4070, 3710, 21100 Solution: Basic; Wavelength λMax, nm: 266, 272, 343; Molar absorption coefficient ε, L/(mol*cm): 4360, 4660, 11800
Solubility in water at 20°C	3.1 mg/L (pH 7)
Solubility in organic solvents at 20°C	Solvent — Solubility (g/L) methanol: >250 acetone: >250 xylene: >250 1,2-dichloroethane: >250 ethyl acetate: >250 n-heptane: 0.20 n-octanol: 8.7
n-Octanol-water partition coefficient (K_{ow})	pH — log K_{ow} pH 5: 4.2 at 20°C pH 7: 4.2 at 20°C pH 9: 4.3 at 20°C
Acid dissociation constant (p*Ka*)	Does not dissociate between pH 4 to 10
Stability (temperature, metal)	Stable to aluminum, iron, lead and their corresponding acetate salts for 14 days at 54°C

End-use product – GF-3840 Fungicide

Property	Result
Colour	Clear yellow
Odour	Mild
Physical state	Liquid
Formulation type	Emulsifiable concentrate
Label concentration	Florylpicoxamid … 100 g/L

Property	Result
Container material and description	0.5 L to bulk plastic containers
Density	1.006 g/mL at 20°C
pH of 1% dispersion in water	4–6 at 1%
Oxidizing or reducing action	No oxidizing or reducing action
Storage stability	The product was stable after storage in HDPE, PET, COEX, and EVOH for 2 weeks at 54°C.
Corrosion characteristics	No corrosion was observed on HDPE, PET, COEX, or EVOH packaging after 2 weeks of storage at 54°C.
Explodability	Not explosive

End-use product – GF-4017 Fungicide

Property	Result
Colour	Yellow
Odour	Mild
Physical state	Liquid
Formulation type	Emulsifiable concentrate
Label concentration	Florylpicoxamid … 50 g/L Pyraclostrobin … 100 g/L
Container material and description	0.5 L to bulk plastic containers
Density	0.97–1.006 g/mL at 20°C
pH of 1% dispersion in water	4–6 at 1%
Oxidizing or reducing action	No oxidizing or reducing action
Storage stability	The product was stable after storage in HDPE, PET, COEX, and EVOH for 2 weeks at 54°C.
Corrosion characteristics	No corrosion was observed on HDPE, PET, COEX, or EVOH packaging after 2 weeks of storage at 54°C.
Explodability	Not explosive

1.3 Directions for use

GF-3840 Fungicide is applied to:

- wheat (spring, winter, durum) at 0.5 L product/ha using ground or aerial application equipment with one or two applications per year to control septoria leaf spot;
- sugar beet to control cercospora leaf spot at 1.0–1.5 L product/ha up to twice per year using ground application equipment;
- canola at 1.5 L product/ha to suppress black leg and/or at 1.0 L product/ha up to twice per year to suppress sclerotinia stem rot using ground application equipment; and,

- established turf on golf courses and sod farms at 1.5 L product/ha up to five times per year to control dollar spot using ground spray equipment.

GF-4017 Fungicide is applied at 0.8–1.0 L product/ha to canola to suppress blackleg and to lentil to control anthracnose. Application to either crop may be made once per year using ground application equipment.

1.4 Mode of action

Florylpicoxamid inhibits respiration in susceptible fungi by targeting the cytochrome bc1 complex of the mitochondrial electron transport chain. Florylpicoxamid is classified by the Fungicide Resistance Action Committee (FRAC) as a Group 21 fungicide. Pyraclostrobin, a FRAC group 11 fungicide that is included as an additional active ingredient in GF-4017 Fungicide, also inhibits respiration by targeting a different site of the cytochrome bc1 complex.

2.0 Methods of analysis

2.1 Methods for analysis of the active ingredient

The methods provided for the analysis of the active ingredient and impurities in the technical product have been validated and assessed to be acceptable.

2.2 Method for formulation analysis

The methods provided for the analysis of the active ingredients in the formulations have been validated and assessed to be acceptable for use as enforcement analytical methods.

2.3 Methods for residue analysis

High performance liquid chromatography methods with tandem mass spectrometric detection (HPLC-MS/MS) were developed and proposed for enforcement purposes (JRFA Method No. AU298R0 in plant and animal matrices), and for data generation (Method No. 190564 in plants; CEMS-8940 and JRFA Method No. AU-298R0 in animals). These methods fulfilled the requirements with regards to specificity, accuracy and precision at the respective method limit of quantitation. Acceptable recoveries (70–120%) were obtained in plant and animal matrices. The proposed enforcement method was successfully validated in plant and animal matrices by an independent laboratory. Extraction solvents used in the method were similar to those used in the metabolism studies; thus, further demonstration of extraction efficiency with radiolabelled crops was not required for the enforcement method.

High-performance liquid chromatography methods with tandem mass spectrometry (HPLC-MS/MS) were developed and proposed for data generation and enforcement purposes. These methods fulfilled the requirements with regards to selectivity, accuracy and precision at the respective method limit of quantitation. Acceptable recoveries (70–120%) were obtained in environmental media.

Methods for residue analysis in plant and animal matrices and environmental media are summarized in Appendix I, Tables 1 and 2.

3.0 Impact on human and animal health

3.1 Hazard assessment

3.1.1 Toxicology summary

Florylpicoxamid (also known as XDE-659 and XR-659) belongs to the picolinamide class of pesticides. Florylpicoxamid targets the Q_i binding site of mitochondrial cytochrome bc1 complex to inhibit the mitochondrial respiratory chains of fungi. Another fungicide of this class, fenpicoxamid, is registered in Canada.

A detailed review of the toxicology database for florylpicoxamid was conducted. The database is complete, consisting of the full array of toxicity studies currently required for hazard assessment purposes. Additional immunotoxicity (primary antibody response sheep red blood cells assay) and genotoxicity assessments (micronucleus assay) were performed as part of the required guideline dietary 90-day toxicity study in the rat. Functional observation battery (FOB) were performed in the short- and long-term dietary toxicity studies in the rat and long-term dietary oncogenicity study in the mouse. An acute inhalation toxicity study in the rat performed with the metabolite X12485647 was also provided. The required studies were carried out in accordance with currently accepted international testing protocols and Good Laboratory Practices. Overall, the scientific quality of the toxicology database is acceptable, and the database is considered adequate to characterize the majority of the toxic effects that may result from exposure.

Toxicokinetics data consisted of studies in which rats were administered single low or high doses via gavage of ^{14}C-florylpicoxamid radiolabelled in the pyridine position or single low dose of radiolabelled florylpicoxamid in the phenyl position. A repeat-dose regimen at a low-dose level consisting of 14 daily gavage doses of unlabelled florylpicoxamid followed by a single gavage dose of ^{14}C-florylpicoxamid radiolabelled in the pyridine position was also conducted. In a bile duct-cannulated study, single low or high doses via gavage of ^{14}C-florylpicoxamid radiolabelled in the pyridine position or single low dose of test substance radiolabelled in the phenyl position were administered. The position of the radiolabel did not have a significant impact on the toxicokinetic profile.

Absorption was rapid with mean uptake half-lives in plasma ranging from 0.2 to 0.5 hours. Time to reach maximum concentration in plasma ranged from 0.5 to 4.5 hours. Measurements of maximum plasma concentration (C_{max}) and systemic exposure (AUC) indicated saturation of absorption with increasing dose from the low to the high dose level. Based on urinary excretion data from the main toxicokinetics study, absorption was approximately 15% and 25% in males and females at the low dose level and approximately 10% and 18% in males and females at the high dose level. Following repeat low dose, urinary excretion was 19% in males and 40% in females. The bile duct-cannulated study confirmed that absorption of a single dose of florylpicoxamid was less than 25% of the administered dose (AD) 48 hours post dosing across dose levels, sexes and radiolabels.

Combined urinary and biliary excretion data represented 19–22% of the AD in males and 21–24% of the AD in female at the low dose level and 8% and 11% of the AD in males and females at the high dose level.

The radioactive label was distributed in all collected tissues although the concentrations were very low. The highest ratios were generally observed in tissues associated with the uptake and elimination of florylpicoxamid, such as the gastro-intestinal (GI) tract and liver. Mean tissue concentrations, with the exception of the GI tract tissue, were less than 41 µg equivalents/g at t_{max} following low or high dose administration of the radiolabelled test substance. Female rats had lower tissue ^{14}C residue levels retained at 168 hours than male rats, but overall, the tissue concentrations were less than 0.7% of the AD, and a number of tissues had concentrations that were less than the limit of quantification (LOQ) in both sexes. Based on repeated dose exposure, the tissue to plasma concentration ratios indicated low potential for tissue retention.

The terminal elimination half-lives ranged from 22 to 36 hours. The radiolabelled test substance was mainly excreted via feces, with higher levels of fecal excretion occurring in males than females. Fecal excretion was rapid with the majority of elimination occurring within 48 hours post-dosing. Urinary excretion was more prominent in female rats. Urinary elimination was substantially complete in both sexes by 48 hours. Elimination in exhaled breath was negligible. The bile duct-cannulated study showed recoveries in bile at up to 21% of the AD at 48 hours post-dose.

In metabolism studies, florylpicoxamid was not detected at any time in plasma. There were twelve identified and tentatively identified components in the plasma of rats. A key initial metabolic step in the metabolism of florylpicoxamid involved deacetylation to form X12485649. Subsequent reactions involved aromatic oxidation, aliphatic and aromatic hydroxylations, ester bridge or amide cleavages, and phase II glucuronide conjugation. Most of the significant metabolites up to or greater than 5% of the AD were observed in feces (X12485473, X12493055, X12632407, X12485631, and X12485649). Chiral analysis of florylpicoxamid and X12485649 in feces indicated no shift in stereoisomers. In urine, two cleaved metabolites, X12485473 and to a lesser extent X12641325, were present at 5.5–38.0% and 2.4–8.4% of the AD, respectively. No preferential formation of metabolites was evident across sexes.

In a number of repeat-dose oral toxicity studies, blood and urine samples were analysed for the levels of florylpicoxamid and several metabolites. All studies suggest a rapid absorption, hydrolysis of florylpicoxamid to X12485649, and metabolism to X12485473, X12584261, and X12641325. Florylpicoxamid was usually not quantifiable in blood samples or was at very low concentrations, close to the LOQ in all studies.

In short-term dietary toxicity studies, metabolite X12485649 was quantifiable in the blood of females at the mid- and high dose levels in F344 rats and in both sexes at all dose levels tested in Sprague-Dawley (SD) rats. In the latter strain, X12485649 had apparent linear blood toxicokinetics across all dose levels in both sexes. X12485473 was also quantified in SD rats and the data suggested sublinear toxicokinetics beginning at the mid-high dose level in female rats, but suggested linear blood toxicokinetics across all dose levels in male rats.

In urine, florylpicoxamid, X12485649 and X12485473 were quantified and suggested linear toxicokinetics across all dose levels in both sexes. Systemic exposure to metabolites was greater in female rats than male rats (1.8 to 3.4-fold).

In a long-term dietary toxicity study in SD rats, X12485473 and X12641325 were detected in blood at the mid- and high dose levels in both sexes. X12485473 was also detected at the low dose level in females. In urine, X12485473 and X12641325 were the prominent metabolites. Florylpicoxamid was detected at the mid-dose level and above in males and at all doses tested in females. X12485649 was detected at all doses and time points in both sexes, while X12584261 and X12485473 were either not detected or not quantifiable in either sex with the exception of X12485473, which was detected in females at all doses tested at the 1-year time point. X12641325 was detected at all doses in males and at the low dose level in females.

In the dietary 2-generation reproductive toxicity study, quantifiable levels of X12485473 and X12641325 were observed in blood of parental animals, and lactational transfer and systemic exposure of pups to these metabolites was observed at levels one to two orders of magnitude lower compared to the dams. Systemic exposure to X12485473, X12584261, and X12641325 appeared to be similar in F1 and F2 pups. Dietary developmental toxicity studies in rats showed quantitation of X12485473 and X12641325 in maternal and fetal blood and confirmed these were the prominent metabolites in maternal rats and fetuses exposed to florylpicoxamid, followed by X12485649 and X12584261, and indicated that there was maternal transfer of these metabolites to the fetus. In the rabbit dietary developmental toxicity study, florylpicoxamid, X12485649, X12584261, and X12530093 were below the limit of detection in the blood samples of the maternal animals and fetuses. X12485473 and X12641325 were the prominent metabolites in blood of does and fetuses with concentrations in adults two to sixfold higher than the corresponding blood concentrations in the fetuses. These metabolites generally showed dose-proportionality with increasing dietary concentration.

In acute toxicity testing, the technical grade active ingredient florylpicoxamid was of low acute toxicity by the oral, dermal and inhalation routes of exposure in rats. It was non-irritating to the eyes and skin of rabbits, and was negative for skin sensitization in mice according to the local lymph node assay (LLNA) method.

The acute toxicity of the end-use product GF-3840 containing florylpicoxamid was low via the oral, dermal and inhalation routes of exposure in rats. It was minimally irritating to the skin and mildly irritating to the eyes of rabbits, and was negative for skin sensitization in mice according to the LLNA method.

The acute toxicity of the end-use product GF-4017 containing florylpicoxamid and pyraclostrobin was moderate via the oral route and low via the dermal and inhalation routes of exposure in rats. It was mildly irritating to the eyes and skin of rabbits, and was negative for skin sensitization in mice according to the LLNA method.

Repeat-dose dietary toxicity studies with florylpicoxamid were available in mice and rats, and capsule administration studies were available in dogs. In these studies, which involved short-term to long-term testing, the most sensitive species for toxicity appeared to be the dog, followed

by the rat and the mouse. The liver was the primary target tissue following repeated oral dosing in the three species, although the thyroid gland in rats and pituitary gland in dogs were also affected by florylpicoxamid. The treatment-related effects on the liver were mostly adaptive effects in short-term studies (increased liver weight, hepatocellular hypertrophy, changes in hepatic enzyme levels), but were clearly adverse in female rats after long-term dosing (diffuse hepatic necrosis and biliary cysts). In rats, thyroid follicular cell hypertrophy (short-term study) and thyroid parafollicular cell hyperplasia (long-term study) were observed. In dogs, soft feces, increased pituitary gland weight and cysts in the pituitary gland were observed. Adverse effects on body weight and body weight gains were common to all species tested in studies of all durations and were often the most sensitive endpoints. Additional findings included decreases in red blood cell counts, hemoglobin concentrations, hematocrit concentrations, and triglycerides, as well as effects on the testes in rats; decreases in leukocytes, neutrophils, monocytes, and albumin in dogs; and skin discoloration and an increased incidence of mortality in female mice.

There was some evidence to suggest a slight increase in toxicity with extended duration of dosing in the rat studies. In rats, longer-term dosing was associated with more severe effects in the liver and thyroid. While hepatic and thyroid cell hypertrophy were noted in shorter term studies, hepatic necrosis and thyroid cell hyperplasia were observed at similar or lower dose levels in long-term studies. Furthermore, effects on testes (increased testes weight, epididymides weight, decreased spermatic element, epididymides and testes periarteritis) were observed in rats only at terminal sacrifice in the long-term dietary study.

In a 28-day dermal toxicity study in rats, there was no indication of systemic toxicity up to the limit dose of testing.

In a rat 2-generation dietary reproductive toxicity study with florylpicoxamid, no adverse impact on reproductive performance was observed. Body weight impairments were noted in parental animals and offspring from both generations at the highest dose tested (HDT). The F2 offspring of both sexes also displayed hematologic changes (decreases in hemoglobin concentration, mean corpuscular volume, and hematocrit percentage) while delayed completion of vaginal opening was observed in F1 female offspring accompanied with a significant increase in body weight at the time of sexual maturation. Although the concern is low with respect to potential sensitivity of the young, as the effects on F1 and F2 offspring occurred in the presence of effects in the parental animals, the delayed puberty observed in F1 female offspring constitutes a serious effect. The concern was tempered by the absence of such an effect in F2 female offspring.

A supplemental dietary developmental/reproductive toxicity screening study was conducted in rats. Parental animals administered florylpicoxamid in the diet exhibited non-adverse, adaptive effects in the liver. The offspring showed decreased body weight at all dose levels. The body weight effects observed in the offspring at the low- and mid-dose levels were not observed in the offspring of either generation in the definitive study at a similar dose level.

In the dietary developmental toxicity studies, there was no evidence of sensitivity of the young in rats or rabbits. In the probe and main developmental toxicity studies in the rat, no maternal or developmental adverse effects were observed up to the HDT. When considering the dose levels tested in these studies in relation to the points of departure established in other studies in the

database as well as those selected for human health risk assessment, there is a low level of concern for potential developmental toxicity that may have been observed at the high-dose level in the rat, had higher dose levels been tested. In the developmental toxicity study in the rabbit, two abortions occurred in presence of other maternal toxicity (decreased body weight gains and food consumption). One abortion was also observed at a higher dose in the probe developmental toxicity study in presence of body weight effects, GI tract disturbances and vaginal bleeding. Although the concern for the incidence of abortions was tempered by the presence of maternal toxicity, they are considered serious in nature.

There was no evidence of genotoxicity in a battery of in vitro and in vivo genotoxicity studies conducted with florylpicoxamid, nor was there evidence of tumourigenicity in mice or rats after long-term dietary administration of florylpicoxamid.

A FOB was incorporated in the 90-day and 24-month dietary studies in rats and in the 18-month dietary study in mice. No treatment-related selective neurotoxic effects were identified from these assessments. Also in the 90-day dietary study, rats dosed with florylpicoxamid were tested for potential immunotoxicity in an anti-sheep red blood cells (SRBC) response assay. There was no evidence of immune system dysregulation noted in this study, or in other studies in the florylpicoxamid database.

The inhalation toxicity of poultry metabolite X12485647 was investigated. An acute inhalation toxicity study showed that this metabolite had moderate acute inhalation toxicity.

The identification of select metabolites is presented in Appendix I, Table 3. Results of the toxicology studies conducted on laboratory animals with florylpicoxamid and with its associated end-use products, are summarized in Appendix I, Tables 4, 5 and 6, respectively. The toxicology reference values for use in the human health risk assessment are summarized in Appendix I, Table 7.

3.1.2 *Pest Control Products Act* hazard characterization

For assessing risks from potential residues in food or from products used in or around homes or schools, the *Pest Control Products Act* requires the application of an additional 10-fold factor to threshold effects to take into account completeness of the data with respect to the exposure of, and toxicity to, infants and children, and potential prenatal and postnatal toxicity. A different factor may be determined to be appropriate on the basis of reliable scientific data.[5]

With respect to the completeness of the toxicity database as it pertains to the toxicity to infants and children, the database contains the full complement of required studies including dietary developmental toxicity studies in rats and rabbits, a dietary reproductive/developmental toxicity screening study and a dietary 2-generation reproductive toxicity study in rats. The highest dose level selected in the dietary developmental toxicity study in rats was not considered adequate.

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[5] SPN2008-01, *The Application of Uncertainty Factors and the Pest Control Products Act Factor in the Human Health Risk Assessment of Pesticides*.

However, there is sufficient information to conclude that additional factors are not warranted in this situation to ensure the protection of human health for potential developmental toxicity.

With respect to concerns regarding potential prenatal and postnatal toxicity, no evidence of sensitivity of the young was observed in the dietary 2-generation reproductive toxicity study in rats or the dietary developmental toxicity studies in rats and rabbits. In these studies, the offspring and developmental effects were observed at the same dose levels as parental effects. In the dietary 2-generation reproductive toxicity study in rats, delayed vaginal opening was observed in females of the F1 generation in the presence of significant parental body weight effects. In a dietary developmental toxicity study in rabbits, abortions were observed in the presence of significant maternal toxicity.

Overall, the database is adequate for determining the sensitivity of the young. There was no evidence of sensitivity of the young in the dietary 2-generation reproductive toxicity study or the rat or rabbit developmental toxicity studies. The developmental effect (abortions) was considered a serious effect although the concern was tempered by the presence of maternal toxicity. Therefore, the *Pest Control Products Act* factor (PCPA factor) was reduced to threefold when using the dietary developmental toxicity study in rabbits to establish the point of departure for assessing risk to youth and adult populations, including women of child-bearing age. The offspring effect (delayed puberty) was considered a serious effect although the concern was tempered by the presence of parental toxicity. Therefore, the PCPA factor was reduced to threefold when using the effect of delayed puberty to establish the point of departure for assessing risk to children. Where the point of departure for delayed puberty not used for risk assessment for children, the PCPA factor was reduced to onefold.

3.2 Toxicology reference values

3.2.1 Route and duration of exposure

Occupational exposure to GF-3840 and GF-4017 Fungicides is expected to occur predominantly via the dermal and inhalation routes for mixers, loaders and applicators (M/L/As), and through the dermal route for postapplication workers and golfers. Exposure is expected to be intermittent over a short-term duration for farmers and intermediate-term duration for custom applicators as there are up to 5 applications made 7–14 days apart and various postapplication activities occurring during that time period (which can result in exposure for greater than 30 days). Exposure for golfers is expected to be short-term in duration.

3.2.2 Occupational and residential toxicology reference values

Short- and Intermediate-term dermal (all populations, excluding children)

For short- and intermediate-term dermal residential (golfing) and occupational exposures for subpopulations excluding children, the NOAEL of 9.6 mg/kg bw/day from the developmental dietary toxicity study in rabbits was selected for risk assessment. Developmental toxicity was observed in this study in the form of abortions.

Worker populations could include pregnant or lactating women and, therefore, this endpoint was considered appropriate for the occupational risk assessment. The available 28-day dermal toxicity study did not assess the prenatal toxicity.

For residential scenarios, the target margin of exposure (MOE) for these scenarios is 300, which includes uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability, as well as a PCPA factor of threefold for the reasons outlined in the *Pest Control Products Act* hazard characterization Section. The selection of this study and target MOE is considered to be protective of all populations, including the unborn children of exposed women.

For occupational scenarios, the target MOE for this endpoint is 300. Tenfold factors were applied each for interspecies extrapolation and intraspecies variability. As the worker population could include pregnant women, it is necessary to afford adequate protection of the fetus that may be exposed via its mother. In light of concerns regarding prenatal toxicity, as outlined in the *Pest Control Products Act* hazard characterization section, an additional threefold factor was applied to this endpoint to protect for a sensitive subpopulation, namely females 13–49 years of age.

Short- and Intermediate-term dermal (children)

For short- and intermediate-term dermal residential risk assessments for children, an offspring NOAEL of 73 mg/kg bw/day from the dietary 2-generation reproductive toxicity study in rats was selected. At the dose level of 297 mg/kg bw/day, decreased offspring body weight followed by delayed puberty were observed in the presence of parental toxicity. The existing short-term dermal toxicity study did not address the endpoint of concern in children, thus necessitating the use of an oral study for risk assessment.

For residential scenarios, the target MOE selected for this endpoint is 300. Tenfold factors were applied each for interspecies extrapolation and intraspecies variability. As outlined in the *Pest Control Products Act* hazard characterization Section, the PCPA factor was reduced to threefold. The selection of this study and target MOE is considered to be protective of the target population, namely children.

Short- and Intermediate-term Inhalation (adults)

For short- and intermediate-term occupational exposures via the inhalation route, the NOAEL of 9.6 mg/kg bw/day from the developmental dietary toxicity study in rabbits was selected for risk assessment. Developmental toxicity was observed in this study in the form of abortions. Worker populations could include pregnant or lactating women and, therefore, this endpoint was considered appropriate for the occupational risk assessment. A short-term inhalation toxicity study was not available.

The target MOE for these scenarios is 1000, which includes uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability, as well as a factor of threefold for the reasons outlined in the *Pest Control Products Act* hazard characterization section. Furthermore, an additional threefold uncertainty factor was applied to account for residual uncertainty with respect to differences in absorption when extrapolating from an oral toxicity

study to the inhalation route of exposure. This uncertainty stems from the fact that the oral absorption of florylpicoxamid was demonstrated to be low at the dose levels tested in the oral toxicity studies, while absorption via the inhalation route can be assumed to be near 100%. The selection of this study and target MOE is considered to be protective of all populations, including nursing infants and the unborn children of exposed female workers.

Short- and Intermediate-term non-dietary incidental oral ingestion (toddlers)

For the short- and intermediate-term incidental oral risk assessment for toddlers exposed via this route, the offspring NOAEL of 73 mg/kg bw/day from the dietary 2-generation reproductive toxicity study in rats was selected. At the offspring LOAEL of 297 mg/kg bw/day, the most relevant effect for this age group was the early decrease in pre-weaning body weight in both sexes of both generations.

The target MOE is 100, which includes standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability. As discussed in the *Pest Control Products Act* hazard characterization section, the PCPA factor was reduced to onefold.

3.2.3 Acute reference dose (ARfD)

Establishment of an acute reference dose is not required, as an endpoint of concern attributable to a single exposure was not identified in the oral toxicity studies. Although abortions occurred in the probe and main rabbit developmental toxicity studies, they were observed late in gestation.

3.2.4 Acceptable daily intake (ADI)

To estimate risk following repeated dietary exposure, the NOAEL of 9.6 mg/kg bw/day from the developmental toxicity study in the rabbit was selected. At the LOAEL of 26 mg/kg bw/day, reductions in body weight gains, food consumption and abortions were observed. This study provides the lowest NOAEL in the database. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied. As discussed in the *Pest Control Products Act* hazard characterization section, the PCPA factor was reduced to threefold. The composite assessment factor (CAF) is thus 300.

The ADI is calculated according to the following formula:

$$\text{ADI} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{9.6 \text{ mg/kg bw/day}}{300} = 0.03 \text{ mg/kg bw/day of florylpicoxamid}$$

The ADI provides a margin of 2433 to the NOAEL for delayed puberty that was observed in the 2-generation reproductive toxicity study in rats, and a margin of 9033 to the highest dose tested in the rat developmental toxicity study.

3.2.5 Cancer assessment

There was no evidence of tumourigenicity and therefore, a cancer risk assessment is not necessary.

3.2.6 Aggregate toxicology reference values

Aggregate exposure is the total exposure to a single pesticide that may occur from dietary (food and drinking water), residential and other non-occupational sources, and from all known or plausible exposure routes (oral, dermal and inhalation). Short- to intermediate-term aggregate exposure to florylpicoxamid may be comprised of food, drinking water and residential exposure via the dermal route (children, youth and adults).

The toxicology endpoint selected for aggregation for youth and adult populations was abortions. For the oral and dermal routes, the NOAEL of 9.6 mg/kg bw/day from the developmental toxicity study in the rabbit was selected with a target MOE of 300. The PCPA factor for all routes was threefold as set out in the *Pest Control Products Act* hazard characterization section.

The toxicology endpoint selected for aggregation for children was delayed puberty. For the oral and dermal routes, the NOAEL of 73 mg/kg bw/day for delayed puberty observed in the 2-generation reproductive toxicity study in the rat was selected with a target MOE of 300. The PCPA factor for all routes was threefold as set out in the *Pest Control Products Act* hazard characterization section.

3.3 Dermal absorption

A human in vitro dermal absorption study was reviewed and found acceptable. Based on the data presented in the study, a dermal absorption value of 9% was selected for the risk assessment of florylpicoxamid (Appendix I, Table 8).

3.4 Occupational and residential exposure assessment

3.4.1 Acute hazards of end-use products and mitigation measures

3.4.1.1 GF-3840 Fungicide

The acute hazard assessment indicated that GF-3840 Fungicide is of low toxicity via the oral, dermal and inhalation routes of exposure in rats. It was minimally irritating to the skin of rabbits and did not cause an allergic skin reaction in mice according to LLNA method. GF-3840 Fungicide was mildly irritating to the eyes of rabbits. Based on these acute hazards, a long-sleeved shirt, long pants, socks, shoes, chemical-resistant gloves and goggles/face shield are required for workers during mixing, loading, application, clean-up and repair.

3.4.1.2 GF-4017 Fungicide

The acute hazard assessment indicated that GF-4017 Fungicide is of moderate toxicity via the oral and of low toxicity via the dermal and inhalation routes of exposure in rats. It was mildly irritating to the eye and skin of rabbits. Based on these acute hazards, a long-sleeved shirt, long pants, socks, shoes, chemical-resistant gloves and goggles/face shield are required for workers during mixing, loading, application, clean-up and repair.

3.4.2 Occupational exposure and risk assessment

3.4.2.1 Mixer, loader and applicator exposure and risk assessment

Individuals have the potential to be exposed to GF-3840 and GF-4017 Fungicides during mixing, loading and application. Exposure estimates were derived for mixers, loaders and applicators applying GF-3840 Fungicide to wheat, canola, sugar beets and turf grass using groundboom, aerial equipment (wheat only) and handheld equipment on turf (backpack, turf gun). Exposure estimates were derived for mixers, loaders and applicators applying GF-4017 Fungicide to canola and lentils using groundboom equipment.

The unit exposure estimates in the risk assessment are based on mixers/loaders/applicators wearing a long-sleeved shirt, long pants, socks, shoes and chemical-resistant gloves (unless inside a closed-cab tractor or cockpit).

As chemical-specific data for assessing human exposure were not submitted, dermal and inhalation exposures for workers were estimated using data from the Agricultural Handlers Exposure Task Force (AHETF) and the Outdoor residential Exposure Taskforce (ORETF), both of which the applicant is a member and has full access to the data, or the Pesticide Handlers Exposure Database (PHED). All three are compilations of generic mixer/loader and applicator passive dosimetry data, which facilitate the generation of scenario-specific exposure estimates (Appendix I, Table 9).

Dermal exposure was estimated using the unit exposure values with the amount of product handled per day and the dermal absorption value of 9% from the supplied in vitro dermal absorption study. Inhalation exposure was estimated by coupling the unit exposure values with the amount of product handled per day and 100% inhalation absorption. Exposure was normalized to mg/kg bw/day by using 80 kg adult body weight.

The exposure estimates were compared to the selected florylpicoxamid toxicology reference values (dermal and inhalation NOAEL = 9.6 mg/kg bw/day) to obtain the margin of exposure (MOE). The target MOEs are 300 for dermal exposure and 1000 for inhalation exposure. The calculated MOEs are greater than the target MOEs (Appendix I, Table 10) when using groundboom, aerial, and handheld equipment (backpack, turf gun equipment). As the dermal and inhalation routes of exposure have the same toxicological effects, but different MOEs, an aggregate risk index (ARI) was calculated. An ARI greater than 1 is considered acceptable. The calculated ARIs are greater than 1 (Appendix I, Table 10) and are therefore not of health concern for mixers, loaders and applicators when the product is use according to the directions of use.

3.4.2.2 Postapplication exposure and risk assessment

There is potential for exposure to workers entering areas treated with either GF-3840 or GF-4017 Fungicides to complete tasks such as scouting, setting irrigation lines, hand weeding and hand harvesting and from mowing, watering, harvesting turf or when performing maintenance on golf courses. Given the nature of activities performed, exposure should be primarily via the dermal route based on dermal contact with treated foliage and turf. Inhalation exposure is not expected

as florylpicoxamid is considered non-volatile with a vapour pressure of 5×10^{-6} kPa (at 20°C), which is less than the North American Free Trade Agreement (NAFTA) criterion for a non-volatile product for outdoor scenarios [1×10^{-4} kPa (7.5×10^{-4} mm Hg) at 20–30°C]. As such, a quantitative inhalation risk assessment is not required. Inhalation risk is not of health concern for postapplication workers as florylpicoxamid is considered to be non-volatile and the restricted-entry interval of 12 hours or until sprays have dried will allow residues to dry, suspended particles to settle and vapours to dissipate.

Agricultural uses

Chemical-specific dislodgeable foliar residue (DFR) study on dry beans was used for assessing human exposure during postapplication activities specific to wheat, canola, sugar beets and lentils. Dry beans are considered an acceptable surrogate crop for the proposed uses as they all have smooth leaf types and therefore should not underestimate DFR levels. The study was conducted at three locations (Indiana, North Dakota, and California). At all three sites, the application rate corresponded to the maximum rate proposed on the label (150 g a.i./ha) and, therefore, is not expected to underestimate exposure. Applications were done at fourteen-day intervals with a maximum of two applications. Sampling was conducted before and after each application as well as spanning 35 days after the last application. Data were corrected for incomplete recovery when field fortification samples were below 95% (Appendix I, Table 11).

For the purpose of the risk assessment, the predicted DFR value from the North Dakota site (19.2% with a daily dissipation of 32.5%) was deemed the most appropriate for estimating postapplication exposure to wheat, canola, sugar beets and lentils. These values were chosen since the R^2 of the regression equation was high, recoveries were sufficient and the weather from the North Dakota location most closely resembled Canadian growing regions for the proposed crops.

Dermal exposure to workers entering treated areas is estimated by coupling DFR values with activity-specific transfer coefficients (TCs). Activity specific TCs are based on data from the Agricultural Re-entry Task Force (ARTF). Exposure estimates were compared to the florylpicoxamid dermal toxicology reference value (NOAEL = 9.6 mg/kg bw/day) to obtain the MOE. The target MOE is 300. Since the calculated MOEs are greater than the target MOE of 300 (Appendix I, Table 12), the postapplication exposure is not of health concern and the REI of 12 hours is adequate.

