Registration Decision RD2023-06

Florylpicoxamid, GF-3840 Fungicide and Zetigo PRM Fungicide

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Under the authority of the *Pest Control Products Act*, pesticides must be assessed before they are sold or used in Canada in order to determine that they do not pose unacceptable risks to humans or the environment and have value when used according to the label instructions. The pre-market assessment considers available data and information[1] from pesticide registrants, published scientific reports, other governments, and international regulatory agencies, as well as comments if received during public consultations. Health Canada applies internationally accepted current risk assessment methods as well as risk management approaches and policies. More details, on the legislative requirements, risk assessment and risk management approach, are provided under the Evaluation Approach Section of this document.

Registration decision statement[2] for florylpicoxamid

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

The Proposed Registration Decision PRD2022-14, *Florylpicoxamid, GF-3840 Fungicide and GF-4017 Fungicide*, containing the detailed evaluation of the information submitted in support of this registration, underwent a 45 day consultation period ending on 18 December 2022. The evaluation found that, under the approved conditions of use, the health and environmental risks and the value of the pest control products are acceptable. Health Canada received comments (and information) relating to the health and environmental assessments during the public consultation period conducted in accordance with section 28 of the *Pest Control Products Act*.

Correction to PRD2022-14, Florylpicoxamid, GF-3840 Fungicide and GF-4017 Fungicide

There was a typographical error in the target margin of exposure (MOE) mentioned in Section 3.6 Aggregate exposure and risk assessment, and the footnote of Table 18 in Appendix 1 of PRD2022-14. The target MOE is 300 for adults, youth, and children. PRD2022-14 erroneously indicated that the target MOE for adults and youth was 1000.

The correct version of Section 3.6 Aggregate exposure and risk assessment is as follows:

> **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 MOE for adults, youth and

[1] Information Note – Determining Study Acceptability for use in Pesticide Risk Assessments.

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

children is 300. The results of the aggregate risk assessment are presented in Appendix I, Table 18. The calculated MOEs were greater than the target MOE, as such, there are no aggregate health risks of concern.

The correct version of footnote 3 of Table 18 in the Appendix is as follows:

> 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 300. 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).

Comments and responses

Comments on the health assessment - Toxicology

Comment related to adequacy of the database with respect to the application of the *Pest Control Products Act*

Ecojustice and Friends of the Earth objected to the registration of florylpicoxamid on the basis that the database to assess the reproductive / developmental toxicity of the technical active ingredient was inadequate and the *Pest Control Products Act* factor (PCPA factor) was reduced to 3-fold without taking into account serious effects in the young.

Health Canada response

In order to adequately assess the potential for reproductive and developmental toxicity, as well as identify potential sensitivity of the young, a reproductive toxicity study in the rat, a developmental toxicity study in the rat and a developmental toxicity study in the rabbit are typically required to support the application to register, as well as the continued registration, of a pesticide active ingredient. It is important to note that all required studies that assess potential toxicity to infants and children were submitted for this technical active ingredient, and these studies followed OECD test guidelines and Good Laboratory Practices. Specifically, the applicant submitted a guideline 2-generation reproductive toxicity study in the rat and guideline developmental toxicity studies in the rat and rabbit. As noted in the Guidance for Developing Datasets for Conventional Pest Control Product Applications, these are the required core studies for assessing the completeness of the data with respect to the exposure of, and toxicity to, infants and children, and potential prenatal and postnatal toxicity. Therefore, the argument that PMRA relied on supplemental studies is not correct. Each of these guideline studies also had a corresponding dose range-finding study, which Health Canada classified as supplemental, since these are not intended to be guideline studies designed for risk assessment purposes. These studies are conducted to support the dose selection for the main study. Although not relied upon for risk assessment, these supplemental studies were well conducted, and their findings added to the overall weight of evidence. Also, clear NOAELs were identified in all guideline developmental or reproductive toxicity studies. Consequently, the database for florylpicoxamid was deemed complete, consisting of the full array of toxicity studies currently required for hazard assessment purposes and no residual database uncertainty was present.

As noted in PRD2022-14, the *Pest Control Products Act* requires the application of a 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, which includes consideration of whether there is any evidence of sensitivity of the young, the seriousness of any relevant effects observed, and confidence in the database, among other aspects. Full details on how the PCPA factor is assessed are included in Section 4.0 of the Science Policy Note SPN2008-01: The Application of Uncertainty Factors and the *Pest Control Products Act* Factor in the Human Health Risk Assessment of Pesticides. In the case of florylpicoxamid, the rationale for reducing the PCPA factor is based on considerations outlined in Section 4.3.1 (absence of sensitivity of the young) and Section 4.3.2 (seriousness of the endpoint) of SPN2008-01.

In the present assessment for florylpicoxamid, developmental (abortions) or postnatal (delayed puberty) toxicity was observed in the presence of maternal or parental toxicity, demonstrating an absence of sensitivity of the young compared to mature animals, thus lowering the concern for these adverse effects. There were no residual uncertainties relating to completeness of data with respect to the toxicity of infants and children and there were no residual concerns relating to prenatal or postnatal toxicity. Although the endpoints noted in the assessment were serious in nature, they were observed at doses much higher than those selected for risk assessment (i.e., NOAELs), and the degree of concern was lowered by the absence of sensitivity of the young. Hence, the retention of a 3-fold PCPA factor is deemed protective of vulnerable populations, providing an adequate target margin of exposure (MOE).

Comment related to the use of a point of departure from an oral study to assess a dermal scenario of exposure and application of the *Pest Control Products Act*

Ecojustice and Friends of the Earth objected to the reduction of the PCPA factor to 3-fold for short- to intermediate-term dermal toxicity scenarios for occupational exposure despite serious effects in the young. They also objected to the use of an oral study to assess dermal scenarios of exposure and expressed concerns that the 28-day dermal toxicity study did not assess prenatal toxicity.

Health Canada response

For the selection of a point of departure for assessing risks from short- and intermediate-term dermal exposure scenarios, Health Canada selected the NOAEL from the dietary developmental toxicity study in rabbits. This study was selected because the most sensitive and relevant endpoint (effects on the developing fetus) for that population group (adults, excluding children) was not evaluated in the available 28-day dermal toxicity study in rats. Guideline repeat-dose dermal toxicity studies are not typically designed to evaluate prenatal and/or postnatal endpoints. Consequently, it is not unusual for a regulatory authority to use a point of departure from an oral study when assessing risks from dermal exposure if endpoints of concern identified in another type of toxicity study have not been assessed in the dermal toxicity study. The dietary developmental toxicity study in rabbits was designed to evaluate the endpoints of concern (prenatal toxicity). Furthermore, since a xenobiotic substance is rarely fully (100%) absorbed by the skin, the use of a dietary study to set a point of departure for a dermal exposure scenario is considered protective of any potential toxicity that may occur via the dermal route. A dermal

absorption factor of 9% was determined for florylpicoxamid and used for calculations in route-to-route extrapolation. Please note that the reference value used for short and medium-term dermal occupational exposure of 9.6 mg/kg bw/day is 100-fold lower (more protective) than the NOAEL of >1000 mg/kg bw/day identified in the repeat-dose dermal toxicity study in rats.

For additional information on the rationale supporting the use of a 3-fold PCPA factor in the assessment of florylpicoxamid, please refer to Health Canada's response to Comment 1 above.

Comment related to the selection of the point of departure to assess dermal exposure scenarios in children

Ecojustice and Friends of the Earth objected to the study selection and the point of departure to assess dermal risk in children. They noted that the lowest NOAEL was not selected for the short- and intermediate-term dermal risk assessment for children. Instead of the NOAEL of 9.6 mg/kg bw/day from the developmental dietary toxicity study, the NOAEL of 73 mg/kg bw/day from the dietary 2-generation reproductive toxicity study in rats was selected. They further objected to the use of a dietary study for risk characterization of a dermal route of exposure. The NOAEL for parental males in the reproductive toxicity study was 58 mg/kg bw/day, and they suggested that this value should have been used as the point of departure rather than that of female parental animals of 73 mg/kg bw/day. They also claimed that the parental effect at this level was not taken into consideration.

Health Canada response

The lowest NOAEL of the database, based on abortions at the next dose in the developmental toxicity study in rabbits, was not considered to be relevant to children of this age group, as this sub-population is not at risk for abortion. For assessing risks to children, effects in parental animals in a reproductive toxicity study are also not relevant for this age group. The most relevant endpoint to serve as a point of departure for short- and intermediate-term dermal scenarios in children was observed in offspring from the 2-generation reproductive toxicity study in rats. The offspring effects in this study included reduced body weights during early development and delayed puberty in females. The offspring NOAEL for these adverse effects was 73 mg/kg bw/day. These endpoints were considered most relevant for children, which in this assessment, covered the ages of 6 to <11 years old, as they were observed following exposure of rat offspring during a comparable life stage as children of this age group.

When evaluating offspring dosage in a reproductive toxicity study, it is standard practice to base the exposure of offspring on the parental female generation dosage. Offspring may be exposed directly in utero or indirectly to the test substance through milk until they commence eating for themselves during the last week of the lactation period. However, such a transfer to offspring does not occur from parental males. Therefore, basing offspring dosage on male parental exposure for these endpoints is not appropriate.

The rationale for the use of an endpoint from a dietary study as a point of departure for a dermal exposure scenario is further explained in response to Comment 2 above.

Comment related to the requirement of additional uncertainty factors

Ecojustice and Friends of the Earth suggested that Health Canada should require a dermal toxicity study that addresses the appropriate endpoint of concern in children or apply additional uncertainty factors when using an oral study to assess a dermal endpoint.

Health Canada response

For a response to this comment, please refer to the response to Comment 2.

Comment related to the reduction of the PCPA factor for certain scenarios and/or target populations

Ecojustice and Friends of the Earth disagree with the assessment of the PCPA factor and resulting target of MOE of 100 for assessing oral ingestion risks to toddlers.

Heath Canada response

The most relevant endpoint to establish a point of departure for incidental oral ingestion in toddlers was the decreased body weight observed in the offspring of the dietary 2-generation reproductive toxicity study in rats. The offspring NOAEL for this adverse effect was 73 mg/kg bw/day. The retention of the full 10-fold PCPA factor was obviated for this exposure scenario in toddlers as the point of departure selected was based on effects in the young, the effect of reduced body weight is not considered serious in nature, and no sensitivity of the young was observed, consistent with SPN2008-01. The serious effects observed in the developmental toxicity study in rabbits and in the reproductive toxicity study were not relevant to toddlers (abortions and delayed vaginal opening, respectively).