Turf uses

Chemical-specific transferable turf residue (TTR) study conducted on turf grass was not quantitatively used for assessing human exposure during postapplication activities specific to sod farms and golf courses. The study was conducted at three locations (Florida, California and Pennsylvania) on turf grass and used the California roller technique for sampling. At all three sites, the application rate (50 g a.i./ha) was much lower than the proposed rate (150 g a.i./ha) and, therefore, may underestimate exposure.

Applications were done at fourteen-day intervals with a maximum of five applications. Sampling was conducted before the last application and as well as spanning 14 days after the last application. Most samples showed no residues and data were not corrected for field recoveries (Appendix I, Table 13).

The study was considered to be unacceptable on its own for estimating exposure to GF-3840 Fungicide since the combination of the lower rate, and LOQ/LOD not being very sensitive, resulted in residues not being detected and regression analysis could not be performed. Therefore, the results were not used quantitatively. As the chemical-specific TTR data were deemed not acceptable, the standard turf transferable residue value of 1% of the application rate coupled with 10% daily dissipation of residues were used in the exposure assessment. The results from the submitted TTR study showed similar peak values (1%) and therefore give weight to the standard values not underestimating exposure. Dermal exposure to workers entering treated areas is estimated by coupling TTR values with activity-specific TCs. Activity TCs are based on data from the Agricultural Re-entry Task Force (ARTF).

Exposure estimates were compared to the florylpicoxamid dermal toxicology reference value (NOAEL = 9.6 mg/kg bw/day) to obtain the MOE. The target MOE is 300. Since the calculated MOEs are greater than the target MOE of 300 (Appendix I, Table 14), the postapplication exposure is not of health concern and the REI of 12 hours for sod farm and until sprays have dried for golf courses are adequate.

3.4.3 Residential exposure and risk assessment

3.4.3.1 Handler exposure and risk assessment

GF-3840 and GF-4017 Fungicides are not domestic class products; therefore, a residential handler risk assessment is not required.

3.4.3.2 Postapplication exposure and risk assessment

GF-3840 Fungicide is proposed for use on turf which includes recreational areas where the public may be exposed. As such, a postapplication residential/recreational risk assessment is required.

3.4.3.2.1 Golf courses treated with GF-3840 Fungicide

Since GF-3840 Fungicide is for use on golf courses, there is the potential for recreational postapplication exposure to florylpicoxamid for golfers (adults, youth and children) entering treated turf areas. The primary route of exposure for these individuals is through the dermal route. The duration of exposure for golfing is expected to be of short-term in duration.

Dermal exposure to golfers is estimated by coupling the TTR value with the activity specific transfer coefficient based on ARTF studies data from the 2012 United States Environmental Protection Agency Residential Standard Operating Procedures. TTR values were calculated by using the standard 1% of the application rate with the 10% daily dissipation rate. Exposure estimates after correcting for the dermal absorption of 9% were compared to the toxicological

reference value to obtain the MOE; the target MOE is 300. The calculated MOEs for dermal exposure are presented in Appendix I, Table 15. The estimated MOEs were all greater than the target MOE of 300. Therefore, health risks are not of concern for golfers entering treated golf courses after the sprays have dried.

3.4.4 Bystander exposure and risk assessment

Bystander exposure is considered negligible as application is limited to agricultural crops and golf courses only when there is low risk of drift to areas of human habitation and human activity (other than golf courses) such as parks, school grounds, and playing fields, taking into consideration wind speed, wind direction, temperature inversions, application equipment and sprayer settings.

Therefore, bystander exposure and risk are not of health concern since the potential for drift is expected to be minimal.

3.5 Dietary exposure and risk assessment

3.5.1 Exposure from residues in food of plant and animal origin

The residue definition for enforcement in plant products is florylpicoxamid and in animal commodities is florylpicoxamid and the metabolite X12485649 (expressed as parent equivalents). The residue definition for risk assessment in human food commodities of plants and animals is florylpicoxamid and the metabolite X12485649 (expressed as parent equivalents); and in animal feed items, an additional metabolite (X12563767, expressed as parent equivalents) is included. The data gathering analytical method is valid for the quantitation of florylpicoxamid and X12485649 residues in crops for human consumption (and X12563767 for animal feed items) and animal matrices. The residues of florylpicoxamid are stable in representative matrices from five crop categories (high water, high oil, high protein, high starch, and high acid content) for up to 9 months when stored at -18°C. Therefore, florylpicoxamid residues are considered stable in all frozen crop matrices and processed crop fractions for up to 9 months. Residues of florylpicoxamid did not concentrate in any food items resulting from the processing of the raw agricultural commodities of canola, sugar beets, and wheat. Adequate feeding studies were carried out to assess the anticipated residues in animal matrices resulting from the current uses. Crop field trials conducted throughout Canada and the United States using end-use products containing florylpicoxamid at approved rates in or on canola, sugar beets, and wheat and at exaggerated rates in or on dry peas and beans are sufficient to support the proposed maximum residue limits. Field rotational crop studies were not conducted since no residues of concern were observed at the 30-day plant-back interval (PBI) (in other words; shortest PBI studied) in the confined accumulation in rotational crop studies.

3.5.2 Exposure from residues in drinking water

A Level 1 drinking water assessment was conducted using conservative assumptions with respect to environmental fate, application rate and timing, and geographic scenario. Level 1 estimated environmental concentrations (EECs) are conservative values intended to screen out pesticides

that are not expected to pose any concern related to drinking water sources (groundwater and surface water). EECs for florylpicoxamid in drinking water sources were calculated using the Pesticide in Water Calculator (PWC) version 2.0.

For surface water, PWC calculates the amount of pesticide entering a water body by runoff and spray drift, and the subsequent degradation of the pesticide in the water system. Groundwater EECs are calculated by simulating leaching through a layered soil profile and reporting the average concentration in the top 1-metre of a water table for several scenarios representing different regions of Canada. Only the highest EECs from across the groundwater scenarios are reported. Most scenarios were run for 50 years, but two were run for 100 years as they were slow to come to steady state.

The use pattern selected for the drinking water modelling was a subset of use patterns intended to represent all proposed uses: five applications of 150 g a.i./ha with a 7-day re-application interval. Florylpicoxamid was modelled as a combined residue with the transformation products X12485649 and X12485631. The combined residue was determined based on potential for exposure and toxicity. The major fate inputs for drinking water modelling and the drinking water EECs are presented in Appendix I, Tables 16 and 17, respectively.

Details of water modelling inputs and calculations are available upon request.

3.5.3 Dietary risk assessment

A chronic dietary risk assessment was conducted using the Dietary Exposure Evaluation Model (DEEM–FCID™, Version 4.02, 05-10-c), which incorporates consumption data from the National Health and Nutrition Examination Survey/What We Eat in America (NHANES/WWEIA) for the year 2005-2010.

3.5.3.1 Acute dietary exposure results and characterization

No appropriate toxicological reference value attributable to a single dose was identified for the general population (including children and infants). Hence, an acute dietary risk assessment is not required.

3.5.3.2 Chronic dietary exposure results and characterization

The following assumptions were applied to the basic chronic analysis for florylpicoxamid: 100% crop treated, default processing factors, residues in food commodities at the Canadian MRL levels, and proposed American tolerances for imported commodities. The basic chronic dietary exposure from all supported florylpicoxamid food uses (food alone) for the total population, including infants and children, and all representative population subgroups is less than 4% of the ADI. The PMRA estimates that chronic dietary exposure to florylpicoxamid from food and drinking water is 20% (0.006 mg/kg bw/day) of the ADI for the total population. The highest exposure and risk estimate is for all infants (< 1 year) at 74% (0.022 mg/kg bw/day) of the ADI. Therefore, aggregate exposure from food and drinking water is acceptable as there are no dietary risks of concern.

3.6 Aggregate exposure and risk assessment

There is potential for individuals to be exposed to florylpicoxamid via different routes of exposure concurrently. As such, aggregation of chronic dietary (food and drinking water) and dermal exposure to florylpicoxamid from golfing activities was assessed.

For golfers, the chronic dietary exposure values (food plus drinking water) for specific subpopulations for florylpicoxamid were aggregated with the dermal exposure values while golfing. Aggregate exposure estimates were compared to the aggregate toxicological reference value to obtain the MOE; the target MOEs are 1000 for adults and youth and 300 for children. The results of the aggregate risk assessment are presented in Appendix I, Table 18. The calculated MOEs were greater than the target MOEs, as such, there are no aggregate health risks of concern.

3.7 Cumulative assessment

The *Pest Control Products Act* requires the Agency to consider the cumulative effects of pest control products that have a common mechanism of toxicity. Accordingly, an assessment of a potential common mechanism of toxicity with other pesticides was undertaken for florylpicoxamid. Florylpicoxamid is a fungicide from the picolinamide class of fungicides. Another fungicide in this class, fenpicoxamid, has an import maximum residue limit (MRL) and therefore, Canadians may be exposed to this pesticide through their diet. Although both fungicides share similar structures and toxicity profiles, the common adverse effects, which included liver toxicity and soft feces, were indicative of generalized toxicity rather than the manifestation of a common mechanism of action. Overall, for the current evaluation, the PMRA did not identify information indicating that florylpicoxamid shares a common mechanism of toxicity with other pest control products to which exposure is expected to occur in Canada. Therefore, no cumulative health risk assessment is required at this time.

3.8 Maximum residue limits

Dietary risks from the consumption of food commodities listed in Table 3.8.1 were shown to be acceptable when florylpicoxamid is used according to the supported label directions. Therefore, foods containing residues at these levels are safe to eat, and the PMRA recommends that the following MRLs be specified for residues of florylpicoxamid.

Table 3.8.1 Recommended maximum residue limits

MRL (ppm)	Food commodity
0.02	Eggs; fat, meat, and meat byproducts of cattle, goats, horses, hogs, poultry and sheep; milk
0.015	Rapeseeds (crop subgroup 20A revised)
0.01	Dried shelled beans, except soybeans (crop subgroup 6-21E), dried shelled peas (crop subgroup 6-21F), wheat (crop subgroup 15-21A), sugar beet roots

MRLs are proposed for each commodity included in the listed crop groupings in accordance with the Residue Chemistry Crop Groups webpage in the Pesticides section of the Canada.ca website.

For additional information on MRLs in terms of the international situation and trade implications, refer to Appendix II.

The nature of the residues in animal and plant matrices, analytical methodologies, field trial data, and chronic dietary risk estimates are summarized in Appendix I, Tables 1B, 19 and 20.

3.9 Health incident reports

Florylpicoxamid is a new active ingredient pending registration for use in Canada and as of 5 May 2022, no human or domestic animal incident reports have been submitted to the PMRA.

4.0 Impact on the environment

4.1 Fate and behaviour in the environment

A summary of the major transformation products (TPs) for florylpicoxamid is provided in Appendix I, Table 21. The environmental fate parameters for florylpicoxamid and its major TPs are provided in Appendix I, Table 22. Florylpicoxamid and its TP, X12485649, are the residues of primary concern from an environmental perspective. X12485649 is similar to florylpicoxamid in both structure and toxicity; however, it is much more persistent in the environment.

Terrestrial environment:

Hydrolysis is an important transformation process for florylpicoxamid. Florylpicoxamid is rapidly hydrolyzed to the major TP, X12485649. At pH 9, X12485649 is further hydrolyzed to two major TPs: X12485473 and X12485631.

Phototransformation on soil was determined to be a negligible process for both florylpicoxamid and X12485649.

Biotransformation in soil is a major route of transformation for florylpicoxamid. Florylpicoxamid is non-persistent in aerobic and anaerobic soil. One major TP, X12485649, was formed in aerobic soils. Up to four major TPs, X12485649, X12485631, X12485473 and X696476, were formed in anaerobic soils.

X12485649 is classified as moderately persistent to persistent in aerobic and anaerobic soils. Data were insufficient to calculate degradation kinetics in soil for the other major TPs.

A terrestrial field dissipation study was conducted at bare soil sites in California, Florida, North Dakota and Ontario; a site cropped with cucumber was also used in Florida. The California and Florida sites are not in Canadian-relevant ecozones; however, they were included in this assessment as supporting information given that the application rates used at the Ontario and North Dakota (2 × 50 g a.i./ha) sites were below the maximum proposed seasonal application rate. In all the field sites, florylpicoxamid was not detected in soil within 14 days after last

application (DALA). After 360 days, X12485649 remaining in the field were 22.1, 23.0, 17.5, and 23.3% of initial measured soil concentrations (0 DALA) at the California, Florida (bare soil), Florida (cropped) and North Dakota sites, respectively; florylpicoxamid and X12485649 were not detected past 7 DALA at the Ontario site. As such, carryover is not a concern for florylpicoxamid.

Florylpicoxamid and X12485649 were not detected in soil deeper than 30.5 cm; however, the available weight-of-evidence (in other words, mobility information, leaching criteria of Cohen et al., (1984), groundwater ubiquity scores (GUS), and groundwater modelling) indicates that leaching of X12485649 to groundwater may be a concern (Appendix I, Table 23). Based on this information, and because X12485649 is included in the residue definition for drinking water, a precautionary label statement is proposed to inform users to avoid use of GF-3840 Fungicide and GF-4017 Fungicide in areas where the soils are permeable, particularly where the water table is shallow, because X12485649 may leach to groundwater.

Aquatic environment:

Florylpicoxamid is broken down in water via the combined processes of hydrolysis, aqueous phototransformation and biotransformation. As noted above, hydrolysis is an important transformation process for florylpicoxamid. Florylpicoxamid also undergoes rapid aqueous phototransformation, completely transforming within one day of irradiation. Six major TPs were produced from the aqueous phototransformation of florylpicoxamid: X12485649, X12485631, X12719657 and three unidentified compounds.

Florylpicoxamid is non-persistent in aquatic systems, with half-lives in the total system (water + sediment) of <0.5 days. The biotransformation of florylpicoxamid in aquatic systems resulted in the production of one major TP, X12485649, in the water and sediment of all tested systems. X12485649 is persistent in aquatic systems.

The log K_{ow} values for florylpicoxamid (4.2 to 4.3) and X12485649 (3.4 to 3.5) indicate that these chemicals may have the potential to bioaccumulate; however, the submitted bioconcentration studies indicate that these chemicals are not expected to bioaccumulate in fish and are quickly depurated (<5 days for florylpicoxamid and ≤ 6.3 days for X12485649). The bioconcentration factors for both compounds range from 82 to 106.

Atmospheric fate:

Florylpicoxamid and its major TPs, with the exception of X12485631, have low vapour pressures and low Henry's law constants, which indicate a low potential for volatilization in the field. X12485631 has intermediate to high volatility based on its vapour pressure; however, it is very soluble in water and it is not expected to be volatile from a water surface or moist soil based on its Henry's law constant. This is supported by the laboratory fate studies which did not find significant amounts of radioactivity in the organic traps (generally <3 % of applied radioactivity (AR)) despite the formation of X12485631 at up to almost 50% AR. As such, long-range atmospheric transport of these compounds in the gas phase is unlikely to occur.

4.2 Environmental risk characterization

An environmental risk assessment integrates environmental exposure and ecotoxicology information in order to estimate the potential for adverse effects to non-target species. This integration is achieved by comparing EECs to the concentrations at which adverse effects occur. The EECs are estimated using standard models considering application rate(s), and chemical and environmental fate properties, including the dissipation of the pesticide between applications. The EECs used in the risk assessment are presented in Appendix I, Table 24.

Acute and chronic ecotoxicological data for non-target terrestrial, freshwater and marine organisms were submitted by the applicant and are summarized in Appendix I, Table 25. In the risk assessment, toxicity endpoints were adjusted to calculate an effects metric. The effects metric accounts for potential differences in species sensitivity as well as varying protection goals (in other words, protection at the community, population, or individual level). For characterizing acute risk, the effects metric was calculated by dividing acute toxicity values (for example, LC_{50}, LD_{50}, and EC_{50}) by an uncertainty factor (UF; for example, 10 for fish, birds and small wild mammals, 2 for earthworms, aquatic invertebrates and plants, and 1 for bees and beneficial arthropods). Chronic risks to terrestrial and aquatic organisms were assessed using no-observed effect concentration (NOEC) values with an UF of 1. The effects metrics used in the risk assessment are presented in Appendix I, Table 26.

Initially, a screening level risk assessment was performed to identify specific uses that do not pose a risk to non-target organisms, and groups of organisms for which there may be a potential risk. The screening level risk assessment used simple methods, conservative exposure scenarios and sensitive toxicity endpoints. A risk quotient (RQ) was calculated by dividing the EEC by the effects metric, and was then compared to the level of concern (LOC). If the screening level RQ was below the LOC, risk was considered negligible and no further risk characterization was required. If the screening level RQ was equal to, or greater than the LOC, a refined risk assessment was performed to further characterize the risk.

The refined risk assessment evaluated more realistic exposure scenarios, including consideration of spray drift and runoff, as well as endpoints that were more reflective of potential exposure in the environment. Refinements to the risk assessment were continued until the risk was adequately characterized or no further refinements were possible.

The proposed end-use product, GF-4017 Fungicide, contains 50 g/L florylpicoxamid and 100 g/L pyraclostrobin. The proposed use pattern for GF-4017 Fungicide is within the currently registered use pattern for pyraclostrobin. As such, environmental risks from the pyraclostrobin content of GF-4017 Fungicide are considered to be acceptable with the required risk mitigation measures for pyraclostrobin (in other words, spray buffer zones and a precautionary label statement to inform users of its toxicity to aquatic organisms). Consult Proposed Registration Decision PRD2008-04, *Pyraclostrobin, Insignia EG Fungicide, Headline EC* and Registration Decision RD2008-13, *Pyraclostrobin* for the environmental risk assessment for pyraclostrobin.

4.2.1 Risks to terrestrial organisms

Terrestrial organisms, such as earthworms, bees and other beneficial arthropods, birds, wild mammals and terrestrial vascular plants may be exposed to florylpicoxamid through direct contact with spray or spray drift, contact with sprayed surfaces or from ingestion of contaminated food. A risk assessment for florylpicoxamid, the major TPs and the end-use products, GF-3840 Fungicide and GF-4017 Fungicide, was undertaken based on available toxicity data.

The screening level risk assessment for terrestrial organisms is shown in Appendix I, Table 26. At the screening level, the EEC for florylpicoxamid in soil was calculated based on a direct overspray, considering a cumulative application rate of five applications of 150 g a.i,/ha with a re-application interval of 14 days and a half-life in aerobic soil for florylpicoxamid of 1.01 days (90% upper confidence bound on the mean of four available values). Soil EECs were converted from g a.i./ha to mg a.i./kg using the assumption that florylpicoxamid is homogeneously mixed in the top 15 cm soil layer with a soil bulk density of 1.5 g/cm^3.

The EECs in soil for the major TPs were conservatively calculated based on the maximum application rate (five applications of 150 g a.i,/ha), assuming 100% conversion of the parent on a molar basis. No dissipation of the parent between applications was considered.

The EEC of 196 g a.i./ha on plant surfaces in the field was calculated based on two applications of 150 g a.i./ha with a 7-day re-application interval, and considering a foliar half-life for the combined residue of florylpicoxamid and X12485649 of 4.14 days (Appendix I, Table 24). This use pattern was used to calculate the EEC because the use pattern proposed for turf (five applications of 150 g a.i./ha with a 14-day re-application interval) results in a lower cumulative application rate of 166 g a.i./ha due to the short foliar half-life.

Non-target terrestrial organisms might also be exposed to florylpicoxamid via spray drift. The amount of spray drift depends on the type of equipment used, the size of the spray droplets, as well as the type of crop. To calculate off-field EECs, spray drift factors were applied to the on-field EECs. The spray drift factor is defined as the maximum percentage of spray drift deposition at one metre downwind from the point of application. For florylpicoxamid, application using a field sprayer or aerial equipment with medium spray droplets (as specified on the label), results in spray drift factors of 6 and 23%, respectively.

Earthworms and bees

Earthworms could be exposed to florylpicoxamid when it is applied to crops, resulting in soil exposure. Foraging bees may be exposed to florylpicoxamid spray droplets during application (contact exposure) or through the ingestion of pollen and nectar contaminated with florylpicoxamid (oral exposure). Additionally, bee brood may be exposed to florylpicoxamid if foraging bees bring contaminated pollen and nectar back to the hive. The screening level RQs (≤ 0.32) for these organisms were below the LOCs (0.4 for acute exposure for bees, and one for earthworms and chronic exposure for bees). As such, risks to these organisms from the use of florylpicoxamid are negligible.

Beneficial arthropods

Beneficial arthropods could be exposed to florylpicoxamid spray droplets during application. Toxicity tests for beneficial arthropods were conducted with the end-use product, GF-3840 Fungicide.

The screening level risk assessment for beneficial arthropods, using effects metrics from toxicity tests where the test organisms were exposed to dried residues of GF-3840 on glass plates, is shown in Appendix I, Table 26. The screening level assessment evaluated both on-field and off-field exposure. For foliar-dwelling arthropods (in other words, predatory mite, *Typhlodromus pyri*, and parasitic arthropod, *Aphidius rhopalosiphi*), the maximum cumulative application rate of 196 g a.i./ha was used to estimate on-field exposure. The screening level risk assessment used a LOC of two for spray application on glass plates given that significant ecological effects for these species at the population level are not expected below this value. The screening level risk assessment showed that:

- On-field risk: The on-field RQs (3.55 to 39.2) for both species exceeded the screening level LOC of two.
- Off-field risk: When considering off-field exposure, risks to *T. pyri* due to spray drift are considered to be negligible (RQs ≤ 0.8) and were not further characterized. The off-field RQs for *A. rhopalosiphi* (RQs = 2.35 to 9.02) exceed the LOC of two.

Based on the above, on-field risks to both organisms and off-field risks for *A. rhopalosiphi* were further characterized.

The refined risk assessment considered a LOC of one rather than the LOC of two used in the screening level risk assessment. Risks to beneficial arthropods were further characterized in several ways (Appendix I, Table 27):

(1) Consideration of effects metrics from extended laboratory toxicity tests that exposed test organisms to dried residues on leaf discs or barley seedlings rather than glass plates. Dried residues on leaf discs and barley seedlings are closer approximations of a real-life exposure scenario than glass plates. When considering the refined effects metrics, on-field and off-field risks to the parasitic arthropod, *A. rhopalosiphi,* were considered to be negligible (RQs ≤ 0.66 were below the LOC of one) and were not further characterized. The on-field RQ for *T. pyri* based on reproductive effects (RQ = 3.25) exceeded the LOC. As such, on-field risks to *T. pyri* were further characterized.
(2) Adjustment of on-field EECs for *T. pyri,* to account for varying application rates and the interception of spray droplets by crops.
    a. For wheat, sugar beet and canola (GF-3840 Fungicide), the maximum cumulative application rate (196 g a.i./ha) was adjusted to account for the maximum foliar deposition fraction (F_{int}) of 0.9 for these crops. F_{int} values were obtained from Linders et al. (2000). The RQ of 2.92 for this refinement exceeded the LOC of 1.

b. For turf (GF-3840 Fungicide), the cumulative application rate of 166 g a.i./ha (based on five applications of 150 g a.i./ha with a 14-day re-application interval) was further adjusted to account for a F_{int} of 0.4 for all growth stages of grass. The RQ of 1.10 for this refinement marginally exceeded the LOC of 1.
c. For GF-4017 Fungicide, the maximum seasonal application rate of 50 g a.i./ha was also considered. The RQ of 0.83 for this refinement was below the LOC of 1.

Based on the above, risks to beneficial arthropods associated with the use of GF-4017 Fungicide (also containing pyraclostrobin) are considered to be negligible (RQ < LOC based on the maximum application rate).

The use of GF-3840 Fungicide may result in adverse reproductive effects to predatory arthropods on-field only. No risk was identified for off-field populations. Given that effects are limited to on-field exposure, potential adverse effects are expected to be temporary based on the rapid dissipation of this product and the potential for recolonization from off-field sites within one season. A precautionary label statement indicating toxicity to certain beneficial arthropods is proposed for GF-3840 Fungicide. Risks to beneficial arthropods associated with the use of GF-3840 Fungicide are considered to be acceptable when used according to the label directions.

Terrestrial vertebrates - Birds and wild mammals

A screening level risk assessment was conducted to evaluate the acute and reproductive risks to birds and mammals based on the estimated concentration of florylpicoxamid in various food items in the diet (the estimated daily exposure (EDE)). Exposure is dependent on the body weight of the organism, and the amount and type of food consumed. As such, a set of generic body weights was used to represent a range of species (20, 100, and 1000 g for birds and 15, 35, and 1000 g for mammals) and specialized feeding guilds (in other words, herbivore, frugivore, insectivore and granivore) were considered for each category of animal weights.

The screening level risk assessment evaluated a conservative exposure scenario based on:

(1) The maximum florylpicoxamid residue concentrations in food items;
(2) A diet that is composed entirely (100%) of a particular dietary item; and,
(3) The feeding guild assumed to have the highest exposure for each animal weight category.

If a concern was identified at the screening level (in other words, RQ > LOC of one), the risk was then further characterized.

Based on the screening level risk assessment, acute and reproductive risks to birds and acute risks to wild mammals from the use of florylpicoxamid are negligible (RQs ≤ 0.19; Appendix I, Table 28). The RQ of 1.86 for reproductive risk for medium sized mammals (35 g) marginally exceeded the LOC of 1. As such, risks for this group were further characterized by expanding the assessment to include all relevant food guilds and considering both on-field and off-field maximum and mean residues values (Appendix I, Table 29). Spray drift factors of 6 and 23% for field sprayer and aerial application, respectively, were used to calculate off-field EECs. Risks to wild mammals are considered to be negligible given that the RQs based on mean on-field residue

concentrations (RQs ≤ 0.66) and off-field exposure (RQs ≤ 0.43) were below the LOC. Additionally, it is considered unlikely that the diet of mammals would be composed 100% of food items contaminated with the maximum concentration of florylpicoxamid for multiple days. Risks to wild mammals are considered to be negligible given that the RQs based on mean on-field residue concentrations (RQs ≤ 0.66) and off-field exposure (RQs ≤ 0.43) were below the LOC.

Non-target terrestrial plants

The screening level risk assessment for non-target terrestrial plants considered risk due to a direct overspray of florylpicoxamid. The RQ of 1.47 for non-target terrestrial plants based on the vegetative vigour effects metric and the maximum cumulative application rate (196 g a.i./ha) marginally exceeded the LOC of 1 (Appendix I, Table 26). As such, the risk assessment was further refined to consider (1) the lower application rate for GF-4017 Fungicide (one application of 50 g a.i./ha), and (2) the off-field spray drift of GF-3840 Fungicide one-metre downwind from the point of application (6 and 23% spray drift for field sprayer and aerial application, respectively). The on-field risks from GF-4017 Fungicide and off-field risks from GF-3840 Fungicide to non-target terrestrial plants are negligible (RQs ≤ 0.37; Appendix I, Table 27). Spray buffer zones of up to 1 metre are proposed for the label of GF-3840 Fungicide to protect sensitive terrestrial habitat. Spray buffer zones to protect sensitive terrestrial habitat are not required for GF-4017 Fungicide.

4.2.2 Risks to aquatic organisms

Aquatic organisms, such as invertebrates, fish, amphibians and aquatic plants could be exposed to florylpicoxamid if spray drift or runoff enter aquatic habitat. In the screening level risk assessment, EECs were calculated as follows:

- The EEC for florylpicoxamid in surface water was calculated based on a direct overspray to a one-hectare wetland at the maximum cumulative application rate of 150 g a.i./ha. This rate was calculated using 5 applications of 150 g a.i./ha with a 14-day re-application interval and considering a representative half-life of 1.25 days for florylpicoxamid in water.
- EECs for the major TPs (X12485649, X1248573, X12585631 and X12719657) were calculated considering 100% transformation of florylpicoxamid on a molar basis. The maximum application rate (five applications of 150 g a.i,/ha) with no dissipation of the parent between applications was used in this calculation.
- The EEC to evaluate risks from GF-4017 Fungicide was calculated based on one application of 50 g a.i./ha.

Water bodies of two different depths were evaluated: an EEC in surface water 15 cm deep was used to determine risk to amphibians while an EEC at an 80 cm depth was used to evaluate risks to all other aquatic organisms.

Florylpicoxamid and X12485649 are classified as highly toxic to very highly toxic to freshwater and marine aquatic organisms (Appendix I, Table 25). Toxicity studies for the other major TPs (X12485473, X12485631 and X12719657) using freshwater invertebrates and fish were available. These TPs are classified as practically non-toxic up to 10 or 11 mg/L, with the exception of X12485631 which is classified as moderately toxic to rainbow trout.

In the screening level risk assessment (Appendix I, Table 30), risks to freshwater algae and vascular aquatic plants from the use of florylpicoxamid are considered to be negligible (RQs ≤ 0.37). Furthermore, risks to aquatic organisms (invertebrates, fish, amphibians, algae and vascular plants) from the major TPs, X1248573, X12585631 and X12719657, are also negligible (RQs ≤ 0.45).

The RQs for florylpicoxamid, X12485649 and GF-4017 Fungicide exceed the LOC of 1 for freshwater and marine invertebrates (RQs of 2.63 to 63.1), fish (RQs of 5.56 to 80.8), and amphibians (RQs of 29.8 to 423, considering freshwater fish as a surrogate). As such, risks to these organisms were further characterized by considering exposure via spray drift and runoff.

Spray drift to aquatic habitat

In order to evaluate risks from spray drift, the aquatic EECs were adjusted to account for deposition of spray drift one metre downwind from the point of application using spray drift factors of 6 and 23% for application via field sprayer and aerial application (medium sized spray droplets), respectively. Additionally, EECs for the estuarine/marine environment were refined by considering only one application of florylpicoxamid to account for tidal action and dilution in seawater. The RQs for aquatic invertebrates, fish and amphibians exceed the LOC of 1 for both levels of spray drift (Appendix I, Table 31). Spray buffer zones of 1 to 50 metres are required to protect sensitive freshwater and estuarine/marine habitats.

Runoff to aquatic habitat

EECs for florylpicoxamid residues in surface water from runoff were modelled using PWC version 2.0. The PWC model calculates the amount of pesticide entering the water body via runoff only, and the subsequent degradation of the pesticide in the water and sediment. The EECs were calculated by modelling a 10-ha field adjacent to 1-ha water bodies of two different depths: 15 and 80 cm. The model was run for 50 years using a combined residue of florylpicoxamid and X12485649 given their similar ecotoxicity. The EECs in surface water from runoff, as well as parameters used in the ecological water modelling, are presented in Appendix I, Table 24.

The EECs in surface water from runoff do not consider the pyraclostrobin content of GF-4017 Fungicide. The toxicity endpoints presented for GF-4017 Fungicide were calculated based on the mean measured concentrations of florylpicoxamid in the studies. It is unclear how much of the overall toxicity observed in the studies was the result of each compound given that florylpicoxamid was shown to be unstable in the test systems, pyraclostrobin was stable and the amount of X12485649 formed in the test systems was not measured. As noted in Section 4.2, the use pattern for GF-4017 Fungicide is within the registered use pattern for pyraclostrobin. As

such, environmental risks from the pyraclostrobin content of GF-4017 Fungicide are considered to be acceptable. The refined runoff risk assessment was conducted using only toxicity endpoints for florylpicoxamid and X12485649.

The results of the refined runoff risk assessment are summarized in Appendix I, Table 31. The peak and 21-day EECs were used to calculate acute and chronic risks, respectively, for the highest and lowest exposure scenarios. The RQs exceeded the LOC of 1 for all exposure scenarios (RQs $\leq$ 21.8). No further refinements were possible. As such, there may be a risk to aquatic organisms from runoff containing florylpicoxamid residues. Standard label statements are proposed to mitigate runoff.

4.2.3 Environmental incident reports

Florylpicoxamid is a new active ingredient pending registration for use in Canada, and as of 5 May 2022, no environmental incident reports have been submitted to the PMRA.

5.0 Value

Florylpicoxamid is a new active ingredient for disease management in Canada. The registration of GF-3840 Fungicide and GF-4017 Fungicide will provide Canadian growers, sod producers and golf course superintendents with a unique fungicide mode of action to manage important diseases in wheat, canola, sugar beet, lentil and turf while mitigating the risk of resistance development by causal pathogens to other fungicides that are registered to control the same diseases.

GF-3840 Fungicide

In eight field trials on spring or winter wheat, data demonstrated that GF-3840 Fungicide applied at 0.5 L/ha can be expected to control septoria leaf spot. A subset of trials supported aerial application. While the efficacy of GF-3840 Fungicide against septoria leaf spot was not specifically assessed on durum wheat, the response of this crop, which is also susceptible to this disease, would be expected to be similar to that for other types of wheat.

Efficacy data from five field trials conducted on spring canola demonstrated that GF-3840 Fungicide applied once at 1.5 L product/ha can be expected to suppress blackleg. In a different set of five trials conducted on winter canola in four European countries, results demonstrated that GF-3840 Fungicide applied at 1.0 L product/ha can be expected to suppress sclerotinia stem rot. The data generated for sclerotinia stem rot on winter canola was extrapolated to spring canola in Canada.

Disease severity data from four field trials conducted on sugar beet demonstrated that GF-3840 Fungicide can be expected to control cercospora leaf spot at 1.0–1.5 L product/ha up to twice per year with a minimum of 10 days between applications.