Comments related to the use of a point of departure from an oral study to assess repeated inhalation exposure scenarios and the uncertainty rising from the difference in absorption between these routes

Ecojustice and Friends of the Earth disagreed with the use of an oral developmental toxicity study to assess inhalation risk of exposure and noted uncertainties arising from the difference in absorption between the oral and inhalation routes. They also disagreed with the reduction of the PCPA factor to 3-fold for these inhalation scenarios.

Health Canada response

The developmental toxicity study in rabbits was selected to establish a point of departure for short- and intermediate-term inhalation exposure scenarios in the adult population. In the absence of a repeat-dose inhalation study, the most relevant endpoint for this population was the abortions observed in the oral developmental toxicity study, as pregnant people could be exposed in the workplace.

Although it is not always the case, an inhaled substance is usually assumed to be completely absorbed (100%). As the oral absorption of florylpicoxamid is approximately 25%, a 3-fold uncertainty factor was used in route-to-route extrapolation to account for lower oral absorption, in addition to the 3-fold PCPA factor that was applied when using the rabbit developmental

toxicity for risk assessment, resulting in a total target MOE of 1000. When using this oral endpoint for inhalation risk assessment, margins of exposure greater than 6000 were achieved, indicating adequate protection of workers via the inhalation route.

Comment related to the cumulative risk assessment

Ecojustice and Friends of the Earth noted that in respect of cumulative risk assessment, Health Canada failed to explain whether it required any evidence related to common mechanisms of toxicity for florylpicoxamid and fenpicoxamid.

Health Canada response

The Science Policy Note SPN2018-02, *Cumulative Health Risk Assessment Framework* describes the framework and methodology that Health Canada's Pest Management Regulatory Agency (PMRA) uses for assessing the cumulative health effects of pesticides that have a common mechanism of mammalian toxicity. Consistent with the approach outlined in SPN2018-02, Health Canada followed a weight-of-evidence approach to explore the potential for a common mechanism of mammalian toxicity for this active ingredient with other pesticides. Health Canada considered chemicals within the same class of fungicides, which takes into consideration similarities with respect to structure and pesticidal mode of action. Accordingly, the Cumulative Assessment Section of PRD2022-14 did note that florylpicoxamid belongs to the class of fungicides known as picolinamides. Another fungicide in this class, fenpicoxamid, may be used on food imported into Canada and therefore, Canadians may be exposed to this pesticide through their diet. Given these similarities and potential for co-exposure to these similar pesticides, Health Canada examined the toxicology databases of both active ingredients and compared apical endpoints among the available toxicity studies. Although some of the adverse effects observed were common to both pesticides (effects on the liver and soft feces), they were indicative of generalized toxicity. Based on this information, it was concluded that these compounds do not share a specific common mechanism of mammalian toxicity. This is also consistent with the approach outlined in SPN2018-02, which indicates that effects which may have many possible unrelated causes, or that could be considered nonspecific in origin, are not appropriate as the primary basis for grouping chemicals for cumulative risk assessment. Therefore, Health Canada determined that a cumulative risk assessment was not required at this time.

Comments on the health assessment - Occupational Exposure

Comment related to the inhalation exposure

Ecojustice and Friends of the Earth stated that there is no explanation in PRD2022-14 related to the fact that inhalation exposure is a primary route of exposure, and that the active ingredient is considered "non-volatile" such that an inhalation risk assessment is "not required".

Health Canada response

For occupational workers, inhalation exposure is a primary route of exposure for mixer, loader and applicator. As such, an inhalation risk assessment was conducted, and the results are reported in Appendix I, Table 10 of PRD2022-14. The inhalation MOEs achieved ranged from 6,157 to 3,962,848 and are therefore not of health concern.

For postapplication workers, given the nature of activities performed, exposure should be primarily via the dermal route based on dermal contact with treated foliage and turf. In addition, the restricted-entry interval of 12 hours will allow residues to dry, suspended particles to settle and vapours to dissipate. Inhalation exposure for post-application workers 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.

Comment related to the drift standard label statement

Ecojustice and Friends of the Earth stated that there is no explanation in PRD2022-14 related to how the standard drift label statement is sufficient to protect against health risks to bystanders, especially due to the proximity between golf courses and residential areas, and that the residential areas have increased presence of pregnant women and children.

Health Canada response

Labels are required to have the standard precautionary label statement: “Apply only when the potential for drift to areas of human habitation and human activity (other than golf courses) such as parks, school grounds, and playing fields, is minimal. Take into consideration wind speed, wind direction, temperature inversions, application equipment and sprayer settings”. Also, the end-use products have further restrictions that will reduce drift such as: maximum wind speed, minimum droplet size, minimum boom height and specific nozzle distribution instructions.

Spray drift to non-target areas, including bystander exposure, is expected to be minimal for all scenarios when a product is used according to the label directions. Further, application is limited to agricultural crops, turf farms and golf courses only when there is low risk of drift to areas of human habitation or activity.

A residential/non-occupational risk assessment was conducted for golfers entering treated areas following application and the risks were shown to be acceptable. Therefore, risks from any possible spray drift associated with this use are also considered to be acceptable. The exposure to people on the golf course itself would be higher than exposure to adjacent residences and residential areas, as such, the health risk would also be acceptable to residents. The target margin of exposure selected to assess risk to golfers is protective of pregnant women and children. The risk assessment for golfers is therefore protective of residents living adjacent to a golf course.