In three field studies conducted on established creeping bentgrass turf, GF-3840 Fungicide applied at 1.5 L product/ha was demonstrated to control dollar spot. Creeping bentgrass was shown to be tolerant of GF-3840 Fungicide based on turf quality ratings and the absence of

injury. While only creeping bentgrass was evaluated in these trials, other cool season turf grass species would also be expected to be tolerant to GF-3840 Fungicide due to the high level of tolerance exhibited by creeping bentgrass as well as other tested crops.

GF-4017 Fungicide

The efficacy of GF-4017 Fungicide against blackleg on canola and anthracnose on lentil was evaluated in four and six field trials, respectively. Data demonstrated that GF-4017 Fungicide applied at 0.8–1.0 L product/ha can be expected to suppress blackleg on canola or control anthracnose on lentil.

Both active ingredients were shown to contribute to suppression of blackleg on canola and control of anthracnose on lentil. Therefore, it can be expected that the use of GF-4017 Fungicide will help to reduce the development of resistance by the causal pathogens to pyraclostrobin and other fungicides that are registered for use on these crops.

No injury was observed to either canola or lentil treated with GF-4017 Fungicide at up to 1.5 L product/ha.

The data collectively support the efficacy claims summarized in Appendix I, Table 32 for GF-3840 Fungicide, and Table 33 for GF-4017 Fungicide.

6.0 Pest control product policy considerations

6.1 Assessment of the active ingredient under the Toxic Substances Management Policy

The *Toxic Substances Management Policy* (TSMP) is a federal government policy developed to provide direction on the management of substances of concern that are released into the environment. The TSMP calls for the virtual elimination of Track 1 substances, in other words, those that meet all four criteria outlined in the policy: persistent (in air, soil, water and/or sediment), bio-accumulative, primarily a result of human activity and toxic as defined by the *Canadian Environmental Protection Act*. The *Pest Control Products Act* requires that the TSMP be given effect in evaluating the risks of a product.

During the review process, florylpicoxamid and its transformation products were assessed in accordance with the PMRA Regulatory Directive DIR99-03[6] and evaluated against the Track 1 criteria. The PMRA has reached the conclusion that florylpicoxamid and its transformation products do not meet all of the TSMP Track 1 criteria.

Please refer to Appendix I, Table 34 for further information on the TSMP assessment for florylpicoxamid.

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6 DIR99-03*, The Pest Management Regulatory Agency's Strategy for Implementing the Toxic Substances Management Policy*

6.2 Formulants and contaminants of health or environmental concern

During the review process, contaminants in the active ingredient as well as formulants and contaminants in the end-use products are compared against Parts 1 and 3 of the *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern.*[7] The list is used as described in the PMRA Science Policy Note SPN2020-01[8] and is based on existing policies and regulations, including the *Toxic Substance Management Policy* and *Formulants Policy*,[9] and taking into consideration the *Ozone-depleting Substances and Halocarbon Alternatives Regulations* under the *Canadian Environmental Protection Act, 1999, (*substances designated under the *Montreal Protocol).*

The PMRA has reached the conclusion that XDE-659 Technical Fungicide (florylpicoxamid) and its end-use products GF-3840 Fungicide and GF-4017 Fungicide do not contain any formulants or contaminants identified in the *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern*.

The use of formulants in registered pest control products is assessed on an ongoing basis through PMRA formulant initiatives and Regulatory Directive DIR2006-02.

7.0 Proposed regulatory decision

Health Canada's PMRA, under the authority of the *Pest Control Products Act*, is proposing registration for the sale and use of XDE-659 Technical Fungicide, GF-3840 Fungicide and GF-4017 Fungicide, containing the technical grade active ingredient florylpicoxamid, to manage certain diseases of wheat, sugar beet, canola, lentil, and turfgrass.

An evaluation of available scientific information found that, under the approved conditions of use, the health and environmental risks and the value of the pest control products are acceptable.

Additional information being requested

Since this technical product is manufactured only at pilot scale before registration, five-batch data representing commercial-scale production will be required as postmarket information after registration.

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7 SI/2005-114, last amended on June 24, 2020. See Justice Laws website, Consolidated Regulations, *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern.*

8 PMRA's Science Policy Note SPN2020-01, *Policy on the List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern under paragraph 43(5)(b) of the Pest Control Products Act*

9 DIR2006-02, *Formulants Policy and Implementation Guidance Document*

List of abbreviations

%	percent
<	lesser than
≥	greater than, or equal to
>	greater than
≤	lesser than, or equal to
↑	increased
↓	decreased
µg	microgram(s)
µm	micrometre(s)
♀	female
♂	male
1/n	exponent for the Freundlich isotherm
a.i.	active ingredient
abs	absolute
AD	administered dose
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism and elimination
AHETF	Agricultural Handlers Exposure Task Force
ALB	albumin
ALS	acetolactate synthase
AR	applied radioactivity
ARfD	acute reference dose
ARI	aggregate risk index
ARTF	Agricultural Reentry Task Force
atm	atmosphere
ATPD	area treated per day
AUC	area under curve
BAF	bioaccumulation factor
BBCH	Biologishe Bundesanstalt, Bundessortenamt and Chemical industry
BCF	bioconcentration factor
BCF_{KLG}	growth and lipid corrected bioconcentration factor
bw	body weight
bwg	body weight gain
CAF	composite assessment factor
CAS	Chemical Abstracts Service
CEPA	*Canadian Environmental Protection Act*
CHO	Chinese hamster ovary
cm	centimetre
cm^3	cubic centimetre
C_{max}	Maximum plasma concentration
COEX	Co-extruded plastic
CP	cyclophosphamide
d	day
DAA1	days after first application
DAA2	days after second application

DAA3	days after third application
DAA5	days after fifth application
DALA	days after last application
DF	dry flowable
DFOP	double first order in parallel
DFR	dislodgeable foliar residue
DIR	Directive
DNA	deoxyribonucleic acid
DOC	dissolved oxygen carbon
DT_{50}	dissipation time 50% (the time required to observe a 50% decline in concentration)
DT_{90}	dissipation time 90% (the time required to observe a 90% decline in concentration)
dw	dry weight
EC	emulsifiable concentrate
EC_{25}	effective concentration on 25% of the population
EC_{50}	effective concentration on 50% of the population
EC_x	effective concentration to x% of the population
EDE	estimated daily exposure
EEC	estimated environmental concentration
ER_{25}	effective rate for 25% of the population
ER_x	effective rate to x% of the population
EVOH	Ethylene vinyl alcohol
F0	parental generation
F1	first filial generation
F2	second filial generation
fc	food consumption
F_{int}	foliar deposition fraction
FIR	food ingestion rate
FOB	functional observational battery
FRAC	Fungicide Resistance Action Committee
g	gram(s)
GD	gestation day
GI	gastro-intestinal
GSD	geometric standard deviation
GUS	Groundwater Ubiquity Score
h	hour
ha	hectare(s)
HAFT	highest average field trial
Hb	hemoglobin
HC(D)	historical control (data)
Hct	hematocrit
HDPE	High-density polyethylene
HDT	highest dose tested
Hg	mercury
HPLC	high performance liquid chromatography
HPLC-MS/MS	high performance liquid chromatography with tandem mass spectrometry

hr(s)	hour(s)
IC_{50}	inhibitory concentration to 50% of the population
IgM	immunoglobulin M
ILV	independent laboratory validation
IORE	indeterminate order rate equation
IUPAC	International Union of Pure and Applied Chemistry
K_d	soil-water partition (adsorption) coefficient
K_F	Freundlich adsorption coefficient
kg	kilogram(s)
km	kilometre
K_{oc}	soil organic carbon-water partition coefficient
K_{ow}	*n*–octanol-water partition coefficient
kPa	kilopascal
L	litre(s)
LAFT	lowest average field trial
LC_{50}	concentration estimated to be lethal to 50% of the test population
LD	lactation day
LD_{50}	dose estimated to be lethal to 50% of the test population
LLNA	local lymph node assay
LOAEL	lowest observed adverse effect level
LOC	level of concern
LOD	limit of detection
LOEC	low observed effect concentration
LOQ	limit of quantification
LR_{50}	lethal rate to 50% of the population
LSC	liquid scintillation counting
M/L/A	mixer/loader/applicator
m/z	mass-to-charge ratio of an ion
m^3	cubic metre
MAS	maximum average score for 24, 48 and 72 hours
MCV	mean corpuscular volume
mg	milligram(s)
MIS	maximum irritation score
mL	millilitre(s)
MMAD	mass median aerodynamic diameter
MOE	margin of exposure
mol	mole
MRL	maximum residue limit
MRM	multiresidue method
MS	mass spectrometry
MW	molecular weight
N/A	not applicable
N/R	not required
NA	not applicable
NAFTA	North American Free Trade Agreement
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration

NOED	no-observed effect dose
NOEDD	no-observed effect dietary dose
NOEL	no observed effect level
NOER	no observed effect rate
NR	not reported
NZW	New Zealand white
OC	organic carbon content
°C	degree Celsius
OM	organic matter content
°N	degree North
ORETF	Outdoor Residential Task Force
Pa	Pascal
PBI	plantback interval
PCPA	*Pest Control Products Act*
PET	Polyethylene terephthalate
Ph	phenyl ring
PHED	Pesticide Handlers Exposure Database
PHI	preharvest interval
p*K*a	acid dissociation constant
PMRA	Pest Management Regulatory Agency
PND	postnatal day
PPE	personal protective equipment
ppm	parts per million
PRD	Proposed Registration Decision
PWC	Pesticide in Water Calculator
Py	pyridine ring
R^2	coefficient of determination
RAC	raw agricultural commodity
RBC	red blood cells
RD	residue definition
RD	Registration Decision
REI	restricted-entry interval
rel	relative
Ret	reticulocyte
RQ	risk quotient
RSD	relative standard deviation
S9	mammalian metabolic activation system
SC	soluble concentrate
SD	Sprague-Dawley
SFO	single first order
SI	stimulation index
SPN	Science Policy Note
SRBC	sheep red blood cells
STMdR	supervised trial median residue
STMR	supervised trial mean residue
$t_{1/2}$	half-life
T3	tri-iodothyronine

T4	thyroxine
TC	transfer coefficient
TFD	terrestrial field dissipation
TG	triglyceride
t_{max}	time to reach maximum plasma concentration
TOC	total organic carbon
TP	transformation product
t_R	representative half-life
TRR	total radioactive residue
TSMP	Toxic Substances Management Policy
TTR	turf transferable residue
UAN	urea ammonium nitrate
UF	uncertainty factor
UK	United Kingdom
US	United States
USEPA	United States Environmental Protection Agency
UV	ultraviolet
v/v	volume per volume dilution
wk(s)	week(s)
wt	weight
X12485473	N-[(3-hydroxy-4-methoxypyridin-2-yl)carbonyl]-L-alanine
X12485631	(2S)-1,1-bis(4-fluorophenyl)propan-2-ol
X12485649	(2S)-1,1-bis(4-fluorophenyl)propan-2-yl N-[(3-hydroxy-4-methoxypyridin-2-yl)carbonyl]-L-alaninate

Appendix I Tables and figures

Table 1 Residue analysis

Matrix	Analyte	Method type	LOQ	Reference
Sediment	Florylpicoxamid	HPLC-MS/MS	0.05 mg/kg	PMRA# 3113620
	X12485649			
Clay loam soil	Florylpicoxamid			
	X12485649			
Sandy loam soil	Florylpicoxamid			
	X12485649			
Silt loam soil	Florylpicoxamid			
	X12485649			
Drinking water	Florylpicoxamid		0.010 ng/mL	PMRA# 3113622
	X12485649		0.010 ng/mL	
	X12485473		0.20 ng/mL	
	X12485631		0.20 ng/mL	
Surface water	Florylpicoxamid		0.010 ng/mL	
	X12485649		0.010 ng/mL	
	X12485473		0.20 ng/mL	
	X12485631		0.20 ng/mL	
Groundwater	Florylpicoxamid		0.010 ng/mL	
	X12485649		0.010 ng/mL	
	X12485473		0.20 ng/mL	
	X12485631		0.20 ng/mL	

Table 2 Residue analysis

Analytical methods	Matrix	Analytes	Method ID/ Type	LOQ	Reference
Livestock commodities					
Enforcement method	Cattle cream, fat, kidney, liver, and muscle	Florylpicoxamid and X12485649	QuEChERS JRFA Method No, AU-298R0 / LC-MS/MS	0.01 ppm for each analyte in all matrices	PMRA# 3113594
Data-gathering method	Whole milk, eggs, bovine muscle, fat, kidney, and liver				PMRA# 3143154

Analytical methods	Matrix	Analytes	Method ID/ Type	LOQ	Reference
	Whole milk, skimmed milk, cream, bovine muscle, poultry muscle, bovine liver, poultry liver, bovine kidney, bovine fat, poultry fat		CEMS-8940 / LC-MS/MS		PMRA# 3113594, 3143153
ILV of enforcement method	Cattle cream, fat, kidney, liver, and muscle		QuEChERS JRFA Method No, AU-298R0 / LC-MS/MS		PMRA# 3113595
Radiovalidation	The solvents used in the livestock metabolism studies are similar to the ones used in the enforcement method for livestock commodities. Therefore, the extraction efficiency of the bio-incurred residues is considered to be acceptable, and radiovalidation of the enforcement method is not required.				
Plant commodities					
Enforcement method	Canola seed, cherry, orange, and wheat grain	Florylpicoxamid	JRFA Method No. AU-298R0 / LC-MS/MS	0.01	PMRA# 3113594
Data-gathering method	Wheat forage, grain, and straw		Method No. 190564 / LC-MS/MS		PMRA# 3113625
ILV of enforcement method	Dry bean, canola seed, cherry, and orange		JRFA Method No. AU-298R0 / LC-MS/MS		PMRA# 3113595
Radiovalidation	The solvents used in the plant metabolism studies are similar to the ones used in the enforcement method for plant commodities. Therefore, the extraction efficiency of the bio-incurred residues is considered to be acceptable, and radiovalidation of the enforcement method is not required.				PMRA# 3113594

Table 3 Identification of Select Metabolites of Florylpicoxamid

Code	Chemical name	Source
X12485473	*N*-[(3-hydroxy-4-methoxypyridin-2-yl)carbonyl]-*L*-alanine	Rat, rabbit and environmental metabolite
X12493055	(2S)-1,1-bis(4-fluorophenyl)propane-1,2-diol	Rat metabolite
X12632407	(2S)-1,1-bis(4-fluorophenyl)-1-hyproxypropan-2-yl N-[3-hydroxy-4-methoxy-6-oxo-1,6-dihydropyridin-2-yl)carbonyl]-L-alaninate	Rat metabolite
X12485631	(2S)-1,1-bis(4-fluorophenyl)propan-2-ol	Rat and environmental metabolite
X12485649	(2S)-1,1-bis(4-fluorophenyl)propan-2-yl N-[(3-(hydroxy)-4-methoxypyridin-2-yl)carbonyl]-L-alaninate	Rat, rabbit, livestock, and environmental metabolite
[M+H]-473	Proposed ionic form of O-demethylation of X12485649 with hydroxylation	Rat metabolite
X12641325	1,1-bis(4-fluorophenyl)propan-2-yl hexopyranosiduronic acid	Rat and rabbit metabolite
[M+H]-647	Proposed ionic form of glucuronide conjugate of X12485649	Rat metabolite
X12485647	(2S)-1,1bis(4-fluorophenyl)propan-2-yl L-alaninate hydrochloride)	Poultry and crop metabolite
X12530093	(2S)-1,1-bis(4-fluorophenyl)propan-2-yl N-[(3-hydroxy-4-methoxy-1-oxidopyridin-2-yl)carbonyl]-L-alaninate	N.A.
X12629973	Aromatic oxidation form of (2S)-1,1-bis(4-fluorophenyl)propan-2-yl N-[(3-(hydroxy)-4-methoxypyridin-2-yl)carbonyl]-L-alaninate (X12485649)	Rat and poultry metabolite
X12584261	(2S)-1,1-bis(4-fluorophenyl)-1-hydroxypropan-2-yl N-[(3-hydroxy-4-methoxypyridin-2-yl)carbonyl]-L-alaninate (tentative identification)	Rat and rabbit metabolite
X12641685	Aliphatic hydroxylation form of (2S)-1,1-bis(4-fluorophenyl)propan-2-yl N-[(3-(hydroxy)-4-methoxypyridin-2-yl)carbonyl]-L-alaninate (X12485649, tentative identification)	Rat metabolite
X12714411	Glucoronidation form of (2S)-1,1-bis(4-fluorophenyl)propane-1,2-diol (X12493055)	Rat metabolite
X696476	3-hydroxy-4-methoxypyridine-2- carboxylic acid	Rat and environmental metabolite

N.A.: not applicable

Table 4 Toxicity profile of technical florylpicoxamid (XDE-659)

Effects observed in both sexes are presented first followed by sex-specific effects in males, then females, each separated by semi-colons. Organ weight effects reflect both absolute organ weights and relative organ to body weights unless otherwise noted. Effects seen above the LOAEL(s) have not been reported in this table for most studies for reasons of brevity.

Study type/ Animal/PMRA#	Study results
Toxicokinetics	
Toxicokinetics – Single low and high oral doses, repeat low oral dose (gavage) Sprague-Dawley rats PMRA# 3112038	Toxicokinetics, mass balance, tissue distribution and metabolism with a single dose (oral gavage) of the pyridine labelled XDE-659: 4/sex/dose at the low dose of 25 mg/kg bw, high dose of 250 mg/kg bw or repeat low dose levels of 25 mg/kg bw/day of unlabelled XDE-659 for 14 days followed by a single oral dose of pyridine labelled XDE-659 on test day 15. Time-course blood was collected and radioactivity quantified in plasma and RBC. Tissues, excreta (feces, urine and exhaled breath), cage rinse, and final cage wash were collected and analyzed for radioactivity. Metabolites were profiled from urine and fecal samples. Excreta were collected for 7 days post dosing. The measurements were repeated with a single low dose (25 mg/kg bw) of the phenyl labelled XDE-659. **Absorption:** ^{14}C-XDE-659 was absorbed rapidly with mean uptake half-lives in plasma ranging from 0.2 to 0.5 hours. The t_{max} values ranged from 0.5 to 4.5 hours. Dose normalized values for C_{max} and systemic exposure as measured by the AUC indicated saturation of absorption between 25 and 250 mg/kg bw. As biliary excretion was not characterized in this study, absorption can be estimated from urinary excretion only. Considering the urinary recovery for both labels, absorption was at least 7% to 19% in males and 12% to 40% in females. **Distribution:** Analysis of tissues indicated a systemic uptake and distribution was evident based on the presence of quantifiable ^{14}C residues in most of the collected tissues. However, the percentages and concentration values were very low. The highest ratios were generally observed in tissues associated with the uptake and elimination of XDE-659 (GI tract and liver). Alpha-phase distribution half-lives in plasma ranged from 2.4 to 9.4 hours. **Excretion:** The overall labelled test substance recovery ranged from 85.3 to 96.3% of the AD, the majority (pyridine or phenyl label) was recovered in the feces. By 168 hours, across the single low-, single high-, and repeat-dose groups (pyridine label), the mean percentages of the AD recovered in feces ranged from 73%

	to 78% for male rats and 52% to 59% for female rats. The phenyl ring radiolabelled group had mean recoveries of 85% and 80% for male and female rats, respectively. Fecal excretion was rapid with 87–93% of total elimination occurring within 24 hours post-dosing for the pyridine label and 91–93% of total elimination occurring 48-hour post-dosing for the phenyl label. Recovery in urine ranged from 10 to 19% for male rats and 18 to 40% for females of the pyridine dose groups. Recovery in urine was 7 and 12% for the phenyl label in male and female rats, respectively. Urinary elimination was rapid and substantially complete by 24 hours (pyridine label) and 48 hours (phenyl label). In exhaled breath, the mean recoveries for the low dose pyridine labelled XDE-659 were ≤ 0.2% of AD in both sexes. At 168 hours post-dosing, in all tissue collected, the mean concentration was ≤ 1.21 µg equivalent/g and the total percentage recovered in tissues across all groups ranged from 0.0363% to 0.693% of AD in male rats and 0.00630% to 0.112% of AD in female rats. Tissue-to-plasma ratios indicated very low potential for tissue retention after repeat dosing. The beta-phase terminal elimination half-lives ranged from 22 to 36 hours. RBC pharmacokinetics were similar to plasma with the exception of slower overall beta-phase terminal elimination plasma half-lives that ranged from 87 to 166 hours in male rats and 14 to 64 hours in female rats. Female rats had lower tissue ^{14}C residue levels retained at 168 hours than male rats. **Metabolism:** The metabolite profile of ^{14}C-XDE-659 was qualitatively similar across sexes and dose levels, and bridge cleavage metabolites were observed resulting in different metabolites between the radiolabels. The overall results indicated extensive metabolism of XDE-659 and identified or tentatively identified 11 components in feces and urine. The initial metabolic step in the metabolism of XDE-659 involved deacetylation to form X12485649. Subsequent reactions involved aromatic oxidation, aliphatic and aromatic hydroxylations, ester bridge or amide cleavages, and phase II glucuronide conjugation. Most of the metabolites up to or greater than 5% of the AD were observed in feces (X12485473, X12493055, X12632407, X12485631, and X12485649). Chiral analysis of XDE-659 and X12485649 in feces indicated no shift in stereoisomers. In urine, two cleaved metabolites (X12485473 and to a lesser extent X12641325) were present at 5.5–38% and 2.4–8.4% of the AD, respectively. Collectively, XDE-659 and the 11 identified metabolites in feces accounted for 43–68% of AD, while metabolites in urine

	accounted for 4.0–39% of the AD, across both radiolabels and all dose groups. The overall pharmacokinetics were similar between the pyridine and phenyl radiolabels.
Toxicokinetics - Biliary elimination, tissue distribution and metabolism, single low and high oral doses (gavage) Sprague-Dawley rats PMRA# 3303930	Biliary elimination with a single dose (oral gavage) of the pyridine or phenyl labelled test substance: 4/sex/dose of XDE-659-Py-2-^{14}C at the low dose of 25 mg/kg bw, high dose of 250 mg/kg bw or XDE-659-bis-Ph-UL-^{14}C at the low dose of 25 mg/kg bw. Animals were euthanized 48 hours after dosing. Tissue distribution was evaluated with a single dose (oral gavage) of the pyridine or phenyl labelled test substance: 8/sex/dose of XDE-659-Py-2-^{14}C at the low dose of 25 mg/kg bw, high dose of 250 mg/kg bw or XDE-659-bis-Ph-UL-^{14}C at the low dose of 25 mg/kg bw. Animals were euthanized at t_{max} or 24 hours. For metabolite profiling, bile and urine were collected pre-dose and at 0–6, 6–12, 12–24, and 24–48 hours post-dosing. Feces were collected pre-dose and at 0–12, 12–24, and 24–48 hours post-dosing for metabolite profile. Samples for metabolite profiling and chiral analysis were collected (at t_{max} and 24 hours) and pooled (4 rats/sex/time point/sample matrix). Bile and plasma samples were submitted for ^{14}C metabolite profiling. Bile, plasma, liver and fats samples and the corresponding dose suspensions were submitted for chiral analysis of XDE-659 and X12485649 stereoisomers. **Absorption:** Maximum absorption, based on urinary and biliary recoveries, occurred at the low dose administration and was similar across sexes and radiolabels. The mean absorption values ranged from 19 to 24% of AD at the low dose. Saturation of absorption occurred at the high dose and was approximately twofold less. **Distribution:** ^{14}C Residues were found in all the collected tissues. The percentages of AD and concentration levels were very low. Mean tissue concentrations, with the exception of the GI tract tissue, were less than 41 µg equivalents/g at t_{max} after low or high dose administration of the XDE-659-Py-2-^{14}C label or low dose administration of the XDE-659-bisPh-UL-^{14}C label. Tissue ^{14}C residues continued to decline after the 24-hour sampling time. **Excretion:** From bile duct-cannulated groups (0-48 hours), the mean recoveries of ^{14}C-XDE-659 ranged from 79% to 93% of the AD across sexes, doses, and radiolabels. The majority of the dose was associated with feces (up to 76% of AD), urine (<10% of AD) and bile (up to 21% of AD).

	Metabolism: There were twelve identified and tentatively identified components in plasma of rats. Unchanged XDE-659 was not detected at any time in plasma. Two metabolites were found to be individually greater than 1 µg equivalents/g in plasma, X12485473 (0-1.52 µg equivalents/g) and [M+H]-473 (0-1.47 µg equivalents/g) from the XDE-659-Py-2-^{14}C label high dose level. In bile, metabolites were extensively conjugated and analyses were performed with or without glucuronidase incubation. Without glucuronidase incubation, there were 12 identified or tentatively identified components. Unchanged XDE-659 was not detected and two metabolites were >5% of AD ([M+H]-647 with both labels and X12641325 with phenyl label only). With glucuronidase incubation, there were eight identified and tentatively identified components. Unchanged XDE-659 was not detected and two metabolites were >5% of AD (X12485631 with phenyl label only and X12485649 with both labels). With or without glucuronidase incubation, recovery in bile accounted for 11.0 to 18.6% of AD at low dose and 4.2 to 4.3% of AD at high dose. No preferential formation of metabolites was evident across sexes in plasma or bile.
Acute toxicity studies	
Acute oral toxicity (acute toxic class) Wistar rats PMRA# 3112022	LD_{50} > 2000 mg/kg bw (♀) No clinical signs of toxicity Low Toxicity
Acute dermal toxicity Wistar rats PMRA# 3112023	LD_{50} > 2000 mg/kg bw (♂/♀) No clinical signs of toxicity Low Toxicity
Acute inhalation toxicity (nose-only) Wistar rats PMRA# 3112024	LC_{50} > 5.48 mg/L (♂/♀) No clinical signs of toxicity. MMAD: 3.59 µm; GSD: 1.60 Low Toxicity
Eye irritation New Zealand White rabbits PMRA# 3112025	MAS = 0/110 MIS = 2.0/110 (at 1 hour) Not an eye irritant
Skin irritation New Zealand White rabbits	MAS = 0/8 MIS = 1/8 (at 1 hour) Not a skin irritant

PMRA# 3112026	
Dermal sensitization Local lymph node assay (LLNA) CBA/J mice PMRA# 3112027	Negative
Short-term toxicity studies	
90-day oral + 28-day recovery (dietary) Crl:CD1(ICR) mice PMRA# 3112028	NOAEL = 192/201 mg/kg bw/day (♂/♀) LOAEL = not determined No adverse effects at the HDT 192/201 mg/kg bw/day (♂/♀): ↑ALP (♂/♀); ↑ALT, ↑incidence of hepatocellular hypertrophy, ↑liver and kidney wt (♂);↓AST (♀) (non-adverse)
28-day oral toxicity (diet) F344 rats PMRA# 3219868	NOAEL= 84/243 mg/kg bw/day (♂/♀) LOAEL= 230 mg/kg bw/day/not determined (♂/♀) Effects at the LOAEL: ↑rel liver wt, ↑incidence of slight centrilobular/ midzonal hepatocellular hypertrophy, ↑rel kidney wt (♂/♀) (non-adverse); ↓bw, ↓bwg, ↓fc, ↓RBC, ↓Hb, ↓Hct, ↑Ret, ↓TG (♂) Toxicokinetics: XDE-659 was not quantifiable in enough blood and urine samples to perform analysis. Metabolite X12485649 was quantifiable in blood of ♀ at mid and high doses. Data suggested that systemic exposure was sublinear at the high dose. X12485649 quantifiable in urine samples of both sexes at mid and high doses (≤ 0.05% of AD). Sublinear kinetics was suggested at the high dose in ♀. Linear kinetics suggested in ♂. Metabolite X12485473 was quantifiable in blood samples and appeared linear across all dose levels in both sexes. In urine samples, X12485473 appeared linear across all dose levels in both sexes and was ≤ 12% and 32% of AD, respectively. Systemic exposure to X12485473 was twofold higher in female rats.
28-day oral toxicity (diet) Crl:CD(SD) rats PMRA# 3219869	NOAEL= 206/320 mg/kg bw/day (♂/♀) LOAEL= 278/355 mg/kg bw/day (♂/♀) Effects at the LOAEL: ↑liver wt (non-adverse), ↑incidence of minimal thyroid follicular cell hypertrophy (♂); ↓bw, ↓bwg (♀) Toxicokinetics: XDE-659 was not quantifiable in enough blood samples to perform analysis. X12485649 had linear blood toxicokinetics across all dose levels in both male and female rats,

	and the data suggested that X12485473 was sublinear at the NOAEL and higher dose levels in female rats, but linear blood toxicokinetics across all dose levels in male rats. XDE-659, X12485649 and X12485473 showed linear urinary toxicokinetics across all dose levels in both sexes. Systemic exposure to metabolites was greater in female rats than male rats (1.8 to 3.4-fold).
90-day oral toxicity (diet) F344 rats PMRA# 3112029 Included FOB, immunotoxicity assessment (SRBC) and peripheral reticulocyte micronucleus	NOAEL = 59/185 mg/kg bw/day (♂/♀) LOAEL = 177 mg/kg bw/day/not determined (♂/♀) Effects at the LOAEL: ↓bw, ↓bwg, ↓fc (♂); ↑incidence very slight hypertrophy of centrilobular/midzonal hepatocytes with ↑cytoplasmic eosinophilia, ↑kidney wt (non-adverse) (♂) Recovery: persistence of ↓ bw and bwg in ♂ rats No evidence of immune system dysregulation No evidence of genotoxicity No evidence of neurotoxicity
90-day oral (capsule) Beagle dogs PMRA# 3124187	NOAEL = 60 mg/kg bw/day (♂/♀) LOAEL = 150 mg/kg bw/day (♂/♀) Effects at the LOAEL: ↓bw, ↓bwg, ↑pituitary glands wt (♂/♀); ↑soft feces, ↑cysts in pituitary glands, ↓leukocytes, ↓neutrophils, ↓monocytes, ↓ALB (♂); ↓fc, ↑spleen wt (♀)
28-day dermal toxicity Sprague-Dawley rats PMRA# 3112030	NOAEL = 1000 mg/kg bw/day (♂/♀) LOAEL: not determined No adverse effects at the HDT
Chronic toxicity/Oncogenicity studies	
18-month oncogenicity (dietary) Crl:CD1(ICR) mice PMRA# 3112032 Included FOB assessment	NOAEL= 55/72 mg/kg bw/day (♂/♀) LOAEL= 172/230 mg/kg bw/day (♂/♀) Effects at the LOAEL: ↓bw, ↓bwg, ↑swelling, ↑sparse hair, ↑red skin discoloration (♂); ↑pale skin discoloration, ↑thin body figures, ↓fc, ↑mortality (♀) No evidence of tumourigenicity No evidence of neurotoxicity
24-month chronic toxicity/oncogenicity (diet) Crl:CD(SD) rats	NOAEL= 40/47 mg/kg bw/day (♂/♀) LOAEL= 123/200 mg/kg bw/day (♂/♀)

PMRA# 3112031 Included FOB assessment	Effects at the LOAEL: ↓fc, ↓fe (at 52 wks) (♂/♀); ↑abs epididymides wt, ↑abs testes wt, ↓ spermatic element, ↑incidences of minimal to mild (epididymides) and minimal to moderate (testes) periarteritis, ↑ incidence of mild thyroid parafollicular cells hyperplasia (at 52 wks) (♂); ↓bw, ↓bwg, ↑incidence of minimal centrilobular/ midzonal hepatocyte hypertrophy, ↑incidence of diffuse necrosis, ↑biliary cyst (♀) Toxicokinetics: In blood, in both sexes, XDE-659, X12485649, X12584261 were either not detected or sparsely detected up to the HDT. X12485473 and X12641325 were not detected or sparsely detected at the low dose and were detected the mid- and high-dose levels in ♂. X12485473 and X12641325 were detected at the mid-dose level, but only sparsely detected at the high dose level in ♀. X12485473 was also detected at the low dose level in ♀. The fractions detected accounted for up to 15.7% or 22.6% of the intake daily doses in ♂ and ♀, respectively. In urine, XDE-659 was detected at the mid-dose level and higher in ♂ and at all doses tested in ♀. X12485649 was detected at all doses and time points in both sexes, while X12584261 and X12485473 were either not detected or not reportable in both sexes with the exception of X12485473, which was detected in ♀ at all doses tested at the 1-year time point. X12641325 was detected at three (all doses) and six (low and mid-doses) months in ♂ and at 3 months in ♀ at the low dose level. X12485473 and X12641325 were the prominent metabolites in urine. No evidence of tumourigenicity No evidence of neurotoxicity
Developmental/Reproductive toxicity studies	
Reproductive/developmental toxicity (dietary) – Screening study Crl:CD(SD) rats PMRA# 3219871	Supplemental NOAEL and LOAEL not established F0 Parents ≥80 mg/kg bw/day (♂): ↑ rel liver wt, ↑ incidence of very slight hypertrophy of centrilobular/midzonal hepatocytes, with incidence of very slight cytoplasmic eosinophilia (♂) (non-adverse) 238/222 mg/kg bw/day (♂/♀): ↑ abs liver wt, ↑ incidence of very slight hypertrophy of centrilobular/midzonal hepatocytes with incidence of very slight cytoplasmic eosinophilia (♀) (non-adverse) F1 Pups ≥23 mg/kg bw/day: ↓ bw PND 7 (♂/♀)

	≥75 mg/kg bw/day: ↓ bw PND 4 pre- and post cull (♀) 222 mg/kg bw/day: ↓ bw at PND 4 pre- and post cull (♂) There were no treatment-related effects on post-implantation loss, pup survival, sex ratio or litter size.
2-generation reproductive toxicity (dietary) Wistar Crl:WI(Han) rats PMRA# 3173978	Parental Toxicity NOAEL: 58/73 mg/kg bw/day (♂/♀) LOAEL: 179/297 mg/kg bw/day (♂/♀) Effects at the LOAEL: ↑ incidence of very slight centrilobular/midzonal hepatocyte hypertrophy with ↑cytoplasmic eosinophilia [F0 and F1] (♂/♀); ↓ bw [F0 and F1 final; F0 premating, F0 and F1 mating and post-mating], ↓ bwg [F0 and F1 premating; F0 post-mating] (♂); ↓ bw [F1 at start of pre-mating] (♀) Offspring Toxicity NOAEL: 73 mg/kg bw/day LOAEL: 297 mg/kg bw/day Effects at the LOAEL: ↓ bw [F1 final; F1 PND 14-21; F2 PND 4 and 7], ↓ Hb [F2], Hct [F2], MCV [F2]; delay of vaginal opening [F1] (♀) Reproductive Toxicity NOAEL: 179/297 mg/kg bw/day (♂/♀) LOAEL: not determined (♂/♀) No adverse effects at the HDT Toxicokinetics: rapid absorption, hydrolysis of unchanged XDE-659 to X12485649 and metabolism to X12485473, X12584261, and X12641325. Quantification of XDE-659 was very low when quantifiable and limited to few animals. The quantified metabolites generally showed dose-proportionality with increasing dietary concentration during the pre-mating phase. Post-natal analysis of dam blood and milk (LD4) and pup blood (PND4) indicated some lactational transfer and systemic exposure of pups to X12485473 and X12641325 at 1 to 2 orders of magnitude lower than observed in the dams. Systemic exposure to X12485473, X12584261, and X12641325 appeared to be similar in F1 and F2 pups. No evidence of sensitivity of the young

	Serious effect in the young (delayed puberty) in the presence of parental toxicity
Developmental toxicity probe study (diet) Sprague-Dawley rats PMRA# 3303927	Supplemental No adverse effects observed up to 212 mg/kg bw/day (HDT)
Developmental toxicity (dietary) Sprague-Dawley rats PMRA# 3112034	Maternal Toxicity NOAEL = 271 mg/kg bw/day LOAEL = not determined No adverse effects up to the HDT Developmental Toxicity NOAEL = 271 mg/kg bw/day LOAEL = not determined No adverse effects up to the HDT Toxicokinetics: quantitation of X12485473 and X12641325 in blood confirms these are prominent metabolites in maternal rats and fetuses exposed to XDE-659 followed by X12485649 and X12584261. There was maternal transfer of X12485649, X12485473, X12584261, and X12641325 to the fetus through blood. No evidence of treatment-related malformations No evidence of sensitivity of the young
Developmental toxicity probe study (diet) New Zealand White rabbits PMRA# 3303928	Supplemental ≥ 12 mg/kg bw/day: ↓bwg (GD 7-10 and GD 7-28) ≥ 44 mg/kg bw/day: perineal fecal soiling, soft or ↓feces 44 mg/kg bw/day: watery feces, blood in the cage, vaginal bleeding, one abortion [GD 27] ≥ 49 mg/kg bw/day: ↓fc (from GD 7), all animals were euthanized on GD 10 50 mg/kg bw/day: ↓bw
Developmental toxicity (dietary) New Zealand White rabbits	Maternal Toxicity NOAEL = 9.6 mg/kg bw/day LOAEL = 26 mg/kg bw/day

PMRA# 3112035	Effects at the LOAEL: ↓ bwg [GD 7-10; GD 7-28], ↓ fc [GD 7], two abortions [GD 23 and 28] Developmental Toxicity NOAEL = 9.6 mg/kg bw/day LOAEL = 26 mg/kg bw/day Effects at the LOAEL: two abortions Toxicokinetics: rapid absorption, hydrolysis of unchanged XDE-659 to X12485649 and metabolism to X12485473, X12584261, and X12641325. XDE-659, X12485649, X12584261, and X12530093 were below LOD in the blood samples of the maternal rabbits and fetuses. Quantitation of X12485473 and X12641325 in blood confirmed as prominent metabolites in rabbits exposed to XDE-659. These metabolites generally showed dose-proportionality with increasing dietary concentration. The mean blood concentrations of X12485473 and X12641325 in maternal rabbits were 2–6 fold higher than the corresponding mean blood concentrations in the fetuses. No evidence of treatment-related malformations No evidence of sensitivity of the young
Genotoxicity studies	
Bacterial reverse mutation S. typhimurium TA 1535, TA 1537, TA 98, TA 100, TA 102 PMRA# 3112036	Negative ± metabolic activation Tested up to limit concentration
In vitro forward mutation assay in mammalian cells CHO cells PMRA# 3112037	Negative ± metabolic activation Tested up to limit concentration
In vivo micronucleus assay (as part of a standard dietary 90-day toxicity study) F344 rats PMRA# 3112029	Negative For clinical signs, see 90-day toxicity dietary study PMRA# 3112029 Tested up to 177/185 mg/kg bw/day (♂/♀)

Special studies	
Immunotoxicity assessment (as part of a standard dietary 90-day toxicity study) F344 rats PMRA# 3112029	Non-guideline For clinical signs, see 90-day toxicity dietary study PMRA# 3112029 No treatment-related effects on the primary immune response to SRBCs in male and female rats Positive control CP produced a greater than 99% reduction in the anti-SRBC IgM response.
Metabolite Studies	
Acute inhalation toxicity (nose-only) with metabolite X12485647 Wistar rats PMRA# 3329752	LC_{50} > 0.05 to 0.5 mg/L (♂/♀) 0.52 mg/L: death (6/6) by day 1 post-exposure, abdominal breathing during exposure and lethargy post-exposure, reddish discolouration of the lungs at necropsy 0.051 mg/L: ↓bw [day 1 or days 1 and 3] with recovery by day 3 or 7 MMAD: 2.74 and 2.95 µm; GSD: 1.78 and 1.68 Moderate Toxicity

Table 5 Toxicity profile of GF-3840 containing 10.1% florylpicoxamid

Effects are known or assumed to occur in both sexes unless otherwise noted; in such cases, effects observed in both sexes are presented first followed by sex-specific effects in males, then females, each separated by semi-colons.

Study type/Animal/PMRA#	Study results
Acute oral toxicity (acute toxic class) Wistar rats PMRA# 3113568	LD_{50} > 2000 mg/kg bw (♀) No clinical signs of toxicity Low Toxicity
Acute dermal toxicity Wistar rats PMRA# 3113569	LD_{50} > 2000 mg/kg bw (♀) No clinical signs of toxicity Low Toxicity

Study type/Animal/PMRA#	Study results
Acute inhalation toxicity (nose-only) Wistar rats PMRA# 3113570	LC_{50} > 5.8 mg/L (♂/♀) One male and one female died on test day 3 and 2, respectively. Clinical signs included lung noise, rapid breathing, gasping, lethargy and/or red nasal discharge. Low Toxicity
Eye irritation New Zealand White rabbits PMRA# 3113572	MAS= 6.2/110 MIS= 9.0/110 (at 14 days) Mild eye irritant
Skin irritation New Zealand White rabbits PMRA# 3113573	MAS= 0.33/8 MIS= 2/8 (at 1 hour) Minimally irritant
Dermal sensitization Local lymph node assay (LLNA) CBA/J mice PMRA# 3113574	Negative

Table 6 Toxicity profile of the GF-4017 containing 4.9% florylpicoxamid and 9.8% pyraclostrobin

Effects are known or assumed to occur in both sexes unless otherwise noted; in such cases, effects observed in both sexes are presented first followed by sex-specific effects in males, then females, each separated by semi-colons.

Study type/Animal/PMRA#	Study results
Acute oral toxicity (acute toxic class) Wistar rats PMRA# 3112176	500 mg/kg bw < LD_{50} < 2000 mg/kg bw (♀) Moderate oral acute toxicity
Acute dermal toxicity Wistar rats	LD_{50} > 2000 mg/kg bw (♀) No clinical signs of toxicity

Study type/Animal/PMRA#	Study results
PMRA# 3112177	Low Toxicity
Acute inhalation toxicity (nose-only) Wistar rats PMRA# 3112178	LC_{50} > 2.4 mg/L (♂/♀) Clinical signs of toxicity included lung noise and slow and labored breathing in one rat Low Toxicity
Eye irritation New Zealand White rabbits PMRA# 3112179	MAS= 8.0/110 MIS= 8.0/110 (at 24 hours) Mild eye irritant
Skin irritation New Zealand White rabbits PMRA# 3112180	MAS= 2.7/8 MIS= 3/8 (at 1 hour) Mild irritant
Dermal sensitization Local lymph node assay (LLNA) CBA/J mice PMRA# 3112181	Negative

Table 7 Toxicology reference values for use in health risk assessment for florylpicoxamid

Exposure scenario	Study	Point of departure and endpoint	CAF[1] or Target MOE
Acute dietary general population	An acute reference dose was not established as an endpoint of concern attributable to a single exposure was not identified in the oral toxicity studies.		
Repeated (chronic) dietary	Dietary developmental toxicity study in rabbits	NOAEL = 9.6 mg/kg bw/day Increased incidence of abortions	300
ADI = 0.03 mg/kg bw/day			
Short and intermediate-term dermal (adult, excluding children)[2]	Dietary developmental toxicity study in rabbits	NOAEL = 9.6 mg/kg bw/day Increased incidence of abortions	300

Exposure scenario	Study	Point of departure and endpoint	CAF[1] or Target MOE
Short and intermediate-term dermal (children)[2]	Dietary reproductive toxicity study in rats	Offspring NOAEL = 73 mg/kg bw/day Delayed vaginal opening	300
Short- and intermediate-term inhalation (adult)[3]	Dietary developmental toxicity study in rabbits	NOAEL = 9.6 mg/kg bw/day Increased incidence of abortions	1000
Non-dietary oral ingestion (short- and intermediate term) (toddlers)	Dietary reproductive toxicity study in rats	Offspring NOAEL = 73 mg/kg bw/day Decreased body weight	100
Short- and intermediate term aggregate (adults and youth) Oral and dermal	Oral and dermal: Dietary developmental toxicity study in rabbits	Common endpoint: abortions Oral and dermal: NOAEL = 9.6 mg/kg bw/day	300
Short- and intermediate term aggregate (children) Oral and dermal	Oral and dermal: dietary reproductive toxicity study in rats	Common endpoint: delayed vaginal opening Oral and dermal: Offspring NOAEL = 73 mg/kg bw/day	300
Cancer	No evidence of tumourigenicity; therefore, a cancer risk assessment is not required.		

[1] CAF (composite assessment factor) refers to a total of uncertainty and PCPA factors for dietary assessments; MOE (margin of exposure) refers to a target MOE for residential and occupational assessments.
[2] Since an oral NOAEL was selected, a dermal absorption factor (9%) was used in a route-to-route extrapolation.
[3] Since an oral NOAEL was selected in absence of an appropriate inhalation study, an uncertainty factor of threefold was used in route-to-route extrapolation to account for low oral absorption (approximately 25% after a single low dose).

Table 8 Percent recovery of applied florylpicoxamid in human skin matrices in vitro (8 hours exposure).

	Undiluted concentrate (100 g XDE-659/L)		Aqueous spray dilution I (2.50 g XDE-659/L)		Aqueous spray dilution II (0.333 g XDE-659/L)		Aqueous spray dilution III (0.167 g XDE-659/L)	
	Mean*	**SD**	**Mean***	**SD**	**Mean***	**SD**	**Mean***	**SD**
Receptor fluid	0.013	0.005	0.22	0.12	0.49	0.15	0.54	0.17
Receptor chamber wash	0.018	0.046	0.026	0.016	0.057	0.022	0.045	0.021
Donor chamber wash	0.29	0.77	0.15	0.04	0.28	0.07	0.27	0.1
Tape strip total	0.19	0.09	5.83	2.99	7.38	1.08	6.89	3.78
Tape strips 1 and 2	0.1	0.04	3.06	1.79	3.31	0.68	3.95	2.4
Tape strips 3–15	0.094	0.057	2.77	1.4	4.08	0.88	2.94	1.51
Skin wash (8 h)	99.02	2.98	87.21	5.17	78.72	9.02	82.15	6.53
Skin wash (24 h)	0.3	0.03	5.72	2.7	8.02	1.27	7.25	2.76
Epidermis	0.032	0.023	0.76	0.63	0.72	0.73	0.79	0.63
Dermis	0.014	0.013	0.11	0.08	0.41	0.24	0.26	0.1
Total recovery	99.88	2.76	100.03	0.62	96.09	8.13	98.19	2.91
Absorbed dose (including all tape strips)	**0.27**	0.08	**6.95**	2.5	**9.06**	3.12	**8.53**	2.91

*Mean of 8 cells

Table 9 AHETF, ORETF and PHED unit exposure estimates for mixers, loaders and applicators handling GF-3840 and GF-1407 fungicides (µg/kg a.i. handled)

Exposure scenario and PPE		Dermal	Dermal absorbed*	Inhalation[1]
Mixer/loader AHETF estimates				
A	Open mix/Load liquids (Single layer and CR gloves)	58.5	5.265	0.63
Applicator AHETF estimates				
B	Aerial application – (Single layer)	2.67	0.2403	0.01
C	Open cab groundboom application - (Single layer and CR gloves)	25.40	2.286	1.68
Mixer/loader + applicator AHETF estimates				
A+C	Open mix/Load liquids (Single layer and CR gloves) and open cab groundboom application (Single layer)	83.9	7.551	2.31
PHED Mixer/loader/applicator				
E	Liquid/Open pour/Backpack (M/L/A) (Single layer and CR gloves)	5445.85	490.13	62.10
ORETF Estimates for Turf				
F	Liquid/Open pour/Turf gun (Single layer and CR gloves)	785	70.65	4.00

[1] Light inhalation rate (moderate for backpack)
* Based on 9% dermal absorption from human skin in vitro study.

Table 10 Mixer/loader/applicator risk assessment for florylpicoxamid

Exposure scenario	Dermal unit exposure (µg/kg a.i. handled)[1]	Inhalation Unit Exposure (µg/kg a.i. handled)[1]	ATPD (ha/day)[2]	Rate (kg a.i./ha)	Dermal daily exposure (mg/kg bw/day)[3]	Inhalation daily exposure (mg/kg bw/day)[4]	Dermal MOE[5]	Inhalation MOE[6]	Aggregate risk index (≥ 1 acceptable)[7]
PPE: Single layer and chemical-resistant gloves									
Open mix/Load liquids and open cab groundboom liquid application (Farmer)	7.551	2.31	107 (wheat, canola and lentils)	0.05	5.05E-04	1.50E-04	19011	62143	31
Open mix/Load liquids and open cab groundboom liquid application (Custom applicator)	7.551	2.31	360 (wheat, canola and lentils)	0.05	1.70E-03	5.20E-04	5650	18470	9
Open mix/Load liquids and open cab groundboom liquid application (Farmer)	7.551	2.31	107 (canola, sugar beet)	0.150	1.52E-03	4.60E-04	6337	20714	10
Open mix/Load liquids and open cab groundboom liquid application (Custom Applicator)	7.551	2.31	360 (canola, sugar beet)	0.150	5.10E-03	1.56E-03	1883	6157	3
Open mix/Load liquids	5.265	0.63	400 (wheat aerial)	0.050	1.32E-03	1.60E-04	7293	60952	17
Aerial applicator	0.2403	0.01	400 (wheat aerial)	0.050	6.70E-04	2.40E-06	159800	3962848	470
Liquid/Open pour/Backpack (M/L/A)	490.13	62.10	0.4 (150L (turf))	0.150	3.45E-04	4.28E-05	27857	219860	65
Open mix/Load liquids and open cab groundboom liquid application	7.551	2.31	16 (golf course)	0.150	2.27E-04	7.00E-05	42378	138528	70

Exposure scenario	Dermal unit exposure (µg/kg a.i. handled)[1]	Inhalation Unit Exposure (µg/kg a.i. handled)[1]	ATPD (ha/day)[2]	Rate (kg a.i./ha)	Dermal daily exposure (mg/kg bw/day)[3]	Inhalation daily exposure (mg/kg bw/day)[4]	Dermal MOE[5]	Inhalation MOE[6]	Aggregate risk index (≥ 1 acceptable)[7]
Open mix/Load liquids and open cab groundboom liquid application	7.551	2.31	30 (sod farm)	0.150	4.25E-04	1.30E-04	22602	73882	37
Open mix/Load liquids and turf gun application	70.65	4.0	2	0.150	2.65E-04	2.00E-05	36235	640000	102

[1] Unit exposure based on AHETF, ORETF or PHED from Table E.1
[2] Default Area Treated per Day table (updated on 2017-09-20) or lowest dilution (400 L/ha); ha = L/day/dilution.
[3] Daily exposure = (Dermal unit exposure × ATPD × Rate) / (80 kg bw × 1000 µg/mg)
[4] Daily exposure = (Inhalation unit exposure × ATPD × Rate) / (80 kg bw × 1000 µg/mg)
[5] Based on NOAEL = 9.6 mg/kg bw/day; Target MOE = 300 (see Section 3.2.2 of this document)
[6] Based on NOAEL = 9.6 mg/kg bw/day; Target MOE = 1000 (see Section 3.2.2 of this document)
[7] Aggregate Risk Index is = $1/((\text{Target MOE}_{dermal}/\text{MOE}_{dermal}) + (\text{Target MOE}_{inhalation}/\text{MOE}_{inhalation}))$

Table 11 Dislodgeable foliar residue regression analysis from dry beans treated with GF-3840 at a rate of 150 g a.i./ha (2 applications 14 days apart)

Site	Florylpicoxamid DFR analysis			
	Trend	R^2	Peak DFR (% of application rate after last application)	Predicted dissipation per day
Iowa	y = -0.4341x + 3.3531	$R^2 = 0.75$	20% (0.302 µg/cm^2)	37.5%
North Dakota	y = -0.5624x + 6.0581	$R^2 = 0.96$	19.2% (0.294 µg/cm^2)	32.5%
California	y = -0.2602x + 6.1135	$R^2 = 0.96$	29% (0.436 µg/cm^2)	16.7%

Table 12 Postapplication exposure and risk estimates to workers for florylpicoxamid on day 0 after the last application for cereals, legumes and sugar beets

Postapplication activity	Peak DFR (µg/cm²)[1]	TC (cm²/hr)[2]	Dermal exposure (mg/kg bw/day)[3]	MOE[4]	REI[5]
Cereals, lentils, sugar beets					
Hand set irrigation	0.3064	1750	0.0048	1989	12 hours
Scouting, harvesting by hand		1100	0.0030	3165	
Scouting (sugar beets)		210	0.0006	16 578	
Hand weeding, thinning		70	0.0002	49 735	

DFR = Dislodgeable foliar residue; TC = Transfer Coefficient; MOE = Margin of Exposure; REI = Restricted-Entry Interval
[1] Calculated using the highest peak DFR value for North Dakota site (19.2%) from the submitted DFR study on dry beans PMRA# 3113578 (calculation PMRA# 3299564) and the VRD supported rates. Dissipation is calculated from North Dakota regression equation (32.5% per day).
[2] Transfer coefficients obtained from PMRA Agricultural TCs Table
[3] Exposure = (Peak DFR [µg/cm²] × TC [cm²/hr] × 8 hours/day × DA 9%) / (80 kg bw × 1000 µg/mg)
[4] Based on a NOAEL of 9.6 mg/kg bw/day; Target MOE = 300 (see Section 3.2.2 of this document).
[5] Minimum REI is 12 hours to allow residues to dry, suspended particles to settle and vapours to dissipate.

Table 13 Transferable turf residue regression analysis from turf grass treated with GF-3840 at a rate of 50 g a.i./ha (5 applications 14 days apart)

Site	Florylpicoxamid TTR analysis		
	Trend	R^2	Peak TTR (% of application rate after last application)
Florida	N/A		0.79% (0.00398 µg/cm²)
California			0.96% (0.0048 µg/cm²)
Pennsylvania			0.38% (0.00199 µg/cm²)

Table 14 Postapplication exposure and risk estimates to workers for florylpicoxamid on day 0 after the last application on golf courses and turf farms

Postapplication activity	Peak TTR (µg/cm²)[1]	TC (cm²/hr)[2]	Dermal exposure (mg/kg bw/day)[3]	MOE[4]	REI[5]
Turf (sod farms and golf courses)					
Harvesting, Slab transplanting/Planting	0.0194	6700	0.0012	8191	12 hours for sod farms Until sprays have dried for golf courses
Transplanting/Planting, mowing, watering, cup changing, irrigation, repair, miscellaneous grooming		3500	0.0006	15,679	
Aerating, fertilizing, hand pruning, mechanical weeding, scouting, seeding		1000	0.0002	54,878	

TTR = Transferable Turf residue; TC = Transfer Coefficient; MOE = Margin of Exposure; REI = Restricted-Entry Interval

[1] Calculated using default transferable turf residue values (1% of the application rate being available for dislodging and 10% dissipation per day) and supported from the submitted TTR study (PMRA# 3113577)

[2] Transfer coefficients obtained from PMRA Agricultural TCs Table

[3] Exposure = (Peak TTR [µg/cm²] × TC [cm²/hr] × 8 hours/day × DA 9%) / (80 kg bw × 1000 µg/mg)

[4] Based on a NOAEL of 9.6 mg/kg bw/day; Target MOE = 300 see Section 3.2.2 of this document.

[5] Minimum REI is 12 hours or until sprays have dried to allow residues to dry, suspended particles to settle and vapours to dissipate.

Table 15 Postapplication Dermal Exposure and Risk Estimates to Golfers on Day 0 from Golf Courses Treated Commercially with Florylpicoxamid

Crop (Max Rate; # App; RTI)	Life Stage	Peak TTR (µg/cm²)[1]	TC (cm²/hr)[2]	Exposure Duration (hr/day)	Dermal Exposure (mg/kg bw/day)[3]	MOE[4, 5]	REI
Golf course (150 g a.i./ha; 5/season; 14-day RTI)	Adults (16+ yrs)	0.02	5300	4	3.58E-4	26 834[4]	Until sprays have dried
	Youth (11 to 16)		4400	4	4.17E-4	23 030[4]	Until sprays have dried

Crop (Max Rate; # App; RTI)	Life Stage	Peak TTR (µg/cm^2)[1]	TC (cm^2/hr)[2]	Exposure Duration (hr/day)	Dermal Exposure (mg/kg bw/day)[3]	MOE[4, 5]	REI
	Children (6 < 11 yrs)		2900	4	4.89E-4	149 170[5]	Until sprays have dried

TTR = transferable turf residue; TC = Transfer Coefficient; MOE = Margin of Exposure
[1] Calculated using default transferable turf residue values (1% of the application rate being available for dislodging and 10% dissipation per day).
[2] A single TC is representative of all activities in golf course. TCs were obtained from the PMRA memo entitled "Review of USEPA Residential SOPs (2012) Section 4: Golf and Lawn" (Sept. 6, 2019).
[3] Dermal Exposure = (Peak TTR [µg/cm^2] × TC [cm^2/hr] × Exposure duration [hours/day] × 9% DA) / (Body weight [80 kg for adults; 57 for youth 11 to 16; 32 kg for children 6<11 kg] × 1000 µg/mg).
[4] Based on a dermal NOAEL of 9.6 mg/kg bw/day; Target MOE of 300 (see Section 3.2.2 of this document).
[5] Based on a dermal NOAEL of 73 mg/kg bw/day; Target MOE of 300 (see Section 3.2.2 of this document).

Table 16 Major fate inputs for the modelling

Fate parameter	Drinking water(1)
K_{oc}	282 L/kg, value for X12485631 estimated with EPISuite
Water half-life(2)	Stable
Sediment half-life (3)	1300 days, 80th%ile of 4 values from flooded soil
Photolysis half-life	Stable
Hydrolysis	Stable
Soil half-life	1190 days, 90% upper confidence bound on the mean of 4 soils

(1) Drinking water parameters were calculated for the combined residue (florylpicoxamid, X12485649 and X12485631), unless otherwise indicated.
(2) Aquatic whole system (aerobic)
(3) Anaerobic soil

Table 17 EECs (in µg a.i./L) for the drinking water risk assessment of florylpicoxamid and relevant transformation products (X12485649 and X12485631)

Use pattern	Groundwater (µg a.i./L)		Surface water (µg a.i./L)		
	Peak(1)	Average(2)	Daily(3)	Yearly(4)	Overall(5)
5 applications of 150 g a.i./ha with a 7-day interval	360	290	36	9.1	6.9

(1) 90th percentile of daily concentrations
(2) 90th percentile of 365-day moving average concentrations
(3) 90th percentile of the highest 1-day average concentration from each year
(4) 90th percentile of yearly average concentrations
(5) Average of all yearly average concentrations

Table 18 Postapplication residential dermal and dietary aggregate exposure on day 0 from golf courses treated commercially with florylpicoxamid

Crop (Max rate; # App; RTI)	Life stage	Dermal exposure (mg/kg bw/day)[1]	Dietary exposure (mg/kg bw/day)	Combined exposure (mg/kg bw/day)	Aggregate MOE[3]
Golf course (150 g a.i./ha; 5/season; 14-day RTI)	Adults (16+ yrs)	3.58E-04	5.43E-03	5.79E-03	1659
	Youth (11 to 16)	4.17E-04	4.34E-03	4.75E-03	2020
	Children (6 < 11 yrs)	4.89E-04	5.80E-03	6.29E-03	11,607

[1] From Table 8 Postapplication dermal exposure and risk estimates to golfers on day 0 from golf courses treated commercially with florylpicoxamid.
[2] The dietary exposure values [basic food plus Level 1 drinking water chronic exposure for specific subpopulations] were aggregated with the recreational dermal exposure from golf turf.
[3] Short- and intermediate-term aggregate (adults and youth) NOAEL = 9.6 mg/kg bw/day from the developmental toxicity study in rabbits with a target MOE of 1000. For short- and intermediate-term aggregate (children 6–11 years of age) NOAEL = 73 mg/kg bw/day from the reproductive toxicity study in rats with a target MOE of 300 (see Section 3.2.2 of this document).

Table 19 Integrated food residue chemistry summary

Nature of the residue in laying hen	PMRA# 3112041
Species and numbers	20 laying hens (Hy-Line Browns)
Radiolabel position	[bis-phenyl-U-^{14}C]florylpicoxamid (PH label) (specific activity: 24.2 mCi/mmol) and [pyridinyl-2-^{14}C]florylpicoxamid (PY label) (specific activity: 28.2 mCi/mmol)
Average dose	[PH-^{14}C]florylpicoxamid: 13.2 mg/kg feed (corresponding to 0.658 mg/kg bw/day)

	[PY-^{14}C]florylpicoxamid: 12.7 mg/kg feed (corresponding to 0.587 mg/kg bw/day)
Treatment regimen	Once daily, via capsule.
Study period	10 consecutive days.
Collection time	Eggs and excreta: 2/day (morning and evening); Excreta: 1/day
Tissues collected	Breast and leg muscle, abdominal fat, skin with fat, liver, GI tract with contents, and eggs. Samples of eggs from am and pm sampling were composited on each day. Cages were rinsed with water:methanol (80:20, v/v) following collection of excreta before dosing commenced on Days 1 and on 10 after final dose.
Interval from last dose to sacrifice	6–8 hours
Plateau of residues in eggs	At 7 days in whole eggs. TRRs at 7 days were 0.048 and 0.040 ppm for PH- and PY-labels, respectively.
Extraction solvents	Acidified ACN:0.25 % phosphoric acid (80:20, v/v) × 3

Matrices	**[PH-^{14}C]florylpicoxamid)**		**[PY-^{14}C]florylpicoxamid**	
	TRRs (ppm)	**% of Administered dose**	**TRRs (ppm)**	**% of Administered Dose**
Pooled excreta (Day 1–10)	NA	92.44	NA	90.35
Cage wash (Day 10)	10.17	0.60	0.410	0.72
GI tract and contents	NR	NR	NR	NR
Pooled whole yolk (Day 1-10)	NA	0.11	NA	0.09
Partly formed eggs	NR	NR	NR	NA
Liver	0.383	0.12	0.315	0.10
Muscle, breast	0.043	0.05	0.036 (0.037)	0.06
Muscle, leg	0.067 (0.068)	0.09	0.057 (0.043)	0.09
Fat, abdominal	0.062	0.02	0.028	0.01
Skin with fat	0.153	0.13	0.106	0.10
Reported TRR values were the same for the samples utilized for extraction and analysis, unless indicated by a separate value listed in parentheses.				

Summary of major identified metabolites in hen matrices	
Radiolabel position	[PH-^{14}C]florylpicoxamid, [PY-^{14}C]florylpicoxamid
Metabolites identified	Major Metabolites
Eggs	X12485649 X12485631 X12563767
Liver	None
Fat	X12485649 X12485631

	X12493055 X12516991
Skin with fat	X12485649 X12629973
Muscle	X12485649 X12629973 X12563767

Nature of the residue in lactating goat	**PMRA# 3112040**
Species and numbers	2 milking goats (Nubian)
Radiolabel position	[bis-phenyl-U-^{14}C]florylpicoxamid (PH label) (specific activity: 4.700 mCi/mmol) and [pyridinyl-2-^{14}C]florylpicoxamid (PY label) (specific activity: 5.179 mCi/mmol)
Average dose	[PH-^{14}C]florylpicoxamid: 13.1 mg/kg feed (corresponding to 0.445 mg/kg bw/day) [PY-^{14}C]florylpicoxamid: 12.8 mg/kg feed (corresponding to 0.363 mg/kg bw/day)
Treatment regimen	Once daily, via capsule
Study period	7 consecutive days
Collection time	Milk: 2/day (morning and evening); Urine and feces 1/day at dosing
Tissues collected	Blood, liver, muscle (flank and loin, separately), fat (subcutaneous, omental, renal), kidney, and GI tract. Cages were rinsed with water:methanol (80:20, v/v) prior to dosing (day -1) and after collection of excreta on Day 7.
Interval from last dose to sacrifice	Within 7.5 hours
Plateau of residues in milk	TRRs at 4 days peaked at 0.009 ppm for PH-label, and at 5 days peaked at 0.019 ppm for the PY-label. Milk was fractionated into cream, skim milk and milk solids (protein) in order to characterize the TRRs.
Extraction solvents	Acidified ACN:0.25 % phosphoric acid (80:20, v/v) × 3 The above extraction was repeated a second time for liver (PY- and PH-labels) and kidney (PY-label only) with the following: Acidified ACN:0.25 % phosphoric acid (20:80, v/v) × 3

Matrices	**[PH-^{14}C]florylpicoxamid**		**[PY-^{14}C]florylpicoxamid**	
	TRRs (ppm)	**% of Administered dose**	**TRRs (ppm)**	**% of Administered dose**
Pooled feces (Day 1–7)	NA	72.74	NA	78.38
Cage wash (sacrifice, Day 7)	0.074	0.05	0.036	0.04
GI tract and contents	3.478	16.15	3.340	16.92
Blood (sacrifice, Day 7)	0.012	0.02	0.010	0.02
Urine (pooled, Day 1–7)	NA	4.39	NA	3.06
Milk (Day 1–7)	NA	0.06	NA	0.06
Liver	0.179	0.13	0.153	0.10
Kidney	0.030	<0.01	0.020	<0.01

Fat, omental	0.051	0.02	0.054	0.04
Fat, subcutaneous	0.036	0.01	0.055	0.03
Fat, renal	0.044	<0.01	0.050	0.03
Muscle, loin	0.006	<0.01	0.007	<0.01
Muscle, flank	0.009	0.01	0.016	0.02

Summary of major identified metabolites in goat matrices	
Radiolabel position	[PH-^{14}C]florylpicoxamid, [PY-^{14}C]florylpicoxamid
Metabolites identified	Major metabolites
Milk	X12485649
Liver	X12485649
Kidney	X12485649 X12641325 X12714411
Fat	X12485649 X12584261
Muscle	X12485649

Nature of the residue in lactating goat	**PMRA# 3112042**
Species and numbers	1 milking goat (Saanen × Toggenburg)
Radiolabel position	[bis-phenyl-U-^{14}C]X12563767 (PH label) (specific activity: 29.7 mCi/mmol)
Average dose	[PH-^{14}C]X12563767: 16.0 mg/kg feed (corresponding to 0.31 mg/kg bw/day)
Treatment regimen	Once daily, via capsule
Study period	7 consecutive days
Collection time	Milk: 2/day (morning and evening); Urine and feces 1/day
Tissues collected	Blood, bile, liver, muscle (flank, and loin, separately), fat (subcutaneous, omental, renal), kidney, and GI tract. Day 5 (composite PM with next AM sample) whole milk sample was separated into skim milk and cream fractions. Cage was washed with water containing 1 % detergent daily and rinsed with ACN following the final cage wash.
Interval from last dose to sacrifice	Within 6 hours of final dose
Plateau of residues in milk	TRR at peaked at 3 days at 0.047 ppm.
Extraction solvents	Acidified ACN:0.25% phosphoric acid (80:20, v/v) × 2 For fat only, a third extraction was conducted using ACN: 0.25% phosphoric acid (80:20, v/v).