Comment related to the aggregate risks

Ecojustice and Friends of the Earth stated that the aggregate risk assessment does not take into account the risks of residential proximity to golf courses.

Health Canada response

As reported in Section 3.6 of PRD2022-14, there is potential for individuals to be exposed to florylpicoxamid via different routes of exposure concurrently. As such, aggregation of chronic dietary exposure (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 were aggregated with the dermal exposure values while golfing. Aggregate exposure estimates were compared to the aggregate toxicological reference value to obtain the MOE achieved; the target MOE is 300 for adults, youth and children. The results of the aggregate risk assessment where MOEs ranged from 1,659 to 11,607 were greater than the target MOEs, as such, there are no aggregate health risks of concern.

The aggregate risk assessment also used very conservative assumptions for the dietary route of exposure: 100% of the crops are treated, default processing factors, residues in food commodities at the Canadian maximum residue limit (MRL) level, the highest estimated environmental concentration (EEC) in drinking water from groundwater sources. As such, it is expected that the aggregate risk assessment for golfers who spend extended time on the treated turf would not underestimate exposure to residents living adjacent to the golf course. The aggregate risk assessment for golfers is considered protective of residents living adjacent to a golf course.

Comment related to the transferable turf residue (TTR) study

Ecojustice and Friends of the Earth stated that since the florylpicoxamid TTR study could not be used quantitatively, acceptable data or added uncertainty factors are required to assess dermal exposure.

Health Canada response

In the absence of a chemical-specific transferable turf residue (TTR) study to register pesticides for use on turf in Canada, TTRs can be estimated using generic assumptions for both the initial residue available and residue dissipation. The generic assumptions, as described in SPN214-02, were determined following analysis of 59 studies (165 data points) that collected turf transferable residues using the Modified California Roller method. The arithmetic mean peak TTR value from these studies was 0.93% of the application rate for liquid applications. Based on this analysis, the standard peak TTR value of 1% (i.e., 0.93% rounded to 1%) of the application rate was determined as acceptable for use in post-application assessments.

In the case of florylpicoxamid, the standard peak TTR of 1% of the application rate available for dislodging on the day of application and 10% dissipation per day were used. Chemical-specific TTRs are usually provided to refine the health risks assessment, if potential risks of concern are identified using the standard generic exposure values. Given that risks were shown to be acceptable based on the above information, neither additional TTR studies nor an additional uncertainty factor was deemed necessary.

As reported in PRD2022-14, the applicant had submitted a TTR study conducted with florylpicoxamid. This study could not be used quantitatively, as the residues were very low, given the rate of application was not representative of the proposed use pattern. In addition,

based on the results of the TTR study, dissipation of residues could not be modelled. However, although the chemical-specific TTR data could not be used to estimate exposure on its own, it could be used as part of an overall weight-of-evidence approach to confirm the use of the standard peak TTR values to assess post-application exposure. Since the amount of florylpicoxamid available for dislodging in the chemical-specific study was less than or equal to 1% following 5 applications, using the standard 1% value will, thus, not underestimate post-application exposure to florylpicoxamid when applied on turf.

Comment related to the dislodgeable foliar residue (DFR) study

Ecojustice and Friends of the Earth stated that PMRA has not sufficiently explained in PRD2022-14 why the DFR on dry beans was used for other crops.

Health Canada response

Dislodgeable foliar residue (DFR) is the amount of pesticide residue (µg/cm^2) on the surface of treated foliage that is available for transfer onto the skin and clothing of an agricultural worker while conducting regular work activities in the treated area. In the absence of chemical-specific DFR data on certain crops, as described in SPN 2014-02, the PMRA regularly uses surrogate DFR values for risk assessment when they meet certain criteria (see below). The term 'surrogate' specifically refers to the use of data from one crop to represent another crop treated with the same pesticide.

DFR values are chemical-specific and can be impacted by a number of factors such as the application rate, application regime (number of applications per year, application interval, etc.), product formulation, geographic site (climatic conditions), foliage type (waxy, hairy, smooth), general crop morphology (trellis, orchard or field crops), and application equipment (groundboom, airblast, etc.).

These factors are important when selecting appropriate surrogate DFR values. DFR data are chemical-specific; however, data from one crop may be used to represent the DFR on another crop treated with the same pesticide when several of the above-mentioned factors are comparable.

As reported in PRD2022-14 for florylpicoxamid, the dry beans DFR study was deemed acceptable for estimating worker exposure in cereals, canola, legumes and sugar beets. The formulation used in the DFR study was comparable to the proposed formulations. The crops proposed for treatment all have smooth leaf types which is similar to the smooth leaf type of dry beans. The groundboom application method used in the study is also identical to the method proposed for these crops. Finally, the rate used (150 g a.i./ha) is equal to or higher than the labelled rate and, therefore, should not underestimate exposure.

Comment related to the standard 12-hour restricted-entry interval (REI) for agricultural uses and of "until sprays have dried" for golf courses

Ecojustice and Friends of the Earth stated that PMRA has not sufficiently explained in PRD2022-14 why or how a 12-hour REI and allowing sprays to dry are adequate mitigation measures.

Health Canada response

A restricted-entry interval (REI) is the period of time that agricultural workers, or anyone else, must not do hand labour in treated areas after a pesticide has been applied. This is to allow residues and vapours to dissipate to safe levels for work to be performed. An REI can range from 12 hours to several days. When the risk assessment shows no health concern on the day of application, a 12-h REI is established, otherwise, a longer REI is required. Pesticide labels may specify a number of REIs depending on crop or worker activity. Complying with REI directions is a legal requirement and part of pesticide safety.