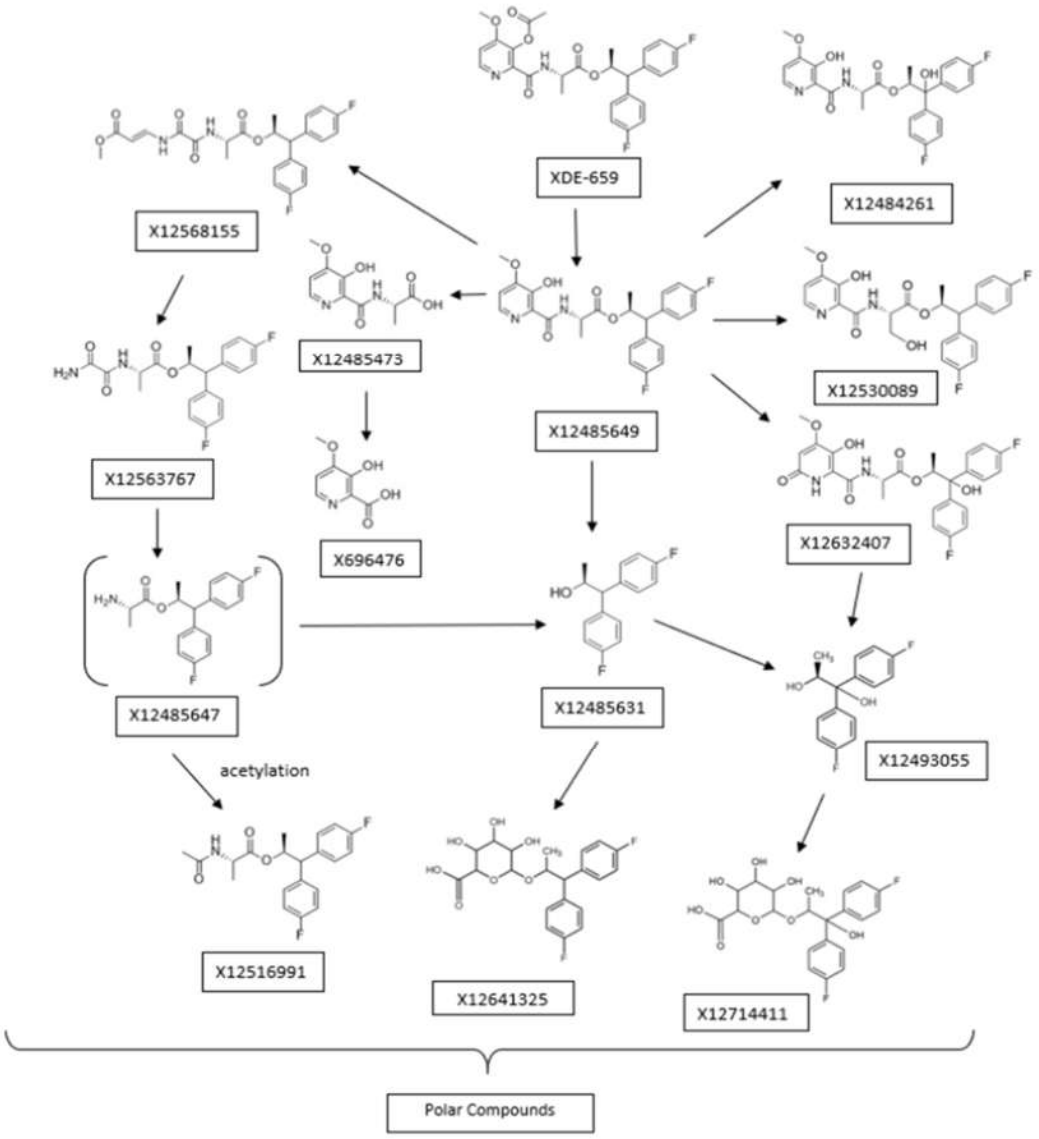
Matrices	**[PH-^{14}C]florylpicoxamid**	
	TRRs (ppm)	**% of Administered Dose**
Pooled feces (Day 1–7)	NA	35.8
Cage wash (Day 1–7)	NA	1.2
Cage rinse	NA	0.1
GI tract contents	1.672	8.0
Blood (sacrifice, Day 7)	0.053	<0.1

Urine (pooled, Day 1–7)	NA	39.4
Milk (Day 1–7)	NA	0.1
Pooled milk (Day 3 pm to Day 6 pm)	0.035	NA
Composited milk (Day 5, am and pm)	0.026	NA
Skim milk (Day 5, am and pm)	0.021	NA
Cream (Day 5, am and pm)	0.123	NA
Liver	0.454	0.3
Kidney	0.489	0.1
Fat, omental	0.081	<0.1
Fat, subcutaneous	0.078	<0.1
Fat, renal	0.073	<0.1
Muscle, loin	0.029	<0.1
Muscle, flank	0.058	<0.1

Summary of major identified metabolites in goat matrices	
Radiolabel position	[PH-^{14}C]florylpicoxamid
Metabolites identified	Major metabolites
Milk	**X12563767**[1] X12493055 X12562911 Sulfate conjugate X12485631
Liver	**X12563767** X12641325 X12493055 X12562911
Kidney	X12641325 X12562911
Fat	**X12563767** X12493055 X12485631
Muscle	**X12563767** X12493055 X12485631

[1] **X12563767** is bolded in order to indicate that it was the test substance in the feed.

Proposed metabolic scheme in livestock



Freezer storage stability in animal matrices

Freezer storage stability data were not required as the samples in the feeding study were analyzed within 30 days of sampling.

Livestock feeding – Dairy cattle	**PMRA# 3113601**

Lactating dairy cows were administered florylpicoxamid at dose levels of 3.2 ppm, 6.2 ppm, 19.0 ppm, and 63.7 ppm in the feed for 29 consecutive days. The dose levels represent 6.4×, 12.4×, 38×, and 127×, respectively, the estimated more balanced diet (MBD) to beef cattle and 1.9×, 3.6×, 11.0×, and 36.8×, respectively, for dairy cattle. Animals were sacrificed approximately 6–24 hours after the last dose. A depuration study was conducted using the 62.4 ppm feeding level and selected animals were sacrificed at 33, 37, 44, and 51 days after the last dose. Residues of the depuration study indicate that residues of florylpicoxamid and metabolite X12485649 were <LOQ in all samples analyzed.

Commodity/Collection day	Actual feeding level (ppm)	Highest residues[1] (ppm)	Mean residues[1] (ppm)
Whole milk/4–28	3	<0.02	<0.02
	6	<0.02	<0.02
	19	<0.02	<0.02
	64	<0.02	<0.02
Skim milk/21 and 28	3	<0.02	<0.02
	6	<0.02	<0.02
	19	<0.02	<0.02
	64	<0.02	<0.02
Cream/21 and 28	3	<0.02	<0.02
	6	<0.02	<0.02
	19	<0.02	<0.02
	64	0.052	0.038
Fat (mesenteric)/29	3	0.022	0.021
	6	0.037	0.034
	19	0.108	0.087
	64	0.241	0.189
Fat (perirenal)/29	3	0.023	0.022
	6	0.039	0.034
	19	0.113	0.094
	64	0.270	0.211
Fat (subcutaneous)/29	3	<0.02	<0.02
	6	0.032	0.027
	19	0.083	0.064
	64	0.189	0.143
Liver	3	<0.02	<0.02
	6	<0.02	<0.02
	19	<0.02	<0.02
	64	0.202	0.157
Kidney	3	<0.02	<0.02
	6	<0.02	<0.02
	19	<0.02	<0.02
	64	0.063	0.059
Muscle (composite)/29	3	<0.02	<0.02
	6	<0.02	<0.02
	19	<0.02	<0.02
	64	0.033	0.030

[1] Combined residues of florylpicoxamid and metabolite X12485649 (expressed as parent equivalents).

Anticipated residues in animal matrices

Matrices	Residue definition	Dietary burden (ppm)	Anticipated combined residues of florylpicoxamid and X12485649 (ppm)
Dairy cattle			
Whole milk	Florylpicoxamid including the metabolite X12485649 (expressed as parent equivalents)	1.73	0.011
Cream			0.007
Fat			0.008
Liver			0.007

Kidney			0.014
Muscle			0.012
Swine			
Fat	Florylpicoxamid including the metabolite X12485649 (expressed as parent equivalents)	0.003	0
Liver			
Kidney			
Muscle			

Livestock feeding – Laying hens	**PMRA# 3113600**
Laying hens were administered florylpicoxamid at dose levels of 0.6 ppm, 1.3 ppm, 6.4 ppm, and 17.4 ppm in the feeds for 29 consecutive days. The dose levels represent 30×, 65×, 320×, and 870×, respectively, the estimated MBD to poultry. Animals were sacrificed approximately 2 hours after the last dose. A depuration study was conducted using the 17.4 ppm feeding level and selected animals were sacrificed at 33, 36, 44, and 51 days after the last dose. Residues of the depuration study indicate that residues of florylpicoxamid and metabolite 12485649 were <LOQ in all samples analyzed.	

Commodity/Collection day	**Actual feeding level (ppm)**	**Highest residues (ppm)**	**Mean residues (ppm)**
Whole Eggs/1–28	0.6	<0.02	<0.02
	1.3	<0.02	<0.02
	6.4	<0.02	<0.02
	17.4	<0.02	<0.02
Fat (abdominal and subcutaneous)/29	0.6	<0.02	<0.02
	1.3	<0.02	<0.02
	6.4	<0.02	<0.02
	17.4	<0.02	<0.02
Liver/29	0.6	<0.02	<0.02
	1.3	<0.02	<0.02
	6.4	<0.02	<0.02
	17.4	<0.02	<0.02
Muscle (thigh and breast)/29	0.6	<0.02	<0.02
	1.3	<0.02	<0.02
	6.4	<0.02	<0.02
	17.4	<0.02	<0.02

Anticipated residues in poultry matrices

Matrices	**Residue definition**	**Dietary burden (ppm)**	**Anticipated combined residues of florylpicoxamid and X12485649 (ppm)**
Eggs	Florylpicoxamid including the metabolite X12485649 (expressed as parent equivalents)	0.02	<0.02
Fat			
Liver			
Muscle			

Nature of the residue in wheat	**PMRA# 3112043**
Radiolabel position	[bis-phenyl-U-^{14}C]florylpicoxamid (PH label) (specific activity: 24.6 mCi/mmol) and [pyridinyl-2-^{14}C]florylpicoxamid (PY label) (specific activity: 28.2 mCi/mmol)
Treatment	
Test site	In individual boxes containing clay loam soil grown outdoors
Treatment	Post-mergence foliar treatment at BBCH 32 and 69
Total rate	[PH-^{14}C]florylpicoxamid: Total rate of 119 g a.i./ha.

	PY-^{14}C]florylpicoxamid: Total rate of 115 g a.i./ha.
Formulation	Emulsifiable concentrate (EC; guarantee: 9.91 %, w/w)
Harvest	Samples of forage (BBCH 47, 14 days after 1st application), hay (BBCH 83, 13 days after 2nd application), and grain and straw (BBCH 89, 48 days after 2nd application) were harvested.
Extraction solvents	Forage, hay, and straw were sequentially extracted with the following: 3 × ACN:water (80:20, v/v) with 0.25% phosphoric acid (Extract A) 3 × ACN:water (20:80, v/v) with 0.25% phosphoric acid (Extract B) Grain was extracted sequentially as follows: 1 × hexane 3 × ACN:water (80:20, v/v) with 0.25% phosphoric acid (Extract A), both labels 2 × ACN:water (20:80, v/v) with 0.25% phosphoric acid (Extract B), PY-label only Hay and grain (PY-label only) were additionally extracted as follows: 2 × ACN:water (50:50, v/v) with 1.0% phosphoric acid (Extract C)

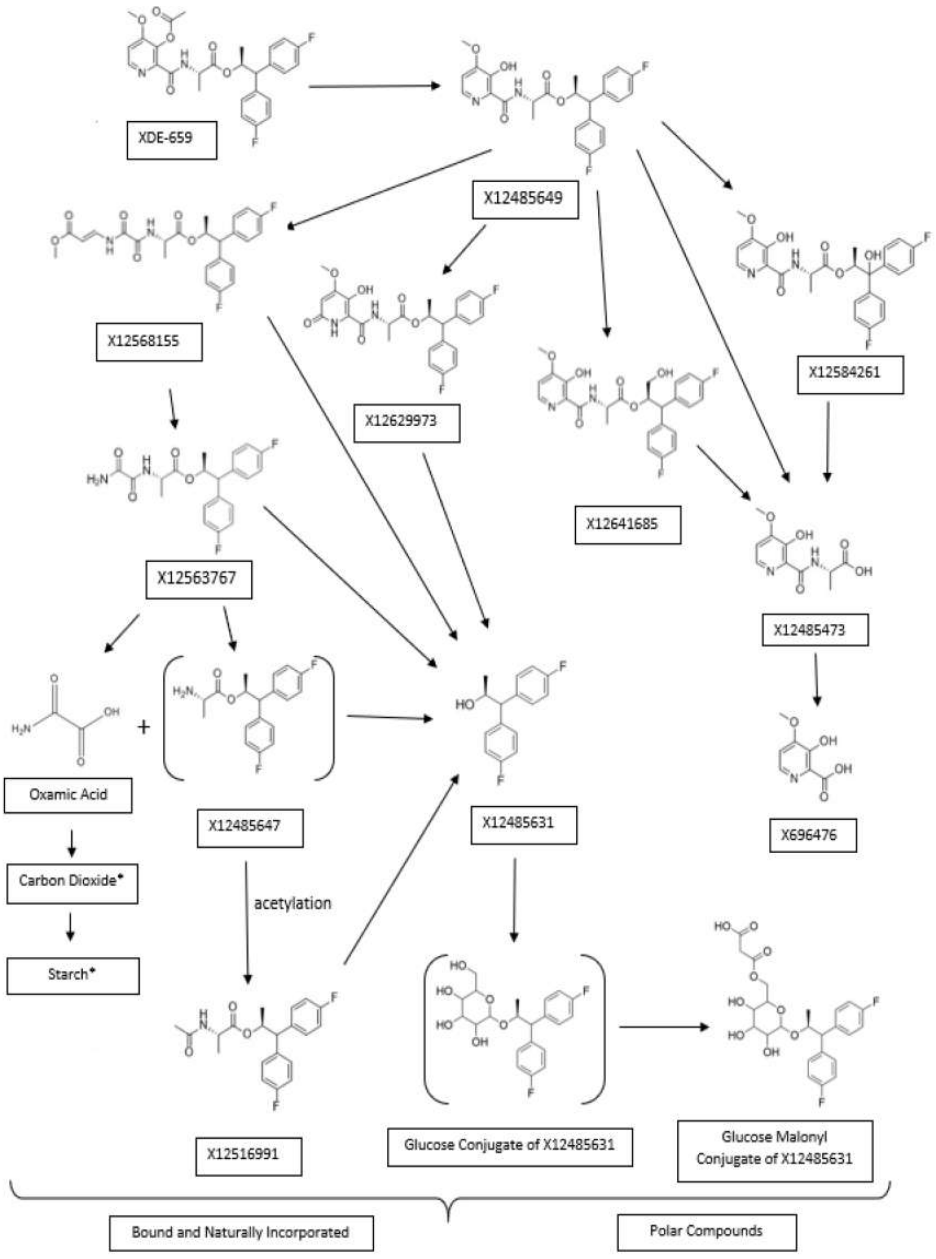
Matrices	**PHI (days)**	**[PH-^{14}C]florylpicoxamid**	**[PY-^{14}C]florylpicoxamid**
		TRR (ppm)	**TRR (ppm)**
Forage	14 DAA1	0.648	0.550
Hay	13 DAA2	2.898	2.633
Straw	48 DAA2	2.229	2.544
Grain		0.001	0.134

Summary of major identified metabolites in plant matrices	
Radiolabel position	[PH-^{14}C]florylpicoxamid, [PY-^{14}C]florylpicoxamid
Metabolites identified	Major Metabolites
Forage	X12485649 X12675171 (glucose-malonyl conjugate of X12485631)
Hay	X12485649
Straw	X12563767
Grain	None

Nature of the residue in tomato	**PMRA# 3112044**
Radiolabel position	[bis-phenyl-U-^{14}C]florylpicoxamid (PH label) (specific activity: 24.6 mCi/mmol) and [pyridinyl-2-^{14}C]florylpicoxamid (PY label) (specific activity: 28.2 mCi/mmol)
Treatment	
Test site	Individual boxes containing sandy clay loam soil were grown outdoors
Treatment	Five postemergent foliar treatments at BBCH 12–13, 29, 62, 76, and 89
Total rate	[PH-^{14}C]florylpicoxamid: Total rate of 817 g a.i./ha. [PY-^{14}C]florylpicoxamid: Total rate of 818 g a.i./ha.
Formulation	Suspension concentrate (SC; guarantee: 9.52 %, w/w)
Harvest	Samples of immature whole plant (7 days after 3rd application), mature fruit (1 day after 5th application; 7 days after 5th application), and mature fruit with vines (14 days after 5th application) were harvested.
Extraction solvents	3 × ACN:water (80:20, v/v) with 0.25% phosphoric acid (both radiolabels)

Matrices	PHI (days)	[PH-^{14}C]florylpicoxamid	[PY-^{14}C]florylpicoxamid
		TRR (ppm)	TRR (ppm)
Immature whole plant	7 DAA3	1.940	2.046
Mature fruit	1 DAA5	0.113	0.195
Mature fruit	7 DAA5	0.039	0.048
Mature fruit	14 DAA5	0.092	0.061
Mature vines		1.553	1.632
Summary of major identified metabolites in plant matrices			
Radiolabel position	[PH-^{14}C]florylpicoxamid, [PY-^{14}C]florylpicoxamid		
Metabolites identified	Major metabolites		
Immature plant Mature fruit (1 DAA5) Mature fruit (7 DAA5) Mature fruit (14 DAA5) Mature vines (14 DAA5)	Florylpicoxamid X12485649		
Nature of the residue in lettuce			**PMRA# 3112045**
Radiolabel position	[bis-phenyl-U-^{14}C]florylpicoxamid (PH label) (specific activity: 24.2 mCi/mmol) and [pyridinyl-2-^{14}C]florylpicoxamid (PY label) (specific activity: 27.6 mCi/mmol)		
Treatment			
Test site	In individual boxes containing sandy loam soil was grown outdoors		
Treatment	Five postemergent foliar treatments at BBCH 14, 22, 36, 46, and 49		
Total rate	[PH-^{14}C]florylpicoxamid: Total rate of 876 g a.i./ha. [PY-^{14}C]florylpicoxamid: Total rate of 790 g a.i./ha.		
Formulation	Suspension concentrate (SC; guarantee: 9.52 %, w/w)		
Harvest	Samples of immature lettuce (7 days after 3rd application) and mature lettuce (1 day after 5th application and 8 days after 5th application) were harvested.		
Extraction solvents	Samples of immature lettuce and mature lettuce (1 DAA5): 3 × ACN:water (80:20, v/v) with 0.25% phosphoric acid (both radiolabels) Samples of mature lettuce (8 DAA5): 3 × ACN:water (80:20, v/v) with 0.25% phosphoric acid (both radiolabels) 3 × ACN:water (20:80, v/v) with 0.25% phosphoric acid (both radiolabels) 3 × ACN:water (50:50, v/v) with 1.0% phosphoric acid (both radiolabels)		
Matrices	**PHI (days)**	**[PH-^{14}C]florylpicoxamid**	**[PY-^{14}C]florylpicoxamid**
		TRR (ppm)	**TRR (ppm)**
Immature lettuce	7 DAA3	2.246	1.648
Mature lettuce	1 DAA5	2.779	3.212
	8 DAA5	1.640	1.971
Summary of major identified metabolites in plant matrices			
Radiolabel position	[PH-^{14}C]florylpicoxamid, [PY-^{14}C]florylpicoxamid		
Metabolites identified	Major metabolites		
Immature lettuce Mature lettuce (1 DAA5) Mature lettuce (8 DAA5)	Florylpicoxamid X12485649		

Proposed metabolic scheme in plants



Freezer storage stability in plant matrices				**PMRA# 3113596**
Tested matrices	**Analyte**	**Tested intervals (months)**	**Temperature (°C)**	**Category**
Spinach	Florylpicoxamid	0–1.0, 1.8–1.9, 5.7–6.2, 8.8–9.0, 12.0–12.2, 18.0–19.1	-18	High-water
Dry navy bean seed				High-protein
Wheat grain and carrot				High-starch
Soybean seed				High-oil
Orange				High-acid

Crop field trials and residue decline on dried shelled pea and beans	PMRA# 3113605, 3113609, 3113611, 3113612

Crop field trials were conducted in 2018–2019 in Canada and the United States. Trials were conducted in North American growing regions 5 (7 trials), 7 (3 trials), 10 (2 trials), and 11 (1 trial) for a total of 13 trials for dried beans and in regions 7 (4 trials), 11 (1 trial), and 14 (4 trials) for a total of 9 trials for dried peas. The number and geographic distribution of trials were generally in accordance with Health Canada's SPN2017-02. GF-3840 EC, containing florylpicoxamid, was applied twice as foliar broadcast sprays at a nominal rate of 150 g a.i./ha/application at growth stages that were around BBCH 69 for a seasonal application rate of 300 g a.i./ha. The applications were made at 14 ± 1 day intervals with the last application occurring approximately 22–56 days before harvest of dry bean seed and straw and dry pea seeds. Dry pea vines and hay were harvested at 7- to 14-day PHIs.

Adjuvants were not used. Independence of trials was assessed. Residue decline could not be assessed as all residues were <LOQ. Adequate storage stability data are available on diverse crop types to support the storage intervals of the crop field trials. Samples were analyzed using a validated analytical method.

Crop	Total application rate (g a.i./ha)	PHI (days)	Analyte	Florylpicoxamid levels (ppm)					
				n	LAFT	HAFT	Median	Mean	SDEV
Dry bean seed	299-310	22-56	Florylpicoxamid	13	<0.010	<0.010	<0.010	<0.010	-
Dry bean straw				13	<0.010	0.15	0.010	0.04	0.05
Dry pea seed	296-312	27-47	Florylpicoxamid	9	<0.010	<0.010	<0.010	<0.010	-
Dry pea vines		7-14		9	0.05	1.1	0.20	0.41	0.41
Dry pea hay				9	0.12	3.2	0.58	1.1	1.1

n = number of independent trials. LAFT = lowest average field trial; HAFT = Highest average field trial; SDEV = standard deviation

Crop field trials and residue decline on rapeseeds (Canola)	PMRA# 3113608, 3113613

Crop field trials were conducted in 2018–2019 in Canada and the United States. Trials were conducted in North American growing regions 5 (3 trials), 7 (2 trials), and 14 (7 trials) for a total of 12 trials for canola. The number and geographic distribution of trials were generally in accordance with Health Canada's SPN2017-02. GF-3840 EC, containing florylpicoxamid, was applied twice as foliar broadcast sprays at a nominal rate of 125 g a.i./ha/application 28 and 21 days before normal commercial harvest for a total seasonal application rate of 250 g a.i./ha. The applications were made at 7-day intervals with the last application occurring approximately 21 ± 2 days before harvest of canola seed and straw.

Adjuvants were not used. Independence of trials was assessed. Residue decline data show that florylpicoxamid residues decrease in canola straw with increasing PHIs, and could not be assessed in canola seed as all residues were <LOQ. Adequate storage stability data are available on diverse crop types to support the storage intervals of the crop field trials. Samples were analyzed using a validated analytical method.

Crop	Total application rate (g a.i./ha)	PHI (days)	Analyte	Florylpicoxamid levels (ppm)					
				n	LAFT	HAFT	Median	Mean	SDEV
Canola seed	244-257	23-23	Florylpicoxamid	12	<0.010	0.011	0.010	0.01	<0.001
Canola straw				12	<0.010	0.61	0.28	0.26	0.19

n = number of independent trials. LAFT = lowest average field trial; HAFT = Highest average field trial; SDEV = standard deviation

Crop field trials and residue decline on sugar beets — **PMRA# 3113614, 3113607**

Crop field trials were conducted in 2018–2019 in Canada and the United States. Trials were conducted in North American growing regions 5 (10 trials), 5B (1 trial), 7 (1 trial), 7A (2 trials), 10 (1 trial), and 11 (3 trials) for a total of 18 trials for sugar beets. The number and geographic distribution of trials were generally in accordance with Health Canada's SPN2017-02. GF-3840 EC, containing florylpicoxamid, was applied twice as foliar broadcast sprays at a nominal rate of 125 g a.i./ha/application 31 and 21 days before normal commercial harvest for a total seasonal application rate of 250 g a.i./ha. The applications were made at 10-day intervals with the last application occurring approximately 20–22 days before harvest of sugar beet roots and tops.

Adjuvants were not used. Independence of trials was assessed. Residue decline data show that florylpicoxamid residues decrease in sugar beet tops with increasing PHIs, but could not be assessed in sugar beet roots as all residues were <LOQ. Adequate storage stability data are available on diverse crop types to support the storage intervals of the crop field trials. Samples were analyzed using a validated analytical method.

Crop	Total application rate (g a.i./ha)	PHI (days)	Analyte	Florylpicoxamid levels (ppm)					
				n	LAFT	HAFT	Median	Mean	SDEV
Sugar beet roots	243–258	20–22	Florylpicoxamid	18	<0.010	<0.010	0.010	0.01	N/A
Sugar beet tops				18	<0.010	0.059	0.012	0.022	0.018

n = number of independent trials. LAFT = lowest average field trial; HAFT = Highest average field trial; SDEV = standard deviation

Crop field trials and residue decline on wheat	**PMRA# 3113604, 3113615**

Crop field trials were conducted in 2018–2019 in Canada and the United States. Trials were conducted in North American growing regions 2 (1 trial), 5 (5 trial), 6 (2 trials), 7 (5 trials), 8 (2 trials), 11 (2 trials), and 14 (5 trials) for a total of 22 trials for spring and winter wheat. The number and geographic distribution of trials were generally in accordance with Health Canada's SPN2017-02. GF-3840 EC or GF-3712 EC, containing florylpicoxamid, was applied twice as foliar broadcast sprays at a nominal rate of 50 g a.i./ha/application 14 ± 1 and 7 ± 1 days before BBCH 37–39 for hay and forage sampling and 7 ± 1 days before BBCH 67–69 and at BBCH 67–69 for grain and straw sampling. The total seasonal application rate was 100 g a.i./ha. The last application occurring approximately 6–8 days before harvest of forage and hay, and 21-66 days before harvest of straw and grain.

Adjuvants were not used. Independence of trials was assessed. Residue decline data show that florylpicoxamid residues decrease in wheat forage and hay with increasing PHIs, and could not be assessed in grain as all residues were <LOQ. Adequate storage stability data are available on diverse crop types to support the storage intervals of the crop field trials. Samples were analyzed using a validated analytical method.

Crop	**Total application rate (g a.i./ha)**	**PHI (days)**	**Analyte**	**Florylpicoxamid levels (ppm)**					
				n	**LAFT**	**HAFT**	**Median**	**Mean**	**SDEV**
GF-3840 EC									
Wheat forage	96–104	6–8	Florylpicoxamid	22	0.023	0.76	0.092	0.19	0.23
Wheat hay					0.019	1.5	0.17	0.31	0.38
Wheat straw	99–104	21–66		22	<0.010	0.038	0.010	0.013	0.008
Wheat grain					<0.010	<0.010	0.010	0.010	N/A
GF-3712 EC									
Wheat forage	100–102	6–7	Florylpicoxamid	4	0.027	0.72	0.067	0.22	0.33
Wheat hay					0.067	1.7	0.18	0.53	0.78
Wheat straw	100–101	25–49		4	<0.010	<0.010	0.010	0.010	N/A
Wheat grain					<0.010	<0.010	0.010	0.010	N/A

n = number of independent trials. LAFT = lowest average field trial; HAFT = Highest average field trial; SDEV = standard deviation

Processed food and feed – Wheat	**PMRA# 3113597, 3113616**

Processing studies were conducted in 5 distinctive EU growing regions using GF-3840 at 473–511 g a.i./ha (fivefold of maximum single seasonal use rate). Adequate storage stability data are available on diverse crop types to support the storage intervals of the processed food and feed. Samples were analyzed using a validated analytical method.

Florylpicoxamid residues were all <LOQ (<0.01 ppm) in wheat grain and all processed commodities. Processing factors could not be calculated for florylpicoxamid in wheat processed fractions.

Processed food and feed - Soybean	**PMRA# 3113610**
A soybean processing study was submitted for translation to canola. Processing studies were conducted in 3 distinctive North American growing regions using GF-3840 at 595–626 g a.i./ha (twofold of maximum single seasonal use rate). Adequate storage stability data are available on diverse crop types to support the storage intervals of the processed food and feed. Samples were analyzed using a validated analytical method. Florylpicoxamid residues were all <LOQ (<0.01 ppm) in soybean seeds and processed commodities (including refined and crude oil). Processing factors could not be calculated for florylpicoxamid in soybean processed fractions (for translation to canola).	

Processed food and feed – Sugar beets	**PMRA# 3113607**
Processing studies were conducted in 3 distinctive North American growing regions using GF-3840 at 1237–1269 g a.i./ha (fourfold of maximum single seasonal use rate). Adequate storage stability data are available on diverse crop types to support the storage intervals of the processed food and feed. Samples were analyzed using a validated analytical method.	

RAC	**Processed Fractions**	**HAFT$_{[RAC]}$ (ppm)**	**Median processing factor of florylpicoxamid**	**Anticipated residues of florylpicoxamid (ppm)**
Sugar beet roots	Molasses	<0.01	0.2×	<0.01
	Dried pulp		0.3×	<0.01
	Refined sugar		0.2×	<0.01
	Wet pulp		0.2×	<0.01
	Raw sugar		0.2×	<0.01

Confined accumulation in rotational crops – Lettuce, radish, wheat, and oilseed rape	**PMRA# 3113599**
Radiolabel Position	[bis-phenyl-U-^{14}C]florylpicoxamid (PH label) (specific activity: 24.6 mCi/mmol) and [pyridinyl-2-^{14}C]florylpicoxamid (PY label) (specific activity: 27.6 mCi/mmol)
Treatment	
Test site	Outdoors (May-September) and in a greenhouse (October-May) in plastic crates.
Soil type	Sandy loam
Treatment	Bare soil was treated according to two different scenarios: 1. at 760–778 g a.i./ha (5 × 133–162 g a.i./ha), and aged for 30, 60, 120 and 270 days (radish, lettuce, and wheat) and 2. at 99–100 g a.i./ha (1 × 99–100 g a.i./ha) at 90 (all crops) and 375 (wheat and rapeseed) days
Formulation	The 1st treatment scenario (760–778 g a.i./ha) used a suspension concentrate (SC) formulation of florylpicoxamid, and the 2nd treatment scenario used an emulsifiable concentrate (EC) formulation of florylpicoxamid.
Extraction solvents	Samples with TRRs > 0.01 ppm were extracted as follows: 2 × ACN:water (8:2, v/v)

	If the resulting extract contained >10% TRR, samples were further extracted as follows: ACN:water (2:8, v/v), repeated until the extraction released <10 % TRR. For oilseed rape, samples were first extracted with hexane and ACN:water (8:2, v/v), followed by the extraction scenarios described above if TRR > 10%. For samples from 30- and 60-day PBIs, the extraction solvents contained 3% H_3PO_4 in order to stabilize florylpicoxamid.