Hand labour tasks involve worker contact with treated surfaces such as plants, plant parts or soil. Activities can include harvesting, detasseling, thinning, weeding, scouting, planting, etc. Agricultural employers have a responsibility to ensure that agricultural workers and others on site are aware of any REIs in effect, and that everyone remains outside treated areas until the interval period ends.

REIs protect workers, and others, from risks that may occur from both immediate and longer-term exposure to pesticide residues, vapours and particulates. A minimum 12-hour REI allows residues to dry and vapours to dissipate, limiting potential effects such as irritation or allergic reactions.

For golfing, when the risk assessment shows no health concern on the day of application, it is considered protective to allow golfers on the treated course when residues have dried. If there are risks of concern that would require a longer re-entry interval, then the pesticide would not be registered for turf use on golf course.

Comments on the health assessment - Dietary Exposure

Comment related to the version of DEEM used in the florylpicoxamid dietary risk assessment

Ecojustice and Friends of the Earth stated that newer versions of DEEM were available and not used to conduct the dietary risk assessment as reported in PRD2022-14, and Canadian use patterns were not considered.

Health Canada response

The version 4.02 05-10-c of DEEM is the most up-to-date version available. This version of the software incorporated the food consumption data from the United States' National Health and Nutritional Examination Survey, What We Eat in America (NHANES/ WWEIA) from 2005 to 2010. An analysis of Canadian dietary consumption data from the Canadian Community Health Survey (CCHS) and American consumption data from WWEIA also showed no significant differences. The WWEIA data were adopted by the PMRA primarily due to its larger sample size, the fact that it is a continuous survey and that it represents the most recent food consumption data available (as reported in SPN2014-01).

For florylpicoxamid, the major contributor to the dietary exposure of infants and other subpopulations is drinking water. As such, the impact of food consumption on dietary exposure is not significant. Residues in food commodities were included at the MRL level which

corresponded to the limit of quantitation (LOQ) of the enforcement method of 0.01 ppm as there were no quantifiable residues observed, except for canola seed for which the highest residues were just above the LOQ at 0.011 ppm. The basic (most conservative or Tier I) chronic dietary exposure assessment from all supported florylpicoxamid food uses (food alone) for the total population, including infants and children, and all representative population subgroups is less than or equal to 3.2% of the ADI.

With regard to consideration of Canadian use patterns, residue data were generated at exaggerated rates compared to the proposed use rates. However, even at exaggerated rates, no quantifiable residues were observed in the human foods. Thus it is not necessary to have data generated according to the Canadian use patterns, as the resulting residues would be expected to be even lower at the lower rate of application, and would be non-quantifiable.

Comment related to the drinking water modelling and the Level 1 EECs

Ecojustice and Friends of the Earth stated that PMRA has not provided sufficient details in PRD2022-14 about the modelling of Level 1 EECs and how the residue definition in drinking water was determined.

Health Canada response

The residue definition for drinking water was determined to be florylpicoxamid and the two degradates X12485649 and X12485631 on the basis of exposure and toxicity. The selected residue definition was determined to be protective of exposure to other major transformation products.

Estimated environmental concentrations (EECs) in drinking water are expressed as parent equivalents. The major transformation products, X12485631 and X12485473, are formed by the splitting of the X12485649 molecule. Including X12485473 in the residue definition would have resulted in double counting of the transformation products, overestimating the EECs in drinking water. X12719657 and X696476 were not included in the residue definition due to low exposure potential and because the toxicity was covered by florylpicoxamid. Based on the above, the inclusion of the additional major transformation products in the drinking water residue definition was not warranted.

As noted in PRD2022-14, Level 1 EECs in drinking water sources (surface water and groundwater) were calculated using the Pesticide in Water Calculator (PWC) version 2.0. For surface water, PWC calculates the amount of pesticide entering the water body by runoff and drift, and the subsequent degradation of the pesticide in the water system. EECs in surface water were calculated by modelling a total land area of 173 ha draining into a 5.3 ha reservoir with a depth of 2.7 m. Groundwater EECs were calculated by simulating leaching through a layered soil profile and reporting the average concentration in the top 1m of a water table.

The Level 1 EECs for surface water were calculated based on a single standard Canadian scenario and a use pattern of 5 applications of 150 g a.i./ha per year with a 7-day retreatment interval. Thirty-five (35) simulations were run with application dates ranging from April to September. EECs in groundwater were calculated for seven scenarios representing different regions of Canada; however, only the highest EECs from across these scenarios were reported. Most scenarios were run for 50 years, but two were run for 100 years as they were slow to come

to steady state. Two hundred forty (240) simulations were run in total, spread among the 7 scenarios based on regional application dates. The Level 1 EECs in groundwater were based on 5 applications of 150 g a.i./ha per year with a 7-day retreatment interval, as shown in Table 17 of PRD2022-14.

Further details of water modelling inputs and calculations are available upon request.

Comments on the environmental assessment

Comments related to the PMRA's consideration of only one transformation product in the Toxic Substances Management Policy (TSMP) assessment

Ecojustice and Friends of the Earth stated that the PMRA did not explain why only one transformation product was assessed against track 1 criteria.

Health Canada response

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 (those that are CEPA-toxic, as defined under the *Canadian Environmental Protection Act*, or equivalent; predominantly anthropogenic; persistent; and bio-accumulative). If all four criteria are met, the substance will be deemed Track 1 and designated for virtual elimination. In evaluating pest control products, the Minister shall give effect to the TSMP.

In the environment, florylpicoxamid is rapidly hydrolyzed into its major transformation product (TP), X12485649. Three additional TPs, X12485631, X12485473, and X696476, are secondary and tertiary major TPs formed from the degradation of X12485649 at high pH (hydrolysis at pH 9) and/or under anaerobic conditions in soil. Anaerobic conditions in flooded Canadian agricultural soils are expected to be transient. A fifth major TP, X12719657, is produced from the aqueous phototransformation of florylpicoxamid, which occurs only in the surface layer of water. With the exception of X12485649, the major TPs are not expected to be present in the environment at significant amounts due to the limited conditions under which they are formed.

PRD2022-14 (Table 34) provided a comparison of florylpicoxamid and X12485649 to the TSMP Track 1 criteria. A comparison of the additional major TPs to the TSMP Track 1 criteria is provided in Table 1 below. Based on the available information, these major TPs do not meet all four criteria for a Track 1 substance.

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

TSMP Track 1 Criterion	TSMP Track 1 Criterion value		Florylpicoxamid	X12485649	X12485631, X12485473, X12719657 X696476
CEPA toxic or CEPA toxic equivalent[(1)]	Yes		Yes	Yes	Yes
Predominantly anthropogenic[(2)]	Yes		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	Data not available or required[(4)]
	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, volatilisation is not an important route of dissipation. Long-range atmospheric transport is unlikely to occur based on the vapour pressure ($<5 \times 10^{-6}$ Pa) and Henry's Law constants ($<3.51 \times 10^{-7}$).	No, volatilisation is not an important route of dissipation. Long-range atmospheric transport is unlikely to occur based on the vapour pressure ($<5 \times 10^{-9}$ Pa) and Henry's Law constants ($<3.80 \times 10^{-11}$).	
Bioaccumulation[(5)]	Log $K_{ow} \geq 5$		No, log K_{ow} = 4.2 to 4.3	No, log K_{ow} = 3.4 to 3.5	**X12485473** No, log K_{ow} = -2.0 to -3.7 **X12485631** No, log K_{ow} 3.24 to 3.26 **X696476** No, log K_{ow} = -1.7

TSMP Track 1 Criterion	TSMP Track 1 Criterion value	Florylpicoxamid	X12485649	X12485631, X12485473, X12719657 X696476
				X12719657 Data are not available; however, the log K_{OW} was estimated to be 3.94 using Epi Suite. It is expected that the log K_{ow} of X12719657 will be <5 based on the log K_{OW} values of florylpicoxamid and the other major TPs given the structural similarities between X12719657 and these compounds.
	BCF ≥ 5000	No, BCF = 86.8 to 105(6)	No, BCF = 82.7 to 106	Data are not available or required based on the log K_{ow} values, low exposure potential and the weight-of-evidence of results from florylpicoxamid and X12485649 studies which show that bioaccumulation is not expected.
	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.	No, do not meet TSMP Track 1 criteria.

(1) All pesticides will be considered CEPA-toxic or equivalent for the purpose of initially assessing a pesticide against the TSMP criteria. Assessment of the CEPA-toxic criterion may be refined if required (i.e., 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) then the criterion for persistence is considered to be met.
(4) Persistence data were not required for these major TPs based on:
  (a) The low environmental exposure potential due to the limited conditions under which these TPs are formed;
  (b) Available information shows that these TPs are less toxic to non-target organisms than florylpicoxamid and X12485649. Ecotoxicity data for X696476 were not available; however, these data were not required based on the limited exposure potential. X696476 is a major TP that forms only during anaerobic biotransformation in soil (maximum of 11.6% AR).
  (c) The results of the screening level environmental risk assessment showed negligible risk to non-target organisms from X12485631, X12485473 and X12719657 when 100% transformation of the applied florylpicoxamid was assumed for

TSMP Track 1 Criterion	TSMP Track 1 Criterion value	Florylpicoxamid	X12485649	X12485631, X12485473, X12719657 X696476
each individual TP (no dissipation considered). When considering the formation pathways of these compounds, assuming 100% transformation of the florylpicoxamid overestimates their potential environmental concentrations, ensuring that the assumptions used in the screening level risk assessment are protective of the environment. (5) Field data (e.g., BAFs) are preferred over laboratory data (e.g., BCFs) which, in turn, are preferred over chemical properties (e.g., log K_{OW}). (6) The BCF is reflective of florylpicoxamid + X12485649 due to the instability of florylpicoxamid.				

Comments related to the PMRA's consideration of formulated products in the TSMP assessment.

Ecojustice and Friends of the Earth stated that the PMRA did not explain whether formulated products were considered in the Toxic Substances Management Policy assessment.

Health Canada response

The PMRA assesses the active ingredient, its transformation products, contaminants in the active ingredient and formulants in the end-use products to prevent unacceptable risks to human health or the environment from the use of pest control products.

As described in Section 6.2 of PRD2022-14, a review of contaminants in the active ingredient, as well as formulants in the end-use products was conducted against Parts 1 and 3 of the *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern*. The list is based on several existing policies and regulations, including the TSMP. Part 1 of the list includes formulants of health or environmental concern while Part 3 of the list includes contaminants of health or environmental concern. Please see 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* for more information.