Matrices	TRR (ppm [^{14}C]florylpicoxamid equivalents)					
	Application at ~750 g a.i./ha				Application at ~100 g a.i./ha	
	30-day PBI	60-day PBI	120-day PBI	270-day PBI	90-day PBI	375-day PBI
PH label						
Radish tops	0.047	0.024	0.022	0.004	0.010[2]	NA
Radish root	0.046	0.017	0.013	0.004	0.006	NA
Lettuce, immature	0.056	0.021	0.017	0.003	0.006	NA
Lettuce, mature	0.045	0.027	0.012	0.004	0.008	NA
Wheat forage	0.120	0.048	0.030	0.009	0.032	0.002
Wheat hay	0.455	0.191	0.095	0.032	0.171	0.008
Wheat straw	0.186	0.287	0.073	0.024	0.196	0.009
Wheat grain	0.112	0.103	0.036	0.006	0.096	0.003
Oilseed rape forage	NA	NA	NA	NA	0.024	0.002
Oilseed rape straw	NA	NA	NA	NA	0.096	0.003
Oilseed rape seed	NA	NA	NA	NA	0.116	0.004
PY label						
Radish tops	0.011	0.012	0.009	0.002	0.008	NA
Radish root	0.011	0.008	0.008	0.002	0.006	NA
Immature lettuce	0.016	0.009	0.005	0.003	0.005	NA
Mature lettuce	0.011	0.010	0.007	0.002	0.008	NA
Wheat forage	0.031	0.022	0.015	0.005	0.018	0.001
Wheat hay	0.161	0.104	0.068	0.015	0.078	0.005
Wheat straw	0.070	0.121	0.044	0.012	0.086	0.004
Wheat grain	0.079	0.068	0.030	0.005	0.067	0.002
Oilseed rape forage	NA	NA	NA	NA	0.013	0.001
Oilseed rape straw	NA	NA	NA	NA	0.058	0.002
Oilseed rape seed	NA	NA	NA	NA	0.079	0.003

Summary of major identified metabolites in rotated crops				
Radiolabel position	**[PH-^{14}C]florylpicoxamid, [PY-^{14}C]florylpicoxamid**			
Metabolites identified	**Major metabolites**			
High rate (760–778 g a.i./ha)				
Plantback intervals (PBI)	1st Rotation (30-day PBI)	2nd Rotation (60-day PBI)	3rd Rotation (120-day PBI)	4th Rotation (270-day PBI)
Radish tops	-	X12675171	-	
Radish roots	-			
Immature lettuce leaves	Glucose conjugate of X12674243		-	
Mature lettuce leaves	Glucose conjugate of X12674243	X12675171 Glucose conjugate of X12674243	-	-
Wheat forage	Glucose conjugate of X12674243			-
Wheat hay	Glucose conjugate of X12674243	-	Glucose conjugate of X12674243	-
Wheat straw			X12675171	Glucose conjugate of X12674243
Wheat grain	-			
Low rate (99–100 g a.i./ha)				
Plantback intervals (PBI)	1st Rotation (90-day PBI)		2nd Rotation (375-day PBI)	
Wheat forage	-		-	
Wheat hay	Glucose conjugate of X12674243			
Wheat straw	-			
Wheat grain				
Oilseed rape forage				
Oilseed rape straw				
Oilseed rape grain				

Proposed metabolic scheme in rotational crops

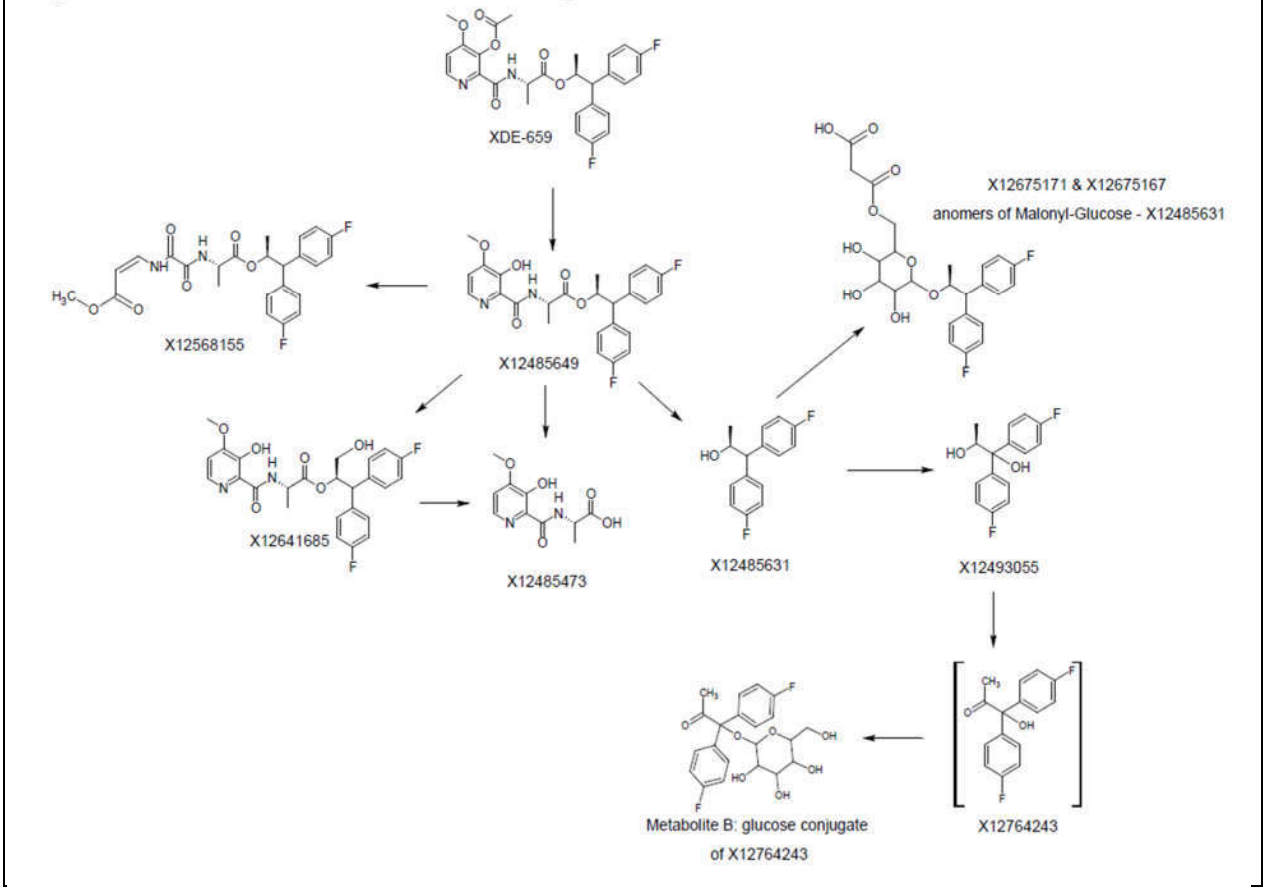
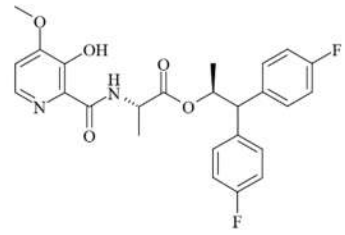


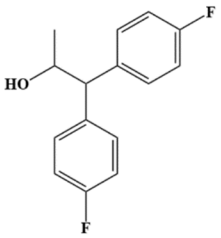
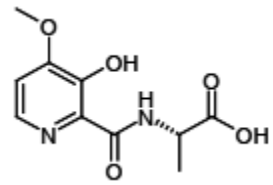
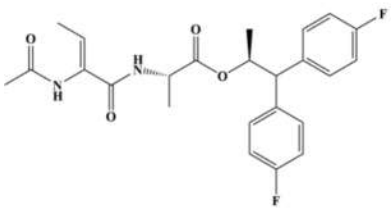
Table 20 Food residue chemistry overview of metabolism studies and risk assessment

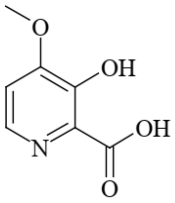
Plant studies	
Residue definition for enforcement **Primary crops (Wheat, tomato, lettuce)** **Rotational crops**	Florylpicoxamid
Residue definition for risk assessment **Primary crops** **Rotational crops**	Human food: Florylpicoxamid including the metabolite X12485649 (expressed as parent equivalents) Animal feed: Florylpicoxamid including the metabolites X12485649 and X12563767 (expressed as parent equivalents)
Metabolic profile in diverse crops	Similar in wheat, tomato, and lettuce.
Animal studies	
Animals	**Ruminant and Poultry**
Residue definition for enforcement	Florylpicoxamid including the metabolite X12485649 (expressed as parent equivalents)
Residue definition for risk assessment	

Metabolic profile in animals (goat, hen, rat)		Similar in ruminants, poultry, and rats	
FAT SOLUBLE RESIDUE		Yes	
Dietary risk from food and drinking water			
	Population	**Estimated risk % of acceptable daily intake (ADI)**	
		Food alone	**Food and drinking water**
Basic chronic dietary exposure analysis **ADI = 0.03 mg/kg bw/day** **Estimated chronic drinking water concentration = 0.29 ppm**	All infants <1 year	0.9	73.8
	Children 1–2 years	3.2	30.1
	Children 3–5 years	1.9	23.8
	Children 6–12 years	1.1	17.3
	Youth 13–19 years	0.5	14.3
	Adults 20–49 years	0.4	19.8
	Adults 50+ years	0.4	19.2
	Females 13-49 years	0.4	19.5
	Total population	0.6	20.1

Table 21 Summary of the major transformation products of florylpicoxamid in the environment

Major transformation product (TP)	Maximum mean concentration	Comments
X12485649  (2S)-1,1-bis(4-fluorophenyl)propan-2-yl N-[(3-(hydroxy)-4-methoxypyridin-2-yl)carbonyl]-L-alaninate MW: 470.47 g/mol	Hydrolysis - 107.2% AR Phototransformation on dry soil - 52.93% AR (irradiated); 58.45% AR (dark) Aqueous phototransformation - 8.95% AR (reached a maximum of 13.9% AR in one sample) Aerobic biotransformation in soil - 90.95% AR Anaerobic biotransformation in soil - 86.73% AR Aerobic aquatic biotransformation - 102.2% AR Terrestrial field dissipation (TFD) - 36.4% applied (Florida, bare soil)[(1)]	Major TP for hydrolysis, aqueous phototransformation, aerobic and anaerobic biotransformation in soil and in aerobic aquatic systems.

Major transformation product (TP)	Maximum mean concentration	Comments
X12485631  (2S)-1,1-bis(4-fluorophenyl)propan-2-ol MW: 248.27 g/mol	Hydrolysis - 30.90% AR Phototransformation on dry soil - 6.15% AR (irradiated); not formed in dark soil. Aqueous phototransformation - 47.45% AR Aerobic biotransformation in soil - not produced Anaerobic biotransformation in soil - 32.75% AR Aerobic aquatic biotransformation - 7.10% AR TFD - Not analyzed	Major TP for hydrolysis, aqueous phototransformation and anaerobic biotransformation in soil. Not produced in aerobic soil. Minor TP for phototransformation on dry soil and aerobic aquatic biotransformation.
X12485473  *N*-[(3-hydroxy-4-methoxypyridin-2-yl)carbonyl]-*L*-alanine MW: 240.22 g/mol	Hydrolysis - 37.15% AR Phototransformation on dry soil - n/a Aqueous phototransformation - n/a Aerobic biotransformation in soil - n/a Anaerobic biotransformation in soil - 45.4% AR Aerobic aquatic biotransformation - n/a TFD - Not analyzed	Major TP for hydrolysis at pH 9 and in anaerobic soil. Not produced by other transformation pathways or via hydrolysis at pH 4 and 7.
X1271957  [(2S)1,1-bis(4-fluorophenyl)propan-2-yl] (2S)-2-[[(Z)-2-(acetylamino)but-2-enoyl]amino]propionate MW: 444.48 g/mol	Hydrolysis - n/a Phototransformation on dry soil - n/a Aqueous phototransformation - 9.15% AR (reached maximum mean of 11.2% AR in pyridine radiolabelled samples) Aerobic biotransformation in soil - n/a Anaerobic biotransformation in soil - n/a Aerobic aquatic biotransformation - n/a TFD - Not analyzed	Major TP for aqueous phototransformation. Not produced by other transformation pathways.
X696476	Hydrolysis - 3.60% AR Phototransformation on dry soil - n/a Aqueous phototransformation - n/a	Major TP for anaerobic biotransformation in

Major transformation product (TP)	Maximum mean concentration	Comments
 3-hydroxy-4-methoxypyridine-2-carboxylic acid MW: 169.14 g/mol	Aerobic biotransformation in soil - n/a Anaerobic biotransformation in soil - 11.6 Aerobic aquatic biotransformation - n/a TFD - Not analyzed	soil. Minor TP for hydrolysis at pH 9 (25 and 35°C). Not produced by other transformation pathways or via hydrolysis at pH 4, 7 or 9 (10°C).
MW488 (unidentified)	Aqueous phototransformation - 16.13% AR (maximum of 19.9% AR in one sample)	These unidentified TPs were only produced by aqueous phototransformation.
MW419 (unidentified)	Aqueous phototransformation - max. of 10.4% AR in one sample	
MW486 (unidentified)	Aqueous phototransformation - max. of 10.2% AR in one sample	

n/a: not applicable

[1] Florida does not represent an ecoregion that is relevant to Canada; however, it was included in this assessment as supporting information because the application rate used at the Canadian relevant sites (two applications of 50 g a.i./ha at the Ontario and North Dakota sites) was below the maximum proposed cumulative rate and resulted in very low measured concentrations in soil (many samples were below the limit of quantification).

Table 22 Fate and behaviour of florylpicoxamid in the environment

Property	Test substance	Medium	Value	Kinetic model	Major transformation products[1, 2]	Comments	PMRA#
Abiotic transformation							
Hydrolysis	Florylpicoxamid (XDE-659)	pH 4 buffer, 10°C	t_R/DT_{50} = 54.6 days	SFO	X12485469	Hydrolysis is an important transformation process for florylpicoxamid.	3113630
		pH 4 buffer, 25°C	t_R/DT_{50} = 12.7 days				
		pH 4 buffer, 35°C	t_R/DT_{50} = 5.59 days				
		pH 7 buffer, 10°C	t_R/DT_{50} = 112 days				
		pH 7 buffer, 25°C	t_R/DT_{50} = 16.7 days				
		pH 7 buffer, 35°C	t_R/DT_{50} = 5.64 days				
		pH 9 buffer, 10°C	t_R/DT_{50} = 2.44 days		X12485649 X12485631 X12485473		
		pH 9 buffer, 25°C	t_R/DT_{50} = 8.01 hours				
		pH 9 buffer, 35°C	t_R/DT_{50} = 2.84 hours				
	X12485649	pH 4 and 7 buffer	Stable	--	None	Hydrolysis is not expected to be an important route of dissipation for X12485649 in the environment.	3113631
		pH 9 buffer, 10°C	t_R/DT_{50} = 122 days	SFO	X12485631 X12485473		
		pH 9 buffer, 25°C	t_R/DT_{50} = 26.3 days				
		pH 9 buffer, 35°C	t_R/DT_{50} = 8.34 days				
Phototransformation on soil	Florylpicoxamid (XDE-659)	n/a – phototransformation on soil is a negligible process for florylpicoxamid and X12485649					3113632
Phototransformation in water	Florylpicoxamid (XDE-659)	pH 7 buffer, 25°C	t_R/DT_{50} (summer sunlight equivalent at	SFO	X12719657 X12485631 MW419	Phototransformation may be a route of dissipation of	3113633

Property	Test substance	Medium	Value	Kinetic model	Major transformation products[1, 2]	Comments	PMRA#
			40°N) = 0.28 days		MW488 MW486	florylpicoxamid in the photic zone of clear/shallow waterbodies.	
Phototransformation in air	n/a – volatilization of florylpicoxamid and its major TPs in the field is expected to be negligible.						
Biotransformation							
Biotransformation in aerobic soil[3]	Florylpicoxamid (XDE-659)	Raymondville (sandy clay; pH 7.9, 0.45% organic carbon (OC))	*XDE-659* t_R = 0.65 days DT_{50} = 0.57 days *X12485649* t_R/DT_{50} = 2113 days	IORE SFO	X12485649	Florylpicoxamid is non-persistent and X12485649 is persistent in this soil.	3113634
	Florylpicoxamid (XDE-659)	Site J3 – Hareby (light clay; pH 7.6, 1.3% OC)	*XDE-659* t_R = 0.67 days DT_{50} = 0.34 days *X12485649* t_R/DT_{50} = 694 days	IORE SFO	X12485649 Unextracted residues	Florylpicoxamid is non-persistent and X12485649 is persistent in this soil.	
		Am Fischteich (clay loam; pH 5.5., 1.8% OC)	*XDE-659* t_R = 1.21 days DT_{50} = 0.54 days *X12485649* t_R = 1590 days DT_{50} = 1452 days	IORE DFOP	X12485649 Unextracted residues	Florylpicoxamid is non-persistent and X12485649 is persistent in this soil.	
		Site I2 – Longwoods Quarry (sandy loam; pH 7.9, 1.1% OC)	*XDE-659* t_R = 0.44 days DT_{50} = 0.22 days *X12485649*	IORE	X12485649 Unextracted residues	Florylpicoxamid is non-persistent and X12485649 is moderately persistent in this soil.	

Property	Test substance	Medium	Value	Kinetic model	Major transformation products[1, 2]	Comments	PMRA#
			t_R/DT_{50} = 166 days	SFO			
		Sterile soil (Site I2 – Longwoods Quarry)	*XDE-659* t_R = 1.25 days DT_{50} = 0.46 days	IORE	X12485649 X12485631	Florylpicoxamid is non-persistent in this soil. Degradation kinetics for the major TPs could not be calculated due to an insufficient number of data points.	
Biotransformation in anaerobic soil	Florylpicoxamid (XDE-659)	Raymondville (sandy clay loam, pH 7.7, 0.72% OC)	*XDE-659* t_R = 1.11 days DT_{50} = 0.46 days *X12485649* t_R/DT_{50} = 91.2 days	IORE SFO	X12485649 X12485631 X696476 Unextracted residues	Florylpicoxamid is non-persistent and X12485649 is moderately persistent in this soil.	3113635
		Hareby (clay loam, pH 7.5, 2.6% OC)	*XDE-659* t_R = 6.01 days DT_{50} = 0.75 days *X12485649* t_R = 602 days DT_{50} = 466 days	IORE DFOP	X12485649 X12485631 X12485473 Unextracted residues	Florylpicoxamid is non-persistent and X12485649 is persistent in this soil.	
		Am Fischteich (silt loam, pH 5.0, 1.7% OC)	*XDE-659* t_R = 4.1 days DT_{50} = 1.72 days *X12485649* t_R/DT_{50}= 288 days	IORE SFO	X12485649 X12485631 X12485473 Unextracted residues	Florylpicoxamid is non-persistent and X12485649 is persistent in this soil.	

Property	Test substance	Medium	Value	Kinetic model	Major transformation products[1, 2]	Comments	PMRA#
		Longwoods Quarry (sandy clay loam; pH 7.5, 2.0% OC)	*XDE-659* t_R = 7.93 days DT_{50} = 0.76 days *X12485649* t_R/DT_{50}= 457 days	IORE SFO	X12485649 X12485631 Unextracted residues	Florylpicoxamid is non-persistent and X12485649 is persistent in this soil.	
Biotransformation in aerobic aquatic systems[4]	Florylpicoxamid (XDE-659)	Calwich Abbey – water (pH 6.8, 13.0 ppm dissolved organic carbon (DOC))	*XDE-659* t_R/DT_{50} = 0.14 days *X12485649* t_R = 19.6 days DT_{50} = 9.61 days	SFO IORE	X12485649	Florylpicoxamid is classified as non-persistent in this system. X12485649 is persistent in this system.	3113636
		Calwich Abbey – sediment (sand, pH 7.5, 0.12% OC)	*XDE-659* t_R = 0.59 days DT_{50} = 0.05 days *X12485649* t_R/DT_{50} = 321 days	IORE SFO			
		Calwich Abbey – total system	*XDE-659* t_R/DT_{50} = 0.078 days *X12485649* t_R/DT_{50} = 212 days	SFO SFO			
		Lake Needham – water (pH 8.0, 3.5 ppm DOC)	*XDE-659* t_R = 0.57 days DT_{50} = 0.11 days	IORE	X12485649	Florylpicoxamid is classified as non-persistent in this system. This system was not	
		Lake Needham – sediment	*XDE-659* t_R/DT_{50} = 0.10				

Property	Test substance	Medium	Value	Kinetic model	Major transformation products[1, 2]	Comments	PMRA#
		(silt loam, pH 7.5, 5.4% OC)	days	SFO		acceptable for calculating the half-live of X12485649 due to low microbial biomass.	
		Lake Needham – total system	*XDE-659* t_R = 0.10 days	SFO			
		Schofield Pond – water (pH 6.9, 12.7 ppm total organic carbon (TOC))	*XDE-659* t_R = 1.83 days DT_{50} = 0.242 days	DFOP	X12485649	This system had low oxygen in the water phase (1.0 to 5.1 mg/L), with anaerobic sediments. Florylpicoxamid is classified as non-persistent in this system. This system was not acceptable for calculating the half-live of X12485649 due to low microbial biomass.	3113637
		Schofield Pond – sediment (sand, pH 6.4, 0.01% OC)	*XDE-659* t_R = 9.41 days	SFO			
		Schofield Pond – total system	*XDE-659* t_R = 2.47 days DT_{50} = 0.24 days	DFOP			
		Calwich Abbey – water (pH 8.0, 3.5 ppm TOC)	*XDE-659* t_R = 0.678 days DT_{50} = 0.008 days *X12485649* t_R/DT_{50} = 29.4 days	IORE SFO		This system had low oxygen in the water phase (0.3 to 4.6 mg/L), with anaerobic sediments. Florylpicoxamid is classified as non-persistent, and X12485649 is classified as persistent, in this	
		Calwich Abbey – sediment (silt loam, pH 7.5, 5.4% OC)	*XDE-659* t_R/DT_{50} = 0.10 days	SFO			

Property	Test substance	Medium	Value	Kinetic model	Major transformation products[1, 2]	Comments	PMRA#
			X12485649 t_R/DT_{50} = 692 days	SFO		system.	
		Calwich Abbey – total system	*XDE-659* t_R = 0.443 days DT_{50} = 0.024 days	IORE			
			X12485649 t_R/DT_{50} = 176 days	SFO			
Bioconcentration							
Bioconcentration in fish (*Lepomis macrochirus*)	Florylpicoxamid (XDE-659)	Fish	BCF_{KLG} = 86.8 to 105	n/a	n/a	Time to 95% depuration ranged between 2.9 and 4.4 days. Florylpicoxamid is not expected to bioaccumulate in fish	3113657
	X12485649		BCF_{KLG} = 82.7 to 106	n/a	n/a	Time to 95% depuration ranged between 4.5 and 6.3 days. X12485649 is not expected to bioaccumulate in fish	3113658
Mobility							
Adsorption/desorption in soil	Florylpicoxamid (XDE-659)	M1051: Schmallernberg, Germany (loam, pH 5.7, 4.8% OC)	K_{oc} = 903.10 mL/g K_d = 43.35 mL/g	n/a	n/a	Florylpicoxamid has low to slight mobility in soil based on the K_{oc} and K_d values.	3113638
		M1052: Brierlow,	K_{oc} = 528.24				

Property	Test substance	Medium	Value	Kinetic model	Major transformation products[1, 2]	Comments	PMRA#
		UK (silt loam, pH 5.4, 3.1% OC)	mL/g K_d = 16.38 mL/g				
		M1053: Longwoods Quarry, UK (loamy sand, pH 7.6, 1.6% OC)	K_{oc} = 932.66 mL/g K_d = 14.92 mL/g				
		M1054: Raymondville, Texas (sandy loam clay, pH 7.9, 0.45% OC)	K_{oc} = 3311.5 mL/g K_d = 14.90 mL/g	n/a	n/a		
		M1055: Schmallenberg, Germany (loamy sand, pH 5.1, 0.89% OC)	K_{oc} = 1695.3 mL/g K_d = 15.09 mL/g				
		M1056: Hareby, UK (clay loam, pH 7.6, 2.5% OC)	K_{oc} = 884.20 mL/g K_d = 22.10 mL/g				
		M1057: Kessoku, Japan (silt loam, pH 6.6, 2.15% OC)	K_{oc} = 1050.0 mL/g K_d = 22.57 mL/g				
		M1069: Crimmitschau, Germany (silt loam, pH 5.3, 1.8% OC)	K_{oc} = 1289.3 mL/g K_d = 23.21 mL/g				
	X12485649	M1051: Schmallenberg, Germany (loam, pH 5.7, 4.8% OC)	K_{oc} = 903.10 mL/g K_d = 43.35 mL/g			The mobility of X12485649 in soil ranges from low to immobile, depending on the soil type,	3113639
		M1052: Brierlow,	K_{oc} = 528.24				

Property	Test substance	Medium	Value	Kinetic model	Major transformation products[1, 2]	Comments	PMRA#
		UK (silt loam, pH 5.4, 3.1% OC)	mL/g K_d = 16.38 mL/g			based on the K_{oc} and K_d values.	
		M1053: Longwoods Quarry, UK (loamy sand, pH 7.6, 1.6% OC)	K_{oc} = 932.66 mL/g K_d = 14.92 mL/g				
		M1054: Raymondville, Texas (sandy loam clay, pH 7.9, 0.45% OC)	K_{oc} = 22,736 mL/g K_d = 102.3 mL/g	n/a	n/a		
		M1055: Schmallenberg, Germany (loamy sand, pH 5.1, 0.89% OC)	K_{oc} = 5417.8 mL/g K_d = 48.22 mL/g				
		M1056: Hareby, UK (clay loam, pH 7.6, 2.5% OC)	K_{oc} = 4099.4 mL/g K_d = 102.5 mL/g				
		M1057: Kessoku, Japan (silt loam, pH 6.6, 2.15% OC)	K_{oc} = 6442.5 mL/g K_d = 138.5 mL/g				
		M1069: Crimmitschau, Germany (silt loam, pH 5.3, 1.8% OC)	K_{oc} = 3464.2 mL/g K_d = 62.36 mL/g				
Soil leaching	Study not submitted or required.						
Volatilization	Study not submitted or required. Florylpicoxamid is non-volatile.						
Field studies							
Field dissipation	GF-3716 suspension concentrate	California bare soil plot (sandy loam, pH 7.4, 0.59% OC)	DT_{50} (florylpicoxamid + X12485649) =	DFOP	X12485649	Florylpicoxamid and X12485649 were detected in the 0 to	3113640

Property	Test substance	Medium	Value	Kinetic model	Major transformation products[1, 2]	Comments	PMRA#
	formulation; 9.4% a.i.		6.80 days			15.2 cm soil interval only.	
		Florida bare soil (loamy sand, pH 5.9, 0.79% OC)	DT_{50} (florylpicoxamid + X12485649) = 21.5 days	IORE	X12485649	Florylpicoxamid and X12485649 were detected in the 0 to 15.2 cm soil interval only.	3113640
		Florida cucumber cropped plot (loamy sand, pH 5.9, 0.79% OC)	DT_{50} (florylpicoxamid + X12485649) = 13.2 days	DFOP	X12485649	Florylpicoxamid was detected in the 0 to 15.2 cm soil interval only; X12485649 was detected in soil down to a depth of 30.5 cm.	3113640
	GF-3712 emulsifiable concentration formulation; 10.4% a.i.	North Dakota bare soil plot (silty clay, pH 7.5, 3.5% OC)	DT_{50} (florylpicoxamid + X12485649) = 13.1 days	IORE	X12485649	Florylpicoxamid and X12485649 were detected in the 0 to 15.2 cm soil interval only.	3113640
		Ontario bare soil plot (silt loam, pH 6.8, 2.2% OC)	DT_{50} (florylpicoxamid + X12485649) = 4.29 days	SFO	X12485649	Florylpicoxamid and X12485649 were detected in the 0 to 15.2 cm soil interval only.	3113640
Field leaching	Study not submitted, or required						

[1] Unextracted residues are presented as a major TP as they were formed at >10% AR; however, the composition is unknown and may represent a mixture of the parent and TPs.

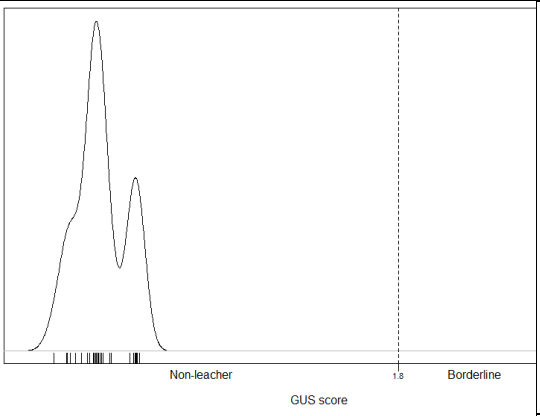
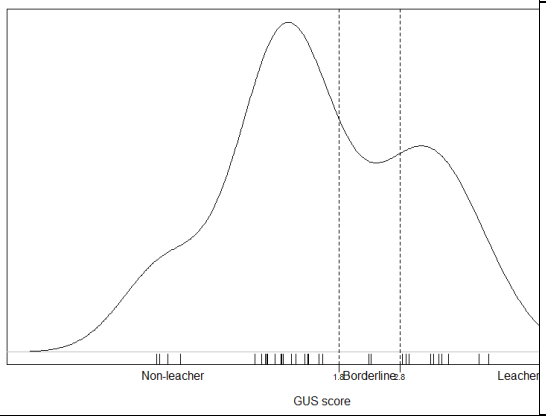
[2] There were insufficient data to calculate degradation kinetics for all major TPs except X12485649.

[3] The 90% upper confidence bound on the mean of the t_R values in aerobic soil for florylpicoxamid and X12485649 are 1.01 and 1857 days, respectively. These values were used to calculate estimated environmental concentrations (EECs) in soil for the risk assessment.

[4] The 80th percentile of the aerobic aquatic half-lives for florylpicoxamid is 1.25 days. This value was used to calculate EECs in water. Only two representative half-lives were available for X12485649. As such, the maximum value of 212 days was used for this TP.

Table 23 Leaching assessment of florylpicoxamid residues

Leaching criteria of Cohen et al. (1984)[1]			
Criteria	**Test item**		**Leaching criteria met?**
	Florylpicoxamid	**X12485649[2]**	
Solubility in water >30 mg/L	≤3.2 mg/L	22 mg/L at pH 5 23 mg/L at pH 7 33 mg/L at pH 9	Florylpicoxamid: No X12485649: Yes at pH 9
K_d (mL/g): <5 and usually <1 or 2	14.90 to 43.35 (mean 21.57)	14.92 to 138.5 (mean 66.07)	No
K_{oc} <300	528.2 to 3311 (mean 1324)	528.2 to 22,736 (mean 5565)	No
Henry's law constant (atm m^3/mol): $<10^{-2}$	pH 5: $<8.04 \times 10^{-9}$ pH 7: $<8.30 \times 10^{-9}$ pH 9: $<8.58 \times 10^{-9}$	pH 5: $<1.03 \times 10^{-12}$ pH 7: $<1.07 \times 10^{-12}$ pH 9: $<7.16 \times 10^{-13}$	Yes
p*K*a: Negatively charged (either fully or partially) at ambient pH	n/a does not dissociate	1st p*K*a <2 2nd p*K*a = 8.8	Florylpicoxamid: No X12485649: Yes
Hydrolysis half-life: >20 weeks (>140 days)	2.84 hours (pH 9, 35ºC) to 112 days (pH 7, 10ºC)	Stable at pH 4 and 7 (50ºC) 8.34 days (pH 9, 35ºC) to 122 days (pH 9, 10ºC)	Florylpicoxamid: No X12485649: Yes at pH 4 and 7
Soil phototransformation half-life: >1 week (>7 days)	Negligible process for florylpicoxamid	Negligible process for X1248649	No
Half-life in soil: >2 to 3 weeks (>14 to 21 days)	≤ 1.21 days	91.2 to 2113 days	Florylpicoxamid: No X12485649: Yes

Leaching criteria of Cohen et al. (1984)[1]			
Criteria	**Test item**		**Leaching criteria met?**
	Florylpicoxamid	**X12485649[2]**	
Groundwater Ubiquity Score (GUS) Assessment[3]			
Test item	**GUS Plot**		**Notes**
Florylpicoxamid			Non-leacher
X12485649			Non-leacher to leacher

1 Cohen et al. (1984). Potential pesticide contamination of groundwater from agricultural uses. In: R.F. Kruger and J.D., Seibor, eds. Treatment and disposal of pesticide wastes. American Chemistry Society Symposium Series No. 259, American Chemical Society: Washington, DC.

2 Information for major TPs other than X12485649 is not available.

3 Gustafson, D.I. 1989. Groundwater ubiquity score: A simple method for assessing pesticide leachability. Environmental Toxicology and Chemistry 8:339-357.

Table 24 EECs for florylpicoxamid in the environment

Substance	EEC	Method of calculation	Notes
Soil: Screening level risk assessment			
Florylpicoxamid	150 g a.i./ha	Cumulative application rate to soil based on 5 × 150 g a.i./ha with a 14-day re-application interval and considering a representative half-life of 1.01 days (90% upper confidence bound on the mean of four available values) for florylpicoxamid in aerobic soil.	EECs in g a.i./ha were used to evaluate risks to beneficial arthropods and non-target terrestrial plants (seedling emergence).
	0.067 mg/kg dw soil	EEC of florylpicoxamid in soil was calculated based on the cumulative application rate to soil (150 g a.i./ha), and assuming a soil bulk density of 1.5 g/cm^3 and a soil depth of 15 cm.	