The PMRA determined that XDE-659 Technical Fungicide and its end-use products, GF-3840 Fungicide and Zetigo PRM Fungicide, do not contain formulants or contaminants identified in the *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern*. By extension, these products do not contain formulants or contaminants that meet the TSMP Track 1 criteria.

Comments related to a requirement for field data to assess bioaccumulation in the TSMP assessment.

Ecojustice and Friends of the Earth stated that the PMRA should explain why it did not require a field bioaccumulation study.

Health Canada response

As noted in Regulatory Proposal PRO2016-01, *Revised Environmental Data Requirements*, bioconcentration or bioaccumulation studies with fish are conducted to assess the potential for accumulation in upper-trophic level organisms. These studies are required for outdoor and

greenhouse uses when the log K_{OW} is equal to or greater than 3. Field studies are not required unless a specific concern has been identified. The log K_{ow} value for florylpicoxamid (4.2 to 4.3) indicates the potential for bioaccumulation. Accordingly, a bioconcentration study was submitted for florylpicoxamid and also for X12485649 (log K_{ow} = 3.4 to 3.5), which is expected to form readily under most environmental conditions. These studies indicate that both florylpicoxamid and X12485649 are not expected to bioaccumulate. The lipid and growth corrected kinetic bioconcentration factor ($BCF_{KLG)}$ values for florylpicoxamid, X12485649, and the sum of other TPs that may have formed in fish range from 82.7 to 106. As these BCF values are well below the TSMP criterion of 5000, additional field studies to determine bioaccumulation factor (BAF) values were not warranted.

While the major TP, X12485631, has log Kow values of 3.24 to 3.26, a bioconcentration study was not required for this TP because of (1) its low environmental exposure potential given the limited conditions under which it is formed as a major TP (aqueous phototransformation and biotransformation in anaerobic soil), and (2) the weight-of-evidence from the florylpicoxamid and X12485649 studies, which show that these chemicals are not expected to bioaccumulate. Considering its structural similarities with florylpicoxamid and X12485649, X12485631 is also not expected to bioaccumulate.

Other information

The relevant confidential test data on which the decision is based (as referenced in PRD2022-14, *Florylpicoxamid, GF-3840 Fungicide and GF-4017 Fungicide* are available for public inspection, upon application, in the PMRA's Reading Room. For more information, please contact the PMRA's Pest Management Information Service.

Any person may file a notice of objection[3] regarding this registration decision within 60 days from the date of publication of this Registration Decision. For more information regarding the basis for objecting (which must be based on scientific grounds), please refer to the Pesticides section of the Canada.ca website (Request a Reconsideration of Decision) or contact the PMRA's Pest Management Information Service.

[3] As per subsection 35(1) of the *Pest Control Products Act.*

Evaluation approach

Legislative framework

The Minister of Health's primary objective under the *Pest Control Products Act* subsection 4(1) is to prevent unacceptable risks to individuals and the environment from the use of pest control products.

As noted in the preamble of the Act, it is in the national interest that the attainment of the objectives of the federal regulatory system continue to be pursued through a scientifically-based national registration system that addresses risks to human health, the environment and value both before and after registration and applies to the regulation of pest control products throughout Canada; and that pest control products with acceptable risk and value be registered for use only if it is shown that their use would be efficacious and if conditions of registration can be established to prevent unacceptable risk impact to human health and the environment.

For the purposes of the Act, the health or environmental risks of a pest control product are acceptable if there is reasonable certainty that no harm to human health, future generations or the environment will result from exposure to or use of the product, taking into account its conditions of registration as per subsection 2(2) of the *Pest Control Products Act*.

Risk for the human health and environment, and value are defined under the Act subsection 2(1) as follows:

> **Health risk**, in respect of a pest control product, means the possibility of harm to human health resulting from exposure to or use of the product, taking into account its conditions or proposed conditions of registration.
>
> **Environmental risk**, in respect of a pest control product, means the possibility of harm to the environment, including its biological diversity, resulting from exposure to or use of the product, taking into account its conditions or proposed conditions of registration.
>
> **Value**, in respect of a pest control product, means 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.

When evaluating the health and environmental risks of a pesticide and determining whether those risks are acceptable, subsection 19(2) of the *Pest Control Products Act* requires Health Canada to apply a scientifically-based approach. The science-based approach to assessing pesticides considers both the toxicity and the level of exposure of a pesticide in order to fully characterize risk.

Pre-market assessments are based on a required set of scientific data that must be provided by the applicants for pesticide registrations. Additional information from published scientific reports, other government departments and international regulatory agencies are also considered.[4]

Risk and value assessment framework

Health Canada uses a comprehensive body of modern scientific methods and evidence to determine the nature as well as the magnitude of potential risks posed by pesticides. This approach allows for the protection of human health and the environment through the application of appropriate and effective risk management strategies, consistent with the purpose described in the preambular text set out above.