Substance	EEC		Method of calculation	Notes
X12485649	0.30 mg/kg dw soil		EECs of the major TPs in soil were calculated as above for florylpicoxamid but using the maximum application rate (5 × 150 g a.i./ha = 750 g a.i./ha). It was assumed that 100% of the parent transformed into the TPs on a molar basis. Dissipation of the parent between applications was not considered. The molar conversion factor was calculated as the molecular weight of the TP divided by the molecular weight of the parent. See Table 1 for the molecular weight of each compound.	EECs in mg/kg dw soil were used to evaluate risks to earthworms.
X12485631	0.16 mg/kg dw soil			
Water: Screening level risk assessment (EEC in mg/L)				
Water depth:	**15 cm**	**80 cm**		
Florylpicoxamid	150 g a.i./ha		Cumulative application rate to water based on 5 × 150 g a.i./ha with a re-application interval of 14 days and considering a representative half-life of 1.25 days (80th percentile of the four available values) for florylpicoxamid (total aquatic system).	The EECs in surface water at 15-cm depth were used to determine risk to amphibians while the 80-cm depth EECs were used to evaluate risks to all other aquatic organisms.
	0.10	0.019	EEC of florylpicoxamid in surface water was calculated considering a direct overspray of florylpicoxamid to a one-hectare wetland with depths of 15 and 80 cm at the above cumulative application rate (150 g a,i./ha) to water.	
X12485649	0.46	0.086	EECs of the major TPs in surface water were calculated as described above for florylpicoxamid, but using the maximum application rate (750 g a.i./ha) and assuming 100% transformation of the parent to the TPs on a molar basis. Dissipation of the parent between applications was not considered.	
X12485473	0.23	0.044		
X12485631	0.24	0. 045		
X12719657	0.43	0.081		
GF-4017(1)	0.033	0.0063		
Water: Refined risk assessment - Spray drift to freshwater (EEC in mg/L)(2)				
Water depth:	**15 cm**	**80 cm**		
Florylpicoxamid	0.0061	0.0011	The screening level surface water EECs were adjusted to account for 6% spray drift deposition of medium sized spray droplets 1-metre downwind of the point of application (field sprayer).	Used in the refined risk assessment for aquatic organisms.
X12485649	0.030	0.0052		
GF-4017(2)	0.0020	0.00038		
Florylpicoxamid	0.023	0.0044	The screening level surface water EECs were adjusted to account for 23% spray drift deposition of medium sized droplets 1-metre downwind of the point of application (aerial application).	
X12485649	0.11	0.020		
GF-4017(2)	0.0076	0.0014		
Refined risk assessment: EEC from spray drift to estuarine/Marine environments (mg/L)(2)				
Water depth:	**15 cm**	**80 cm**		
Florylpicoxamid	-	0.0011	EEC in the estuarine/marine environment considering only one application of 150 g a.i./ha to account for tidal action and dilution in seawater, and 6% spray drift deposition of medium sized droplets 1-metre downwind of the point of application (field sprayer application).	Used in the refined risk assessment for estuarine/marine aquatic organisms.
X12485649	-	0.0010		
Florylpicoxamid	-	0.0043	EEC in the estuarine/marine environment considering only one application of 150 g a.i./ha to account for tidal action and dilution in seawater, and 23% spray drift deposition of medium sized droplets 1-metre downwind of the point of application (aerial application).	
X12485649	-	0.0040		

Substance	EEC		Method of calculation		Notes
Refined risk assessment: EEC in surface water from runoff (EEC in mg/L)[3]					
Water depth:	**15 cm**	**80 cm**			
Florylpicoxamid + X12485649	0.024	0.0088	Peak concentration	5 × 150 g a.i./ha with a 14-day re-application interval	Used in the refined risk assessment for freshwater and estuarine/marine aquatic organisms.
	0.021	0.0087	24-hour concentration		
	0.016	0.0084	96-hour concentration		
	0.0088	0.0075	21-day concentration		
	0.022	0.0078	Peak concentration	2 × 150 g a.i./ha with a 7-day re-application interval	
	0.020	0.0077	24-hour concentration		
	0.015	0.0075	96-hour concentration		
	0.0082	0.0071	21-day concentration		
	0.0077	0.0040	Peak concentration	2 × 50 g a.i./ha with a 14-day re-application interval	
	0.0070	0.0039	24-hour concentration		
	0.0058	0.0039	96-hour concentration		
	0.0040	0.0037	21-day concentration		
Plant surfaces: Screening level and refined risk assessments					
Florylpicoxamid	196 g a.i./ha		On-field EEC: maximum cumulative application rate of florylpicoxamid to plant surfaces considering 2 × 150 g a.i./ha with a 7-day re-application interval and a foliar half-life of 4.14 days (90% upper confidence bound on the mean of 18 foliar half-life values from supervised residue trials for the combined residue of florylpicoxamid + X12485649)[4].		Used to evaluate on-field and off-field risks to beneficial arthropods and non-target terrestrial plants.
	11.8 g a.i./ha		Off-field EEC considering 6% spray drift deposition of medium sized droplets 1-metre downwind of the point of application (field sprayer application).		
	45.2 g a.i./ha		Off-field EEC considering 23% spray drift deposition of medium sized droplets 1-metre downwind of the point of application (aerial application).		
	177 g a.i./ha		Refinement considering the maximum cumulative application rate on plant surfaces and an on-field foliar deposition factor (F_{int}) of 0.9 for sugar beet (maximum value for the proposed crops. F_{int} values were obtained from Linders et al. (2000)).		
	66.4 g a.i./ha		Refinement considering the cumulative application rate proposed for turf (5 × 150 g a.i./ha with a re-application interval of 14 days), and a Fint of 0.4 for grass.		
	50.0 g a.i./ha		Refinement considering one application of 50 g a.i./ha proposed for GF-4017 Fungicide.		

Substance	EEC	Method of calculation	Notes
EECs for bees (Oral exposure to pollen and/or nectar, or via direct contact)			
Florylpicoxamid	4.29 µg a.i./bee (adult)	Oral exposure estimate for bees = application rate (0.15 kg a.i./ha) × adjustment factor 1. Adult adjustment factor of 28.62 µg a.i./bee per kg a.i./ha was calculated as the food consumption of 0.292 g/bee per day × 98 µg a.i./g per kg a.i./ha (default tall grass residues). 2. Larvae adjustment factor of 12.15 µg a.i./bee per kg a.i./ha was calculated as the food consumption of 0.124 g/bee per day × 98 µg a.i./g per kg a.i./ha (default tall grass residues).	Used to evaluate risks to pollinators (bees).
	1.82 µg a.i./bee (larvae)		
	0.360 µg a.i./bee	Estimated contact exposure (µg a.i./bee) = 2.4 µg a.i./bee/1 kg a.i./ha × maximum single application rate (0.15 kg a.i./ha)	

See Tables 28 and 29 for the EECs for food items for birds and mammals. The EECs for birds and mammals were calculated based on 2 × 150 g a.i./ha with a 7-day re-application interval and a foliar half-life of 4.14 days.

[1] Units for GF-4017 are in mg a.i./L.

[2] Refinements for water EECs were only required for florylpicoxamid, X12485649 and/or GF-4017.

[3] EECs in surface water from runoff were calculated based on the combined residue of florylpicoxamid + X12485649. The parameters used in the ecological water modelling are as follows: (1) K_{oc} = 890 L/kg value for florylpicoxamid, 20th percentile of 8 soils; (2) aquatic whole system half-life = stable; (3) sediment half-life = 484 days, 80th percentile of 4 values from flooded soil; (4) photolysis half-life = 24 days, single value; (5) soil half-life = 1190 days, 90% confidence bound on the mean of 4 soils.

[4] Two applications of 150 g a.i./ha with a re-application interval of 7 days was used to calculate EECs on plant surfaces rather than five applications of 150 g a.i./ha with a re-application interval of 14 days because it results in a higher EEC given the short foliar half-life of florylpicoxamid.

Table 25 Toxicity of florylpicoxamid to non-target species

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity(1)	PMRA#
Terrestrial organisms					
Invertebrates					
Earthworm(*Eisenia Andrei)*	14-d Acute	Florylpicoxamid	LC_{50} > 6.5 mg a.i./kg soil dw NOEC = 6.5 mg a.i./kg soil dw	No adverse effects up to the highest concentration tested	3113642
	56-d Chronic	Florylpicoxamid	NOEC ≥ 63.5 mg a.i./kg soil dw		3163743
	56-d Chronic	X12485649	NOEC ≥ 63.5 mg/kg soil dw		3163744
	56-d Chronic	X12485631	NOEC = 36.3 mg/kg soil dw	-	3163745
Honeybee (*Apis mellifera* L.)(2)	48-h Oral	Florylpicoxamid	LD_{50} > 109.2 µg a.i./bee	n/a	3113643
	48-h Contact		LD_{50} > 100 µg a.i./bee	Practically non-toxic	

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[1]	PMRA#
	3-d Brood		LD_{50} = 32.7 µg a.i./larva	-	3163746
	10-d Chronic Oral		NOEDD ≥ 13.4 µg a.i./bee/day	No adverse effects up to the highest concentration tested	3163747
Predatory arthropod (*Typhlodromus pyri)*	14-d Contact (glass plate)	GF-3840	7-d LR_{50} = 55.34 g a.i./ha ER_{50} = 11.61 g a.i./ha	-	3163748
	14-d Contact (leaf disc)	GF-3840	7-d LR_{50} = 213.4 g a.i./ha ER_{50} (reproduction) = 60.5 g a.i./ha	-	3163749
Parasitic arthropod (*Aphidius rhopalopsiphi*)	13-d Contact (glass plate)	GF-3840	48-h LR_{50} = 5.01 g a.i./ha ER_{50} > 5.0 g a.i./ha	-	3163750
	13-d Contact (barley seedlings)	GF-3840	48-h LR_{50} = 296.8 g a.i./ha ER_{50} > 300 g a.i./ha	-	3163751
Birds					
Bobwhite quail (*Colinus viginianus (L.)*)	Acute	Florylpicoxamid	LD_{50} > 2250 mg a.i./kg bw	Practically non-toxic	3113659
	5-d Dietary	Florylpicoxamid	LC_{50} > 5620 mg a.i./kg diet, equivalent to LD_{50} > 1311 mg a.i./kg bw NOEC ≥1311 mg a.i./kg bw	Practically non-toxic	3113660
	Reproduction	Florylpicoxamid	NOEC ≥ 1000 mg a.i./kg diet, equivalent to NOED ≥ 83.0 mg a.i./kg bw/d	No adverse effects up to the highest concentration tested	3113662
Mallard duck (*Anas platyrhynchos*)	Acute	Data were not submitted, but were not required			-
	5-d Dietary	Florylpicoxamid	LC_{50} > 5620 mg a.i./kg diet, equivalent to LD_{50} > 1032 mg a.i./kg bw NOEC (bw) = 241 mg a.i./kg bw	Practically non-toxic	3113661

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[1]	PMRA#
	Reproduction	Florylpicoxamid	NOEC ≥ 1000 mg a.i./kg diet, equivalent to NOED ≥ 133 mg a.i./kg bw/d	No adverse effects up to the highest concentration tested	3113663
Mammals					
Rat (*Rattus norvegicus*)	Acute	Florylpicoxamid	LD_{50} > 2000 mg/kg bw	Practically non-toxic	3112176
	2-Generation dietary reproductive toxicity	Florylpicoxamid	Offspring toxicity: NOAEL: 73.4 mg/kg bw/day, (♂/♀) LOAEL: 297 mg/kg bw/day, (♂/♀)	Delayed puberty in the young at the highest concentration tested.	3173978
	Developmental toxicity (diet)	Florylpicoxamid	NOAEL = 271 mg/kg bw/day LOAEL > 271 mg/kg bw/day	-	3112034
Rabbit (*Oryctolagus cuniculus*)	Developmental toxicity (diet)	Florylpicoxamid	NOAEL = 9.58 mg/kg bw/day LOAEL = 25.9 mg/kg bw/day	Reproductive effects observed at the highest concentraton tested.	3112035
Vascular plants					
Vascular plants	Seedling emergence (ten species)[3]	GF-3840	ER_{25}/ ER_{50} >300 g a.i./ha	-	3113670
	21-d Vegetative vigour (tomato, *Lycopersicon esculentum*)	GF-3840	ER_{25} = 134.08 g a.i./ha	-	3113669
Freshwater organisms					
Daphnia magna	48-h Acute	Florylpicoxamid	EC_{50} = 0.0590 mg a.i./L NOEC = 0.0403 mg a.i./L	Very highly toxic	3113644
		X12485649	EC_{50} = 0.013 mg/L NOEC = 0.0079 mg/L	Very highly toxic	3113645
		X12485473	EC_{50} > 11 mg/L NOEC ≥ 11 mg/L	Practically non-toxic up to 11 mg/L	3113646

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[1]	PMRA#
		X12485631	EC_{50} > 10 mg/L NOEC ≥ 10 mg/L	Practically non-toxic up to 10 mg/L	3113647
		X12719657	EC_{50} > 10 mg/L NOEC ≥ 10 mg/L	Practically non-toxic up to 10 mg/L	3113648
		GF-4017 (end-use product, also containing pyraclostrobin)	EC_{50} = 0.00358 mg a.i./L NOEC = 0.040 mg a.i./L	Very highly toxic	3237006
	21-d Chronic	Florylpicoxamid	NOEC (reproduction) = 0.00723 mg a.i./L	-	3113649
		X12485649	NOEC (reproduction and growth) = 0.0017 mg/L	-	3113650
Rainbow trout (*Oncorhynchus mykiss*)	96-h Acute	Florylpicoxamid	LC_{50} = 0.011 mg a.i./L NOEC = 0.0067 mg a.i./L	Very highly toxic	3113651
		X12485649	LC_{50} = 0.016 mg/L NOEC = 0.0078 mg/L	Very highly toxic	3113652
		X12485473	LC_{50} > 11 mg/L NOEC = 11 mg/L	Practically non-toxic up to 11 mg/L	3113653
		X12485631	LC_{50} = 6.6 mg/L NOEC = 4.8 mg/L	Moderately toxic	3113654
		X12719657	LC_{50} > 9.6 mg/L NOEC ≥ 9.6 mg/L	Practically non-toxic up to 9.6 mg/L	3113655
		GF-4017 (end-use product, also containing pyraclostrobin)	LC_{50} = 0.00078 mg a.i./L NOEC = 0.00054 mg a.i./L	Very highly toxic	3237007
Fathead minnow (*Pimephales promelas*)	96-h Acute	Florylpicoxamid	LC_{50} = 0.0146 mg a.i./L NOEC = 0.0067 mg a.i./L	Very highly toxic	3113656
	33-d Early-life stage	Florylpicoxamid	NOEC (post-hatch and overall survival) = 0.00342 mg a.i./L	-	3163759
		X12485649	NOEC (post-hatch survival) = 0.0011 mg/L	-	3163760
Freshwater alga (*Rhaphidocelis subcapitata*)	96-h Acute	Florylpicoxamid	72-h EC_{50} (AUC)[4] = 0.173 mg a.i./L 72-h NOEC = 0.0610 mg a.i./L	Highly toxic	3113664

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[1]	PMRA#
			96-h EC_{50} (AUC) = 0.103 mg a.i./L 96-h NOEC = 0.0225 mg a.i./L		
		X12485649	72-h EC_{50} (all endpoints) > 0.70 mg/L 72-h NOEC = 0.11 mg/L 96-h EC_{50} (all endpoints) > 0.53 mg/L 96-h NOEC = 0.086 mg/L	At 72 hours, 0.70 mg/L corresponded to a 47% effect on yield when compared to the pooled controls. As such, this TP is likely classified as highly toxic.	3113665
		X12485473	72-/96-h EC_{50} (all endpoints) > 10 mg/L 72-/96-h NOEC ≥10 mg/L	Practically non-toxic up to 10 mg/L	3113666
		X12485631	72-/96-h EC_{50} (yield) = 1.6 mg/L 72-/96-h NOEC = 0.31 mg/L	Moderately toxic	3113667
		X12719657	72-h EC_{50} (all endpoints) > 8.5 mg/L 72-h NOEC ≥ 8.5 mg/L 96-h EC_{50} (all endpoints) > 8.1 mg/L 96-h NOEC ≥ 8.1 mg/L	Practically non-toxic up to 8.5 mg/L	3113668
	72-h Acute	(end-use product, also containing pyraclostrobin)	72-h EC_{50} (yield) = 0.0686 mg a.i./L 72-h NOEC = 0.0270 mg a.i./L	Very highly toxic	3237008
Vascular plants (*Lemna gibba*)	7-d Growth inhibition	Florylpicoxamid	IC_{50} (biomass yield)= 0.955 mg a.i./L NOEC = 0.148 mg a.i./L	Highly toxic	3113671
Marine organisms					
Saltwater mysid	96-h Acute	Florylpicoxamid	LC_{50} = 0.00995 mg a.i./L	Very highly toxic	3163752

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[1]	PMRA#
(*Americamysis bahia*)			NOEC = 0.00555 mg a.i./L		
		X12485649	LC_{50} = 0.0040 mg/L NOEC = 0.0026 mg/L	Very highly toxic	3163753
	28-d Chronic	Florylpicoxamid	NOEC (reproduction) = 0.00154 mg a.i./L	-	3163757
		X12485649	NOEC (reproduction) = 0.00072 mg/L	-	3163755
Eastern oyster (*Crassotrea virginica*)	96-h Acute	Florylpicoxamid	EC_{50} = 0.478 mg a.i./L NOEC = 0.308 mg a.i./L	Highly toxic	3163754
Sheepshead minnow (*Cyprinodon variegatus*)	96-h Acute	Florylpicoxamid	LC_{50} = 0.00761 mg a.i./L NOEC = 0.00315 mg a.i./L	Very highly toxic	3163758
	36-d Early-life stage	Florylpicoxamid	NOEC = 0.000802 mg a.i./L	-	3163761
Marine alga	Study not submitted				

1 USEPA classification, where applicable

2 The data requirements for pollinators have been met; however, (1) the adult bee acute oral/contact tests were conducted as limit tests, (2) the larval toxicity test was a single dose study rather repeated dose (which is preferred but not required), and (3) the chronic adult bee toxic study had dilution errors at the three lowest concentrations, resulting in treatment concentrations below the LOQ. While no adverse effects were observed at the two highest concentrations tested in the chronic study, data for the lower concentrations are not available. Additional data may be required for future use expansions to pollinator attractive crops.

3 The ten species are ryegrass (*Lolium perenne* cultivar Trystar*)*, oats (*Avena sativa* cultivar Firth), corn (*Zea mays* cultivar LG30179), onion (*Allium cepa* cultivar Hytech)**,** soybean (*Glycine max* cultivar Siverka), oilseed rape (*Brassica napus* cultivar Django), sugar beet (*Beta vulgaris* cultivar Degas), carrot (*Daucus carota* cultivar Fidra), sunflower (*Helianthus annus* cultivar Elite Sun) and tomato (*Lycopersicon esculentum* cultivar Shirley).

4 AUC = area under the growth curve

Table 26 Screening level risk assessment for non-target terrestrial organisms (with the exception of birds and mammals)

Organism	Test substance	Exposure type	EEC[1]	Endpoint value	UF	Effects metric	RQ[2]	LOC	LOC exceeded?
Invertebrates									
Earthworm, *E. Andrei*	Florylpicoxamid	14-d Acute	0.067 mg a.i./kg soil dw	LC_{50} > 6.5 mg a.i./kg soil dw	2	> 3.25 mg a.i./kg soil dw	< 0.021	1	No
	Florylpicoxamid	56-d Chronic	0.067 mg a.i./kg soil dw	NOEC ≥ 65.3 mg a.i./kg soil dw	1	≥ 65.3 mg a.i./kg soil dw	≤ 0.001	1	No
	X12485649	56-d Chronic	0.30 mg/kg soil dw	NOEC ≥ 65.3 mg/kg soil dw	1	≥ 65.3 mg/kg soil dw	≤ 0.005	1	No
	X12485631	56-d Chronic	0.16 mg/kg soil dw	NOEC = 36.3 mg/kg soil dw	1	36.3 mg/kg soil dw	0.004	1	No
Bee, *A. mellifera* L.	Florylpicoxamid	48-h Acute Oral	4.29 µg a.i./bee	LD_{50} > 109.2 µg a.i./bee	1	> 109.2 µg a.i./bee	< 0.039	0.4	No
		48-h Acute Contact	0.36 µg a.i./bee	LD_{50} > 100 µg a.i./bee	1	> 100 µg a.i./bee	< 0.004	0.4	No
		3-d Brood	1.82 µg a.i./bee	LD_{50} = 32.7 µg a.i./larva	1	32.7 µg a.i./larva	0.056	0.4	No
		10-d-Chronic Oral	4.29 µg a.i./bee	NOEDD ≥ 13.4 µg a.i./bee/day	1	≥ 13.4 µg a.i./bee/day	≤ 0.32	0.4	No
Predatory arthropod, *T. pyri*	GF-3840	Contact on-field (glass plate)	196 g a.i./ha	LR_{50} = 55.34 g a.i./ha	1	55.34 g a.i./ha	**3.55**	2[3]	**Yes**
		Contact – off-field (6 % drift)	11.8 g a.i./ha				0.2	2[3]	No
		Contact – off-field (23% drift)	45.2 g a.i./ha				0.8	2[3]	No
Parasitic arthropod, *A. rhopalosiphi*	GF-3840	Contact – on-field (glass plate)	196 g a.i./ha	LR_{50} = 5.01 g a.i./ha	1	5.01 g a.i./ha	**39.2**	2[3]	**Yes**

Organism	Test substance	Exposure type	EEC[1]	Endpoint value	UF	Effects metric	RQ[2]	LOC	LOC exceeded?
		Contact – off-field (6 % drift)	11.8 g a.i./ha				**2.35**	2[3]	**Yes**
		Contact – off-field (23% drift)	45.2 g a.i./ha				**9.02**	2[3]	**Yes**
Vascular plants									
Vascular plants	GF-3840	Seedling emergence (ten species)	150 g a.i./ha	ER_{25} >300 g a.i./ha	1	>300 g a.i./ha	0.50	1	No
		21d-Vegetative vigour (tomato)	196 g a.i./ha	ER_{25} = 134.08 g a.i./ha	1	134.08 g a.i./ha	**1.47**	1	**Yes**

Bolded Risk Quotients exceed the Level of Concern.

1 See Table 24 for a description of how the EECs were calculated.

2 RQs were calculated using Microsoft Excel. Values in this table have been rounded for presentation which may result in minor discrepencies in RQs calculated based on the values presented in this table.

3 A LOC of 2 is used for spray applications on glass plates for *T. pyri* and *A. rhopalosiphi*, based on an extensive empirical comparison of the risk quotients and known acceptable effects from field and semi-field studies for the two indicator species. Significant ecological effects of pest control products on non-target arthropod populations are not expected at a risk quotient of 2 or less.

Table 27 Refined risk assessment for beneficial arthropods and non-target terrestrial plants

Organism	Test substance	Exposure type	EEC[1]	Endpoint value	UF	Effects metric	RQ[2]	LOC	LOC exceeded ?
Invertebrates									
Predatory arthropod, *T. pyri*	GF-3840	Contact – on-field (leaf disc)	196 g a.i./ha	LR_{50} = 213.4 g a.i./ha	1	213.4	0.92	1[3]	No
				ER_{50} = 60.5 g a.i./ha	1	60.5	**3.25**	1[3]	**Yes**
		On-field (2 × 150 g.a.i/ha with a 7 day	177 g a.i./ha	ER_{50} = 60.5 g a.i./ha	1	60.5	**2.92**	1[3]	**Yes**

Organism	Test substance	Exposure type	EEC[1]	Endpoint value	UF	Effects metric	RQ[2]	LOC	LOC exceeded ?
		re-application interval), F_{int} of 0.9 for sugar beet							
		On-field, turf (5 × 150 g a.i./ha with a 14-day re-application interval), F_{int} of 0.4 for grass	66.4 g a.i./ha	ER_{50} = 60.5 g a.i./ha	1	60.5	**1.10**	1[3]	**Yes**
		On-field: GF-4017 (1 × 50 g a.i./ha)	50 g a.i./ha	ER_{50} = 60.5 g a.i./ha	1	60.5	0.83	1[3]	No
Parasitic arthropod, *A. rhopalopsiphi*	GF-3840	Contact – on-field (barley seedlings)	196 g a.i./ha	LR_{50} = 296.8 g a.i./ha	1	296.8 g a.i./ha	0.66	1[3]	No
				ER_{50} > 300 g a.i./ha	1	300 g a.i./ha	< 0.65	1[3]	No
		Contact – off-field, 6% spray drift (barley seedlings)	11.79 g a.i./ha	LR_{50} = 296.8 g a.i./ha	1	296.8 g a.i./ha	0.04	1[3]	No
				ER_{50} > 300 g a.i./ha	1	300 g a.i./ha	0.04	1[3]	No
		Contact – off-field, 23% spray drift (barley seedlings)	45.19 g a.i./ha	LR_{50} = 296.8 g a.i./ha	1	296.8 g a.i./ha	0.15	1[3]	No
				ER_{50} > 300 g a.i./ha	1	300 g a.i./ha	0.15	1[3]	No
Vascular plants									
Vascular plant	GF-3840	21d-Vegetative vigour (6% spray drift)	11.8 g a.i./ha	ER_{25} = 134.08 g a.i./ha	1	134.08 g a.i./ha	0.09	1	No

Organism	Test substance	Exposure type	EEC[1]	Endpoint value	UF	Effects metric	RQ[2]	LOC	LOC exceeded ?
		21d-Vegetative vigour (23% spray drift)	45.2 g a.i./ha	ER_{25} = 134.08 g a.i./ha	1	134.08 g a.i./ha	0.34	1	No
		21d-Vegetative vigour (GF-4017)	50 g a.i./ha	ER_{25} = 134.08 g a.i./ha	1	134.08 g a.i./ha	0.37	1	No

Bolded Risk Quotients exceed the Level of Concern.

1 See Table 24 for a description of how the EECs were calculated.

2 RQs were calculated using Microsoft Excel. Values in this table have been rounded for presentation which may result in minor discrepencies in RQs calculated based on the values presented in this table.

3 A LOC of 1 is used for a refined risk assessment for *T. pyri* and *A. rhopalosiphi*, as opposed to a LOC of 2 in the screening level risk assessment.

Table 28 Screening level risk assessment for birds and mammals

Organism	Effects metric (mg a.i./kg bw/d)[1]	Feeding guild (food item)	EDE (mg a.i./kg bw)[2]	RQ[3]	LOC	LOC exceeded?
Small bird (0.02 kg)						
Acute	225	Insectivore	15.99	0.07	1	No
Reproduction	83.0	Insectivore	15.99	0.19	1	No
Medium-sized bird (0.1 kg)						
Acute	225	Insectivore	12.48	0.06	1	No
Reproduction	83.0	Insectivore	12.48	0.15	1	No
Large-sized bird (1 kg)						
Acute	225	Herbivore (short grass)	8.06	0.04	1	No
Reproduction	83.0	Herbivore (short grass)	8.06	0.10	1	No
Small Mammal (0.015 kg)						
Acute	200	Insectivore	9.20	0.05	1	No
Reproduction	9.58	Insectivore	9.20	0.96	1	No
Medium-sized Mammal (0.035 kg)						
Acute	200	Herbivore (short grass)	17.84	0.09	1	No

Organism	Effects metric (mg a.i./kg bw/d)[1]	Feeding guild (food item)	EDE (mg a.i./kg bw)[2]	RQ[3]	LOC	LOC exceeded?
Reproduction	9.58	Herbivore (short grass)	17.84	**1.86**	1	**Yes**
Large-sized Mammal (1 kg)						
Acute	200	Herbivore (short grass)	9.53	0.05	1	No
Reproduction	9.58	Herbivore (short grass)	9.53	0.995	1	No

Bolded Risk Quotients exceed the Level of Concern.

(1) Uncertainty factors of 10 and 1 were applied to the acute oral and reproduction endpoints, respectively.

(2) EDE = Estimated dietary exposure; is calculated using the following formula: (FIR/bw) × EEC, where:

FIR: Food Ingestion Rate (Nagy, 1987). For generic birds with body weight less than or equal to 200 g, the "passerine" equation was used; for generic birds with body weight greater than 200 g, the "all birds" equation was used:

Passerine Equation (body weight < or =200 g): FIR (g dry weight/day) = 0.398 (bw in g) $^{0.850}$

All birds Equation (body weight > 200 g): FIR (g dry weight/day) = 0.648 (bw in g) $^{0.651}$.

For mammals, the "all mammals" equation was used: FIR (g dry weight/day) = 0.235 (bw in g) $^{0.822}$

EEC: Concentration of pesticide on food item based on Hoerger and Kenaga (1972) and Kenaga (1973) and modified according to Fletcher et al. (1994). At the screening level, relevant food items representing the most conservative EEC for each feeding guild are used.

The EECs for birds and mammals were calculated based on 2 × 150 g a.i./ha with a 7-day re-application interval and a foliar half-life of 4.14 days.

(3) RQs were calculated using Microsoft Excel. Values in this table have been rounded for presentation which may result in minor discrepencies in RQs calculated based on the values presented in this table.

Table 29 Refined risk assessment for medium-sized mammals

Exposure Type	Effects metric (mg a.i./kg bw/d)	Feeding guild (food item)	Maximum nomogram residues		Mean nomogram residues	
			EDE (mg a.i./ kg bw)[1]	RQ[2]	EDE (mg a.i./kg bw)[1]	RQ[2]
On-field						
Medium-size mammal (0.035 kg)						
Reproduction	9.58	Insectivore	8.06	0.84	5.57	0.58
		Granivore (grain and seeds)	1.25	0.13	0.60	0.062
		Frugivore (fruit)	2.50	0.26	1.19	0.12
		Herbivore (short grass)	17.8	**1.86**	6.34	0.66
		Herbivore (long grass)	10.9	**1.13**	3.56	0.37
		Herbivore (broad leaf plants)	16.5	**1.72**	5.46	0.57
Off-field (field sprayer: 6% spray drift)						
Medium-size mammal (0.035 kg)						
Reproduction	9.58	Insectivore	0.48	0.05	0.33	0.04
		Granivore (grain and seeds)	0.08	0.01	0.04	0.004
		Frugivore (fruit)	0.15	0.02	0.07	0.007
		Herbivore (short grass)	1.07	0.11	0.38	0.04
		Herbivore (long grass)	0.65	0.07	0.21	0.02
		Herbivore (broad leaf plants)	0.99	0.10	0.33	0.03
Off-field (aerial application: 23% spray drift)						
Medium-size mammal (0.035 kg)						
Reproduction	9.58	Insectivore	1.85	0.19	1.28	0.13
		Granivore (grain and seeds)	0.3	0.030	0.14	0.014
		Frugivore (fruit)	0.6	0.060	0.27	0.029
		Herbivore (short grass)	4.10	0.43	1.46	0.15
		Herbivore (long grass)	2.51	0.26	0.82	0.085
		Herbivore (broad leaf plants)	3.80	0.40	1.25	0.13
		Herbivore (broad leaf plants)	2.03	0.21	0.67	0.07

Bolded Risk Quotients exceed the Level of Concern.

[1] The EDEs for birds and mammals were calculated based on 2 × 150 g a.i./ha with a 7-day re-application interval and a foliar half-life of 4.14 days.

[2] RQs were calculated using Microsoft Excel. Values in this table have been rounded for presentation which may result in minor discrepencies in RQs calculated based on the values presented in this table.

Table 30 Screening level risk assessment for non-target aquatic organisms

Organism	Exposure	Test substance	EEC[1]	Endpoint value[2]	UF	Effects metric	RQ[3]	Exeeded the LOC of 1
Freshwater organisms								
Daphnia magna	48-h Acute	Florylpicoxamid	0.019 mg a.i./L	EC_{50} = 0.0590 mg a.i./L	2	0.0295 mg a.i./L	0.644	No
		X12485649	0.086 mg/L	EC_{50} = 0.013 mg/L	2	0.0065 mg/L	**13.2**	**Yes**
		X12485473	0.044 mg/L	EC_{50} > 11 mg/L	2	> 5.5 mg/L	0.008	No
		X12485631	0.045 mg/L	EC_{50} > 10 mg/L	2	> 5 mg/L	0.009	No
		X12719657	0.081 mg/L	EC_{50} > 10 mg/L	2	> 5 mg/L	0.016	No
		GF-4017 (end-use product, also containing pyraclostrobin)	0.006 mg a.i./L	EC_{50} = 0.00358 mg a.i./L	2	0.00179 mg a.i./L	**3.52**	**Yes**
	21-d Chronic	Florylpicoxamid	0.019 mg a.i./L	NOEC (reproduction) = 0.00723 mg a.i./L	1	0.00723 mg a.i./L	**2.63**	**Yes**
		X12485649	0.086 mg/L	NOEC (reproduction and growth) = 0.0017 mg/L	1	0.0017 mg/L	**50.6**	**Yes**
Rainbow trout (*Oncorhynchus mykiss*)	96-h Acute	Florylpicoxamid	0.019 mg a.i./L	LC_{50} = 0.011 mg a.i./L	10	0.0011 mg a.i./L	**17.3**	**Yes**
		X12485649	0.086 mg/L	LC_{50} = 0.016 mg/L	10	0.0016 mg/L	**53.8**	**Yes**
		X12485473	0.044 mg/L	LC_{50} > 11 mg/L	10	> 1.1 mg/L	< 0.04	No
		X12485631	0.045 mg/L	LC_{50} = 6.6 mg/L	10	0.66 mg/L	0.07	No
		X125719657	0.081 mg/L	LC_{50} > 9.6 mg/L	10	> 0.96 mg/L	< 0.08	No
		GF-4017 (end-use product, also containing pyraclostrobin)	0.006 mg a.i./L	LC_{50} = 0.00078 mg a.i./L	10	0.000078 mg a.i/L	**80.8**	**Yes**
Fathead minnow (*Pimephales promelas*)	33-d Early-life stage	Florylpicoxamid	0.019 mg a.i./L	NOEC = 0.00342 mg a.i./L	1	0.00342 mg a.i./L	**5.56**	**Yes**
		X12485649	0.086 mg/L	NOEC = 0.0011 mg/L	1	0.0011 mg/L	**78.2**	**Yes**

Organism	Exposure	Test substance	EEC[(1)]	Endpoint value[(2)]	UF	Effects metric	RQ[(3)]	Exeeded the LOC of 1
Amphibians (fish endpoints used as a surrogate)	96-h Acute (rainbow trout surrogate)	Florylpicoxamid	0.10 mg a.i./L	LC_{50} = 0.011 mg a.i./L	10	0.0011 mg a.i./L	**92.7**	**Yes**
		X12485649	0.46 mg/L	LC_{50} = 0.016 mg/L	10	0.0016 mg/L	**288**	**Yes**
		X12485473	0.23 mg/L	LC_{50} > 11 mg/L	10	> 1.1 mg/L	< 0.21	No
		X12485631	0.24 mg/L	LC_{50} = 6.6 mg/L	10	0.66 mg/L	0.37	No
		X125719657	0.43 mg/L	LC_{50} > 9.6 mg/L	10	> 0.96 mg/L	< 0.45	No
		GF-4017 (end-use product, also containing pyraclostrobin)	0.033 mg a.i./L	LC_{50} = 0.00078 mg a.i./L	10	0.000078 mg a.i/L	**423**	**Yes**
	33-d Early-life stage (fathead minnow surrogate)	Florylpicoxamid	0.10 mg a.i./L	NOEC = 0.00342 mg a.i./L	1	0.00342 mg a.i./L	**29.8**	**Yes**
		X12485649	0.46 mg/L	NOEC = 0.0011 mg/L	1	0.0011 mg/L	**417**	**Yes**
Freshwater alga (*Rhaphidoceli s subcapitata*)	96-h Acute	Florylpicoxamid	0.019 mg a.i./L	EC_{50} = 0.103 mg a.i./L	2	0.0515 mg a.i./L	0.37	No
		X12485649	0.086 mg/L	EC_{50} > 0.70 mg/L	2	> 0.35 mg/L	<0.25	No
		X12485473	0.044 mg/L	EC_{50} > 10 mg/L	2	> 5 mg/L	<0.01	No
		X12485631	0.045 mg/L	EC_{50} = 1.6 mg/L	2	0.80 mg/L	0.06	No
		X12719657	0.081 mg/L	EC_{50} > 8.5 mg/L	2	> 4.25 mg/L	<0.02	No
		GF-4017 (end-use product, also containing pyraclostrobin)	0.006 mg a.i./L	EC_{50} = 0.0686 mg a.i./L	2	0.0343 mg a.i./L	0.18	No
Vascular plant	7-d Growth inhibition	Florylpicoxamid	0.019 mg a.i./L	IC_{50} = 0.955 mg a.i./L	2	0.4775 mg a.i./L	0.04	No

Organism	Exposure	Test substance	EEC[1]	Endpoint value[2]	UF	Effects metric	RQ[3]	Exeeded the LOC of 1
Marine organisms								
Saltwater mysid (*Americamysis bahia*)	96-h Acute	Florylpicoxamid	0.019 mg a.i./L	LC_{50} = 0.00995 mg a.i./L	2	0.00498 mg a.i./L	**3.82**	**Yes**
		X12485649	0.086 mg/L	LC_{50} = 0.0040 mg/L	2	0.0020 mg/L	**43.0**	**Yes**
	28-d Chronic	Florylpicoxamid	0.019 mg a.i./L	NOEC (reproduction) = 0.00154 mg a.i./L	1	0.00154 mg a.i./L	**26.1**	**Yes**
		X12485649	0.086 mg/L	NOEC (reproduction) = 0.00072 mg/L	1	0.00072 mg/L	**63.1**	**Yes**
Eastern oyster (*Crassotrea virginica*)	96-h Acute	Florylpicoxamid	0.019 mg a.i./L	EC_{50} = 0.478 mg a.i./L	2	0.239 mg/L	0.08	No
Sheepshead minnow (*Cyprinodon variegatus*)	96-h Acute	Florylpicoxamid	0.019 mg a.i./L	LC_{50} = 0.00761 mg a.i./L	10	0.000761 mg a.i./L	**25.0**	**Yes**
	36-d Early-life stage	Florylpicoxamid	0.019 mg a.i./L	NOEC = 0.000802 mg a.i./L	1	0.000802 mg a.i./L	**23.7**	**Yes**
Marine alga	Study not submitted							

Bolded Risk Quotients exceed the Level of Concern.

(1) See Table 24 for a description of how the EECs were calculated.

(2) The most sensitive acute endpoint (for example, EC_{50}/LC_{50}) was used when multiple values were available for a species.

(3) RQs were calculated using Microsoft Excel. Values in this table have been rounded for presentation which may result in minor discrepencies in RQs calculated based on the values presented in this table.

Table 31 Refined risk assessment for non-target aquatic organisms

Organism	Exposure	Test substance	EEC[1]	Endpoint value	UF	Effects metric	RQ[2]	Exceeded the LOC of 1?
6% Spray drift to freshwater environments (Field sprayer application)								
Daphnia magna	48-h Acute	X12485649	0.0052 mg/L	EC_{50} = 0.013 mg/L	2	0.0065 mg/L	0.79	No
		GF-4017 (end-use product, also containing pyraclostrobin)	0.00038 mg a.i./L	EC_{50} = 0.00358 mg/L	2	0.00179 mg a.i./L	0.21	No

Organism	Exposure	Test substance	EEC[1]	Endpoint value	UF	Effects metric	RQ[2]	Exceeded the LOC of 1?
	21-d Chronic	Florylpicoxamid	0.0011 mg a.i./L	NOEC (reproduction) = 0.00723 mg a.i./L	1	0.00723 mg a.i./L	0.16	No
		X12485649	0.0052 mg/L	NOEC (reproduction and growth) = 0.0017 mg/L	1	0.0017 mg/L	**3.04**	**Yes**
Rainbow trout (*Oncorhynchus mykiss*)	96-h Acute	Florylpicoxamid	0.0011 mg a.i./L	LC_{50} = 0.011 mg a.i./L	10	0.0011 mg a.i./L	**1.04**	**Yes**
		X12485649	0.0052 mg/L	LC_{50} = 0.016 mg/L	10	0.0016 mg/L	**3.23**	**Yes**
		GF-4017 (end-use product, also containing pyraclostrobin)	0.00038 mg a.i./L	LC_{50} = 0.00078 mg a.i./L	10	0.000078 mg a.i/L	**4.85**	**Yes**
Fathead minnow (*Pimephales promelas*)	33-d Early-life stage	Florylpicoxamid	0.0011 mg a.i./L	NOEC = 0.00342 mg a.i./L	1	0.00342 mg a.i./L	0.33	Yes
		X12485649	0.0052 mg/L	NOEC = 0.0011 mg/L	1	0.0011 mg/L	**4.69**	**Yes**
Amphibians (fish endpoints used as a surrogate)	96-h Acute (rainbow trout surrogate)	Florylpicoxamid	0.0061 mg a.i./L	LC_{50} = 0.011 mg a.i./L	10	0.0011 mg a.i./L	**5.56**	**Yes**
		X12485649	0.028 mg/L	LC_{50} = 0.016 mg/L	10	0.0016 mg/L	**17.2**	**Yes**
		GF-4017 (end-use product, also containing pyraclostrobin)	0.0020 mg a.i./L	LC_{50} = 0.00078 mg a.i./L	10	0.000078 mg a.i/L	**25.4**	**Yes**
	33-d Early-life stage (fathead minnow surrogate)	Florylpicoxamid	0.0061 mg a.i./L	NOEC = 0.00342 mg a.i./L	1	0.00342 mg a.i./L	**1.79**	**Yes**
		X12485649	0.028 mg/L	NOEC = 0.0011 mg/L	1	0.0011 mg/L	**25.0**	**Yes**

Organism	Exposure	Test substance	EEC[1]	Endpoint value	UF	Effects metric	RQ[2]	Exceeded the LOC of 1?
23% Spray drift to freshwater environments (Aerial application)[3]								
Daphnia magna	48-h Acute	X12485649	0.020 mg/L	EC_{50} = 0.013 mg/L	2	0.0065 mg/L	**3.05**	**Yes**
	21-d Chronic	Florylpicoxamid	0.004 mg a.i./L	NOEC (reproduction) = 0.00723 mg a.i./L	1	0.00723 mg a.i./L	0.60	No
		X12485649	0.020 mg/L	NOEC (reproduction and growth) = 0.0017 mg/L	1	0.0017 mg/L	**11.6**	**Yes**
Rainbow trout (*Oncorhynchus mykiss*)	96-h Acute	Florylpicoxamid	0.004 mg a.i./L	LC_{50} = 0.011 mg a.i./L	10	0.0011 mg a.i./L	**3.97**	**Yes**
		X12485649	0.020 mg/L	LC_{50} = 0.016 mg/L	10	0.0016 mg/L	**12.4**	**Yes**
Fathead minnow (*Pimephales promelas*)	33-d Early-life stage	Florylpicoxamid	0.0044 mg a.i./L	NOEC = 0.00342 mg a.i./L	1	0.00342 mg a.i./L	**1.28**	**Yes**
		X12485649	0.020 mg/L	NOEC = 0.0011 mg/L	1	0.0011 mg/L	**18.6**	**Yes**
Amphibians (fish endpoints used as a surrogate)	96-h Acute (rainbow trout surrogate)	Florylpicoxamid	0.023 mg a.i./L	LC_{50} = 0.011 mg a.i./L	10	0.0011 mg a.i./L	**21.3**	**Yes**
		X12485649	0.11 mg/L	LC_{50} = 0.016 mg/L	10	0.0016 mg/L	**66.0**	**Yes**
	33-d Early-life stage (fathead minnow surrogate)	Florylpicoxamid	0.023 mg a.i./L	NOEC = 0.00342 mg a.i./L	1	0.00342 mg a.i./L	**6.86**	**Yes**
		X12485649	0.11 mg/L	NOEC = 0.0011 mg/L	1	0.0011 mg/L	**96.0**	**Yes**
6% Spray drift to estuarine/Marine environments (Field sprayer application)								
Saltwater mysid (*Americamysis bahia*)	96-h Acute	Florylpicoxamid	0.0011 mg a.i./L	LC_{50} = 0.00995 mg a.i./L	2	0.00498 mg a.i./L	0.23	Yes
		X12485649	0.0010 mg/L	LC_{50} = 0.0040 mg/L	2	0.0020 mg/L	0.52	Yes
	28-d Chronic	Florylpicoxamid	0.0011 mg a.i./L	NOEC (reproduction) = 0.00154 mg a.i./L	1	0.00154 mg a.i./L	0.73	Yes
		X12485649	0.0010 mg/L	NOEC (reproduction) = 0.00072 mg/L	1	0.00072 mg/L	**1.43**	**Yes**

Organism	Exposure	Test substance	EEC[1]	Endpoint value	UF	Effects metric	RQ[2]	Exceeded the LOC of 1?
Sheepshead minnow (*Cyprinodon variegatus*)	96-h Acute	Florylpicoxamid	0.0011 mg a.i./L	LC_{50} = 0.00761 mg a.i./L	10	0.000761 mg a.i./L	**1.48**	**Yes**
	36-d Early-life stage	Florylpicoxamid	0.0011 mg a.i./L	NOEC = 0.000802 mg a.i./L	1	0.000802 mg a.i./L	**1.40**	**Yes**
23% Spray drift to estuarine/Marine environments (Aerial application)[3]								
Saltwater mysid (*Americamysis bahia*)	96-h Acute	Florylpicoxamid	0.0043 mg a.i./L	LC_{50} = 0.00995 mg a.i./L	2	0.00498 mg a.i./L	0.87	No
		X12485649	0.0040 mg/L	LC_{50} = 0.0040 mg/L	2	0.0020 mg/L	**1.98**	**Yes**
	28-d Chronic	Florylpicoxamid	0.0043 mg a.i./L	NOEC (reproduction) = 0.00154 mg a.i./L	1	0.00154 mg a.i./L	**2.80**	**Yes**
		X12485649	0.0040 mg/L	NOEC (reproduction) = 0.00072 mg/L	1	0.00072 mg/L	**5.50**	**Yes**
Sheepshead minnow (*Cy prinodon variegatus*)	96-h Acute	Florylpicoxamid	0.0043 mg a.i./L	LC_{50} = 0.00761 mg a.i./L	10	0.000761 mg a.i./L	**5.67**	**Yes**
	36-d Early-life stage	Florylpicoxamid	0.0043 mg a.i./L	NOEC = 0.000802 mg a.i./L	1	0.000802 mg a.i./L	**5.38**	**Yes**
Runoff (5 × 150 g a.i./ha, 14-day re-application interval) – Freshwater organisms[4]								
Daphnia magna	48-h Acute	X12485649	0.0088 mg/L	EC_{50} = 0.013 mg/L	2	0.0065 mg/L	**1.35**	**Yes**
	21-d Chronic	X12485649	0.0075 mg/L	NOEC (reproduction and growth) = 0.0017 mg/L	1	0.0017 mg/L	**4.41**	**Yes**
Rainbow trout (*Oncorhynchus mykiss*)	96-h Acute	Florylpicoxamid	0.0088 mg a.i./L	LC_{50} = 0.011 mg a.i./L	10	0.0011 mg a.i./L	**8.00**	**Yes**
Fathead minnow (*Pimephales promelas*)	33-d Early-life stage	X12485649	0.0075 mg/L	NOEC = 0.0011 mg/L	1	0.0011 mg/L	**6.82**	**Yes**
Amphibians (fish endpoints	96-h Acute (rainbow trout surrogate)	Florylpicoxamid	0.024 mg a.i./L	LC_{50} = 0.011 mg a.i./L	10	0.0011 mg a.i./L	**21.8**	**Yes**

Organism	Exposure	Test substance	EEC[1]	Endpoint value	UF	Effects metric	RQ[2]	Exceeded the LOC of 1?
used as a surrogate)								
	33-d Early-life stage (fathead minnow surrogate)	X12485649	0.0088 mg/L	NOEC = 0.0011 mg/L	1	0.0011 mg/L	**8.00**	**Yes**
Runoff (5 × 150 g a.i./ha, 14-day re-application interval) – Estuarine/Marine organisms[4]								
Saltwater mysid (*Americamysis bahia*)	96-h Acute	X12485649	0.0088 mg/L	LC_{50} = 0.0040 mg/L	2	0.0020 mg/L	**4.40**	**Yes**
	28-d Chronic	X12485649	0.0075 mg/L	NOEC (reproduction) = 0.00072 mg/L	1	0.00072 mg/L	**10.4**	**Yes**
Sheepshead minnow (*Cyprinodon variegatus*)	96-h Acute	Florylpicoxamid	0.0088 mg a.i./L	LC_{50} = 0.00761 mg a.i./L	10	0.000761 mg a.i./L	**11.6**	**Yes**
	36-d Early-life stage	Florylpicoxamid	0.0075 mg a.i./L	NOEC = 0.000802 mg a.i./L	1	0.000802 mg a.i./L	**9.35**	**Yes**
Runoff (2 × 50 g a.i./ha,14-day re-application rate) – Freshwater organisms[4]								
Daphnia magna	48-h Acute	X12485649	0.0040 mg/L	EC_{50} = 0.013 mg/L	2	0.0065 mg/L	0.62	No
	21-d Chronic	X12485649	0.0037 mg/L	NOEC (reproduction and growth) = 0.0017 mg/L	1	0.0017 mg/L	**2.18**	**Yes**
Rainbow trout (*Oncorhynchus mykiss*)	96-h Acute	Florylpicoxamid	0.0040 mg a.i./L	LC_{50} = 0.011 mg a.i./L	10	0.0011 mg a.i./L	**3.64**	**Yes**
Fathead minnow (*Pimephales promelas*)	33-d Early-life stage	X12485649	0.0037 mg/L	NOEC = 0.0011 mg/L	1	0.0011 mg/L	**3.36**	**Yes**
Amphibians (fish endpoints used as a surrogate)	96-h Acute (rainbow trout surrogate)	Florylpicoxamid	0.0077 mg a.i./L	LC_{50} = 0.011 mg a.i./L	10	0.0011 mg a.i./L	**7.00**	**Yes**
	33-d Early-life stage (fathead	X12485649	0.0040 mg/L	NOEC = 0.0011 mg/L	1	0.0011 mg/L	**3.64**	**Yes**

Organism	Exposure	Test substance	EEC[1]	Endpoint value	UF	Effects metric	RQ[2]	Exceeded the LOC of 1?
	minnow surrogate)							
Runoff (2 × 50 g a.i./ha, 14-day re-application interval) – Estuarine/marine Organisms[4]								
Saltwater mysid (*Americamysis bahia*)	96-h Acute	X12485649	0.0040 mg/L	LC_{50} = 0.0040 mg/L	2	0.0020 mg/L	**2.00**	**Yes**
	28-d Chronic	X12485649	0.0040 mg/L	NOEC (reproduction) = 0.00072 mg/L	1	0.00072 mg/L	**5.14**	**Yes**
Sheepshead minnow (*Cyprinodon variegatus*)	96-h Acute	Florylpicoxamid	0.0040 mg a.i./L	LC_{50} = 0.00761 mg a.i./L	10	0.000761 mg a.i./L	**5.26**	**Yes**
	36-d Early-life stage	Florylpicoxamid	0.0037 mg a.i./L	NOEC = 0.000802 mg a.i./L	1	0.000802 mg a.i./L	**4.61**	**Yes**

Bolded Risk Quotients exceed the Level of Concern.

(1) See Table 24 for a description of how EECs were calculated.

(2) RQs were calculated using Microsoft Excel. Values in this table have been rounded for presentation which may result in minor discrepencies in RQs calculated based on the values presented in this table.

(3) Endpoints for GF-4017 were not considered for the 23% spray drift refinement as aerial application is not proposed for this product.

(4) For brevity, only the most sensitive endpoint between florylpicoxamid and X12485649 is reported for each taxa.

Table 32 List of supported use claims for GF-3840 fungicide

Supported uses
Wheat (spring, durum, winter): Control of septoria leaf spot (*Septoria tritici*) Rate: 0.5 L product/ha Application timing: At the first sign of disease, usually at the beginning of stem elongation followed by a second application no later than 50% head emergence. For one application per year, between just after flag leaf emergence up to 50% head emergence. Maximum number of applications: 2 per year Application interval: minimum of 14 days Application methods: ground or aerial spray equipment Spray volume: minimum of 100 L/ha for ground application and minimum of 50 L/ha for aerial application
Sugar beet Control of cercospora leafspot (*Cercospora beticola*) Rate: 1.0–1.5 L product/ha Application timing: preventively when conditions are favorable for disease development or based on a forecasting system. Maximum number of applications: 2 per year Application interval: minimum of 10 days Application method: ground spray equipment Spray volume: minimum of 100 L/ha
Canola Suppression of blackleg (*Leptosphaeria maculans*) Suppression of sclerotinia stem rot (*Sclerotinia sclerotiorum*) Rates: 1.5 L product/ha (blackleg); 1.0 L product/ha (sclerotinia stem rot) Application timing: preventatively at the 2 to 6-leaf (rosette) stage for blackleg and at 20–50% bloom for sclerotinia stem rot Maximum number of applications: 2 in total per year, 1 for each targeted disease Application interval: minimum of 7 days Application method: ground spray equipment Spray volume: minimum of 100 L/ha
Turf (established turf, golf course, sod farms only) Control of dollar spot (*Sclerotinia homeocarpa*) Rate: 1.5 L product/ha

Supported uses
Application timing: preventatively when environmental conditions are conducive to disease progression; after mowing or before mowing provided that a minimum of 12 hours has lapsed between application and mowing Maximum number of applications: 5 per year Application interval: minimum of 14 days Application methods: ground spray equipment Spray volume: minimum of 400 L/ha

Table 33 List of supported use claims for GF-4017 fungicide

Supported uses
Canola Suppression of blackleg (*Leptosphaeria maculans*) Rate: 0.8–1.0 L product/ha Application timing: preventatively at the 2 to 6-leaf (rosette) stage Maximum number of applications: 1 per year Application methods: ground spray equipment Spray volume: minimum of 100 L/ha
Lentil Control of anthracnose (*Colletotrichum truncatum*) Rate: 0.8–1.0 L product/ha Application timing: at the beginning of flowering, at the first sign of disease, or preventatively when agronomic or weather conditions are conducive to disease development. Maximum number of applications: 1 per year Application methods: ground spray equipment Spray volume: minimum of 100 L/ha

Table 34 Toxic Substances Management Policy considerations – Comparison to TSMP track 1 criteria

TSMP track 1 criterion	TSMP track 1 criterion value	Florylpicoxamid endpoints	X12485649 endpoints
CEPA toxic or CEPA toxic equivalent[(1)]	Yes	Yes	Yes

TSMP track 1 criterion	TSMP track 1 criterion value		Florylpicoxamid endpoints	X12485649 endpoints
Predominantly anthropogenic[2]	Yes		Yes	Yes
Persistence[3]:	Soil	Half-life ≥ 182 days	No, DT_{50} values are < 2 days	Yes, DT_{50} values range from 91.2 to 2113 days
	Water	Half-life ≥ 182 days	No, DT_{50} values are <2 days	No, DT_{50} values range from 9.61 to 29.4 days
	Sediment	Half-life ≥ 365 days	No, DT_{50} values are <9.41 days.	Yes, DT_{50} values range from 321 to 692 days.
	Air	Half-life ≥ 2 days or evidence of long range transport	No, volatilization is not an important route of dissipation. Long-range atmospheric transport is unlikely to occur based on the vapour pressure (<5×10^{-6} Pa) and Henry's law constants (<3.51×10^{-7}).	No, volatilization is not an important route of dissipation. Long-range atmospheric transport is unlikely to occur based on the vapour pressure (<5×10^{-9} Pa) and Henry's law constants (<3.80×10^{-11}).
Bioaccumulation[4]	Log $K_{ow} \geq 5$		No, log K_{ow} = 4.2 to 4.3	No, log K_{ow} = 3.4 to 3.5
	BCF ≥ 5000		No, BCF = 86.8 to 105[5]	No, BCF = 82.7 to 106
	BAF ≥ 5000		Not available	Not available
Is the chemical a TSMP Track 1 substance (all four criteria must be met)?			No, does not meet TSMP Track 1 criteria.	No, does not meet TSMP Track 1 criteria.

(1) All pesticides will be considered CEPA-toxic or CEPA toxic equivalent for the purpose of initially assessing a pesticide against the TSMP criteria. Assessment of the CEPA toxicity criteria may be refined if required (in other words, all other TSMP criteria are met).

(2) The policy considers a substance "predominantly anthropogenic" if, based on expert judgement, its concentration in the environment medium is largely due to human activity, rather than to natural sources or releases.

(3) If the pesticide and/or the transformation product(s) meet one persistence criterion identified for one media (soil, water, sediment or air) than the criterion for persistence is considered to be met.

(4) Field data (for example, BAFs) are preferred over laboratory data (for example, BCFs) which, in turn, are preferred over chemical properties (for example, log K_{ow}).

(5) The BCF is reflective of florylpicoxamid + X12485649 due to the instability of the parent compound.

Appendix II Supplemental maximum residue limit information – International situation and trade implications

Florylpicoxamid is an active ingredient that is concurrently being assessed in Canada and the United States for use on wheat, sugar beets, canola, and lentils. The MRLs proposed for florylpicoxamid in Canada are the same as the corresponding tolerances to be promulgated in the United States.

Once established, the American tolerances for florylpicoxamid will be listed in the Electronic Code of Federal Regulations, 40 CFR Part 180, by pesticide.

Currently, there are no Codex MRLs[10] listed for florylpicoxamid in or on any commodity on the Codex Alimentarius Pesticide Index website.

[10] The Codex Alimentarius Commission is an international organization under the auspices of the United Nations that develops international food standards, including MRLs.

References

A. List of studies/Information submitted by registrant

1.0 Chemistry

PMRA document number	Reference
3112018	2020, Compilation of Spectral Data for Significant Impurities in Florylpicoxamid, DACO: 2.13.2 CBI
3112019	2020, Group B: Physical and Chemical Properties of Florylpicoxamid, DACO: 2.14.1,2.14.10,2.14.11,2.14.12,2.14.13,2.14.14,2.14.2,2.14.3,2.14.4,2.14.5,2.14.6,2.14.7,2.14.8,2.14.9 CBI
3112020	2020, Group A - Product Identity and Composition, Description of Materials Used to Produce the Product, Description of Production Process, Discussion of Formation of Impurities, Preliminary Analysis, Certified Limits, and Enforcement Analytical Method for Florylpicoxamid, DACO: 2.10, 2.11, 2.12, 2.13,2.13.1,2.13.2,2.13.3,2.13.4,2.6,2.7,2.8,2.9,8.2.1 CBI
3113619	2020, Independent Laboratory Validation of XDE-659 and Metabolite in Soil, DACO: 8.2.2.1
3113620	2020, Method Validation for Determination of Residues of XDE-659 and X12485649 in Soil by LCMS/ MS, DACO: 8.2.2.1
3113622	2019, Validation of the Analytical Method for the Determination of XDE-659 and its Metabolites X12485649, X12485473 and X12485631 by HPLC-MS/MS in Drinking, Surface and Ground Waters, DACO: 8.2.2.3
3113623	2020, Method Validation of XDE-659 and its Metabolite in Water, DACO: 8.2.2.3
3113624	2020, Frozen Storage Stability of XDE-659 and its Metabolites X12485649, X12485473 and X12485631 in Water, DACO: 8.2.2.3
3173974	2019, Analysis of Product Samples for Active Ingredient and Impurities in Florylpicoxamid Technical Grade Active Ingredient_[Privacy Removed], DACO: 2.13.3 CBI
3173975	2019, Analysis of Product Samples for Active Ingredient and Impurities in Florylpicoxamid Technical Grade Active Ingredient_[Privacy Removed], DACO: 2.13.3 CBI
3173976	2019, Analysis of Product Samples for Active Ingredient and Impurities in Florylpicoxamid Technical Grade Active Ingredient_[Privacy Removed], DACO: 2.13.3 CBI
3173977	2019, Analysis of Product Samples for Active Ingredient and Impurities in Florylpicoxamid Technical Grade Active Ingredient_[Privacy Removed], DACO: 2.13.3 CBI
3113562	2020, Product Identification, GF-3840 Fungicide, DACO: 3.1.1, 3.1.2, 3.1.3, 3.1.4, 3.5.13, 3.5.14, 3.5.15, 3.5.4, 3.5.5 CBI

PMRA document number	Reference
3113563	2020, Group A-Product Identity and Composition, Description of Materials Used to Produce the Product, Description of Formulation Process, Discussion of Formation of Impurities, Certified Limits, and Enforcement Analytical Method for GF-3840, an End Use Product Containing Florylpicoxamid, DACO: 3.2 CBI
3113564	2020, Group B-Physical/Chemical Properties for GF-3840, A Liquid End Use Product Containing Florylpicoxamid, DACO: 3.5.11, 3.5.12, 3.5.13, 3.5.14, 3.5.15, 3.5.2, 3.5.6, 3.5.7, 3.5.8, 3.5.9 CBI
3113565	2019, GF-3840 Two Week 54°C Accelerated Storage Stability in PET, EVOH, and COEX Packaging and One Week 0°C Low Temperature Stability, DACO: 3.5.10,3.5.5 CBI
3113566	2019, GF-3840 Two-Week Accelerated Storage Stability and Packaging Corrosion Characteristics in Vented HDPE, DACO: 3.5.10,3.5.14,3.5.5 CBI
3113567	2019, Determination of Explosive Properties, Oxidising Properties, Auto-Ignition Temperature and Surface Tension of GF-3840, DACO: 3.5.12,3.5.8 CBI
3112171	2020, Product Identification, GF-4017 Fungicide, DACO: 3.1.1, 3.1.2, 3.1.3, 3.1.4, 3.5.13, 3.5.14, 3.5.15, 3.5.4, 3.5.5 CBI
3112172	2020, Group A-Product Identity and Composition, Description of Materials Used to Produce the Product, Description of Formulation Process, Discussion of Formation of Impurities, Certified Limits, and Enforcement Analytical Method for GF-4017, an End Use Product Containing Florylpicoxamid and Pyraclostrobin, DACO: 3.2.1,3.2.2,3.2.3,3.3.1,3.4.1 CBI
3112173	2020, Group B-Physical/Chemical Properties for GF-4017, A Liquid End Use Product Containing Florylpicoxamid and Pyraclostrobin, DACO: 3.5.11,3.5.12,3.5.13,3.5.14,3.5.15,3.5.2,3.5.6,3.5.7,3.5.8,3.5.9 CBI
3112174	2020, GF-4017 Two Week 54°C Accelerated Storage Stability in PET, EVOH and COEX Packaging and One Week 0°C Low Temperature Stability, DACO: 3.5.10,3.5.5 CBI
3112175	2020, GF-4017 Two Week Accelerated Storage Stability and Packaging Corrosion Characteristics in HDPE, DACO: 3.5.14,3.5.5 CBI
3341764	2018, Determination of Color, Physical State, Odor, Oxidizing and Reducing Action, Flammability, pH, Viscosity, and Density of GF-3840, an End Use Product Containing XDE-659, DACO: 3.5.11, 3.5.12, 3.5.13, 3.5.14, 3.5.15, 3.5.2, 3.5.6, 3.5.7, 3.5.8, 3.5.9 CBI
3341768	2019, Determination of Color, Physical State, Odor, Oxidizing and Reducing Action, Flammability, pH, Viscosity, and Density of GF-4017, an End Use Product Containing XDE-659, DACO: 3.5.1,3.5.11,3.5.2,3.5.3,3.5.6,3.5.7,3.5.9 CBI
3341769	2019, Determination of Relative Density, Surface Tension, Explosive Properties, Auto-Ignition Temperature And Oxidising Properties of GF-4017, DACO: 3.5.11,3.5.12,3.5.14,3.5.6 CBI

2.0 Human and animal health

PMRA document number	Reference
3112022	2015, Acute Oral Toxicity Study of XR-659 in Rats, DACO: 4.2.1
3112023	2016, Acute Dermal Toxicity Study of XR-659 in Rats, DACO: 4.2.2
3112024	2016, Acute Inhalation Toxicity Study of XR-659 in Rats, DACO: 4.2.3
3112025	2016, Acute Eye Irritation Study of XR-659 in Rabbits, DACO: 4.2.4
3112026	2016, Acute Dermal Irritation Study of XR-659 in Rabbits, DACO: 4.2.5
3112027	2016, Skin Sensitisation Study of XR-659 by Local Lymph Node Assay in Mice, DACO: 4.2.6
3112028	2019, XR-659: 90 Day Dietary Toxicity Study in Crl:CD1(ICR) Mice, DACO: 4.3.1
3112029	2018, XR-659: 90-Day Dietary Toxicity Study With a 28-Day Recovery in F344/DuCrl Rats with an Assessment of Immunotoxicity, Neurotoxicity, in vivo Genetic Toxicity, and Toxicokinetics, DACO: 4.3.1,4.5.7
3112030	2019, XDE-659: 28-Day Repeated Dose Dermal Toxicity Study in Rats, DACO: 4.3.5
3112031	2019, XDE-659: A 2-Year Dietary Chronic Toxicity/Carcinogenicity Study in CD Rats, DACO: 4.4.4
3112032	2019, XDE-659: A 18-Month Dietary Oncogenicity Study in Mice, DACO: 4.4.4
3112033	2019, Analytical Phase Report for XDE-659: Two-Generation Dietary Reproduction Toxicity Study in Crl:CD(SD) Rats, Amended report, DACO: 4.5.1
3112034	2019, XDE-659: Dietary Developmental Toxicity Study in Crl:CD(SD) Rats, DACO: 4.5.2
3112035	2019, XDE-659: Dietary Developmental Toxicity Study in NZW Rabbits, DACO: 4.5.3
3112036	2016, Bacterial reverse mutation test OFXR-659 using salmonella typhimurium, DACO: 4.5.4
3112037	2017, In vitro mammalian cell gene forward mutation test at the HPRT locus of the Chinese hamster ovary (CHO)-K1 cell line using XR-659, DACO: 4.5.5
3124187	2019, 4.3.2 170812 Current - XDE-659 A 13-Week oral (Capsule) Toxicity Study in Dogs (Revision), DACO: 4.3.2
3173978	2019, XDE-659: Two-Generation Dietary Reproduction Toxicity Study in Crl:CD(SD) Rats, DACO: 4.5.1
3219868	2018, 28-Day Dietary Toxicity Study in F344-DuCrl Rats v.2, DACO: 4.3.3
3219869	2018, A 28-Day Oral Toxicity Study in CD [Crl.CD(SD)] Rats v.3, DACO: 4.3.3
3219870	2021, Raw data selected HCD, 2-year rat studies, 9 apr 2021, DACO: 4.4.4
3219871	2018, Dietary Reproduction-Developmental Toxicity Screening Test in Crl.CD(SD) Rats (Rev v.4), DACO: 4.5.1
3303923	2020, Dietary Range-Finder Sin FF344-DuCrl Rats and F Crl.CD1(ICR) Mice (Revision), DACO: 4.4.3
3303924	2018, Validation of an LC-MS-MS Assay for XR-659, X12485649, and X12485473 in Rat Whole Blood and Urine v.1, DACO: 4.4.4
3303925	2020, Validation of an UHPLC-MS-MS Assay for XDE-659 and Four Metabolites in Rat K2EDTA Whole Blood fortified with 10% Trichloroacetic Acid in Acetonitrile and Long-Term Stability Assessment, DACO: 4.4.4
3303926	2019, Analytical Phase Report for XR-659. Dietary Crl.CD(SD) Rats v.3, DACO: 4.5.1
3303927	2018, XR-659. Developmental Toxicity Probe in Female Crl.CD(SD) Rats (Revision) v.4, DACO: 4.5.2
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