Health Canada's approach to risk and value assessment is outlined in A Framework for Risk Assessment and Risk Management of Pest Control Products.[5] A high-level overview is provided below.

i) Assessing potential health risks

With respect to the evaluation and management of potential health risks, Health Canada's risk assessments follow a structured, predictable process that is consistent with international approaches and the Health Canada Decision-Making Framework for Identifying, Assessing, and Managing Health Risks.[6]

The evaluation of potential health risks begins with a consideration of the toxicological profile of a pesticide to establish reference doses at which no adverse effect is expected and against which the expected exposure is assessed. This includes, where appropriate, the use of uncertainty (protection) factors to provide additional protection that accounts for the variation in sensitivity among members of human population and the uncertainty in extrapolating animal test data to humans. Under certain conditions, the *Pest Control Products Act* requires the use of another factor to provide additional protection to pregnant women, infants, and children. Other uncertainty factors, such as a database deficiency factor, are considered in specific cases. More details related to the application of the uncertainty factors are provided in SPN2008-01.[7]

Assessments estimate potential health risks to defined populations[8] under specific exposure conditions. They are conducted in the context of the proposed or registered conditions of use, such as the use of a pesticide on a particular field crop using specified application rates, methods and equipment. Potential exposure scenarios consider exposures during and after application of the pesticide in occupational or residential settings, food and drinking water exposure, or exposure when interacting with treated pets. Also considered are the anticipated durations

4 Information Note – Determining Study Acceptability for use in Pesticide Risk Assessments.

5 PMRA Guidance Document, *A Framework for Risk Assessment and Risk Management of Pest Control Products*.

6 Health Canada Decision-Making Framework for Identifying, Assessing, and Managing Health Risks – 1 August 2000.

7 Science Policy Note: The Application of Uncertainty Factors and the Pest Control Products Act Factor in the Human Health Risk Assessment of Pesticides.

8 Consideration of Sex and Gender in Pesticide Risk Assessment.

(short-, intermediate- or long-term) and routes of exposure (oral, inhalation, or skin contact). In addition, an assessment of health risks must consider available information on aggregate exposure and cumulative effects.

ii) Assessing risks to the environment

With respect to the evaluation of environmental risks, Health Canada's environmental risk assessments follow a structured, tiered approach to determine the likelihood that exposure to a pesticide can cause adverse effects on individual organisms, populations, or ecological systems. This involves screening assessments starting with simple methods, conservative exposure scenarios and sensitive toxicity effects metrics, then moving on, where required, to more refined assessments that can include exposure modelling, monitoring data, results from field or mesocosm studies, and probabilistic risk assessment methods.

The environmental assessment considers both the exposure (environmental fate, chemistry, and behaviour, along with the application rates and methods) and hazard (toxic effects on organisms) of a pesticide. The exposure assessment examines the movement of the pesticide in soil, water, sediments and air, as well as the potential for uptake by plants or animals and transfer through the food web. The possibility for the pesticide to move into sensitive environmental compartments such as groundwater or lakes and rivers, as well as the potential for atmospheric transport, is also examined. The hazard assessment examines effects on a large number of internationally recognized indicator species of plants and animals (terrestrial organisms include invertebrates such as bees, beneficial arthropods, and earthworms, birds, mammals, plants; aquatic organisms include invertebrates, amphibians, fish, plants and algae), and includes considering effects on biodiversity and the food chain. Acute and chronic effects endpoints are derived from laboratory and field studies that characterize the toxic response and the dose–effect relationship of the pesticide.

The characterization of environmental risk requires the integration of information on environmental exposure and effects to identify which, if any, organisms or environmental compartments may be at risk, as well as any uncertainties in characterizing the risk.

iii) Value assessment

Value assessments consist of two components: an assessment of the performance of a pest control product and its benefits.

Assessing pesticide performance involves an evaluation of the pesticide’s efficacy in controlling the target pest and the potential for the pesticide to damage host crops or use sites. Where the efficacy of a pesticide is acceptable, the assessment serves to establish appropriate label claims and directions and an application rate (or rate range) that is effective without being excessive, and with no unacceptable damage to the use site or host organism/crop (and subsequent hosts or crops) under normal use conditions.

In many cases, proof of performance alone is sufficient to establish the value of the pesticide, so that an in-depth or extensive evaluation of benefits may not be required. However, a more thorough assessment of benefits may be undertaken in particular cases where performance alone does not sufficiently demonstrate value, or while developing risk management options.

Risk management

The outcomes of the assessments of risks to human health and the environment, and the assessment of value, form the basis for identifying risk management strategies. These include appropriate risk mitigation measures and are a key part of decision-making on whether health and environmental risks are acceptable. The development of risk management strategies take place within the context of the pesticide's conditions of registration. Conditions can relate to, among other things, the specific use (for example, application rates, timing and frequency of application, and method of application), personal protective equipment, pre-harvest intervals, restricted entry intervals, buffer zones, spray drift and runoff mitigation measures, handling, manufacture, storage or distribution of a pesticide. If feasible conditions of use that have acceptable risk and value cannot be identified, the pesticide use will not be eligible for registration.

The selected risk management strategy is then implemented as part of the registration decision. The pesticide registration conditions include legally-binding use directions on the label. Any use in contravention of the label or other specified conditions is illegal under the *Pest Control Products Act*. Implementation of post-market decisions follow the framework articulated in the Policy on Cancellations and Amendments Following Re-evaluation and Special Review.[9]

Following a decision, continuous oversight activities such as post-market assessments, monitoring and surveillance, including incident reporting, all play an essential role to help ensure the continued acceptability of risks and value of registered pesticides.

[9] PMRA Regulatory Directive DIR2018-01, Policy on Cancellations and Amendments Following Re-evaluation and Special Review.