Proposed Registration Decision PRD2020-09

Fluxapyroxad and Xzemplar

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Overview

Proposed Registration Decision for Fluxapyroxad

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 Xemium Technical Fungicide and Xzemplar, containing the technical grade active ingredient fluxapyroxad, to control dollar spot on golf course turf grass.

Fluxapyroxad is currently registered to control or supress various fungal diseases in numerous crops. For details, see Proposed Registration Decision PRD2012-09, *Fluxapyroxad* and Registration Decision RD2012-31, *Fluxapyroxad*.

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 section provides detailed technical information on the human health, environmental and value assessments of fluxapyroxad and Xzemplar.

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 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 Canada.ca.

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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."

Before making a final registration decision on fluxapyroxad and Xzemplar, 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 fluxapyroxad and Xzemplar, 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 section of this consultation document.

What Is Fluxapyroxad?

Fluxapyroxad is a broad-spectrum fungicide registered for use on various crops. It inhibits spore germination, mycelial growth, and sporulation of the fungus on the leaf surface. The current application is for disease management in golf course turf grass.

Health Considerations

Can Approved Uses of Fluxapyroxad Affect Human Health?

Xzemplar, containing fluxapyroxad, is unlikely to affect your health when used according to label directions.

Potential exposure to fluxapyroxad may occur through the diet (drinking water), when handling and applying the end-use product, or when coming into contact with treated turf. When assessing health risks, two key factors are considered: the levels where no health effects occur and the levels to which people may be exposed. The dose levels used to assess risks are established 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 doses 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.

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

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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*.

The acute toxicity of the end-use product Xzemplar, containing fluxapyroxad, was considered to be low via the oral, dermal and inhalation routes of exposure. It was minimally irritating to the skin, non-irritating to eyes and did not cause an allergic skin reaction.

Registrant-supplied short- and long-term (lifetime) animal toxicity tests, as well as information from the published scientific literature, were assessed for the potential of fluxapyroxad to cause neurotoxicity, immunotoxicity, chronic toxicity, cancer, reproductive and developmental toxicity, and various other effects. The most sensitive endpoints for risk assessment were effects on body weight and changes to the liver and thyroid. Fluxapyroxad produced liver and thyroid tumours in rats. There was sufficient information available to determine that a threshold-based cancer risk assessment was appropriate. 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 at which these effects occurred in animal tests.

Residues in Food and Drinking Water

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

No food residue data are required to support the registration of fluxapyroxad for use in/on turf grass on golf courses in Canada. However, due to the potential for residues to enter drinking water sources as a result of the turf grass use, an aggregate dietary assessment was conducted to assess health risks from overall exposure to potential food residues from existing dietary uses and the current proposed use.

Aggregate acute dietary (food plus drinking water) intake estimates for the general population and all population subgroups are expected to be less than 13% of the acute reference dose, and are not of health concern.

Aggregate chronic (cancer and non-cancer) dietary (food plus drinking water) intake estimates for the general population and all population subgroups indicated that drinking water was the major contributor to the dietary exposure, however, based on the conservatism included in the drinking water modelling, this exposure is expected to be over-estimated and, therefore, not of health concern.

As no food residue data are required to support the registration of fluxapyroxad for use in/on turf grass on golf courses in Canada, maximum residue limits (MRLs) are not required for this proposed use. For more details concerning the MRLs for fluxapyroxad on various food commodities, please refer to the Maximum Residue Limit Database in the Pesticides section of Canada.ca

Occupational Risks from Handling Xzemplar

Occupational risks are not of concern when Xzemplar is used according to the label directions, which include protective measures.

Workers who mix, load or apply Xzemplar, as well as workers entering freshly treated golf courses, can come in direct contact with fluxapyroxad residues on the skin. Therefore, the label specifies that workers must wear a long-sleeved shirt, long pants, chemical-resistant gloves, shoes and socks during mixing, loading, application, clean-up and repair. The label also requires that workers and the general public do not enter treated areas in golf courses until sprays have dried. Taking into consideration these label statements, the number of applications and the expectation of the exposure period for handlers and workers, the health risks to these individuals are not of concern.

Risks in Residential and Other Non-Occupational Environments

Residential and non-occupational risks are not of health concern when Xzemplar is used according to the label directions.

Adults, youth and children may be exposed to fluxapyroxad while golfing on courses treated with Xzemplar. Based on the expected short- to intermediate-term duration of this activity, the health risk to children, youth and adults is not a concern. There are no residential turf uses of Xzemplar.

Risks to Bystanders

Bystander risks are not of health concern when Xzemplar is used according to the label directions and spray drift restrictions are observed.

A standard label statement to protect against drift during application is required on the label. Therefore, health risks to bystanders are not of concern.

Environmental Considerations

What Happens When Fluxapyroxad is Introduced into the Environment?

When fluxapyroxad is used according to label directions, the risks to the environment are considered to be acceptable.

Fluxapyroxad enters the environment when it is used outdoors as a fungicide. Once in the environment, fluxapyroxad is slowly broken down by microbes found in soil and water. Two major transformation products are formed in soil, M700F001 and M700F002. Given their properties, fluxapyroxad and M700F002 may leach through soil. Fluxapyroxad could also reach surface water through spray drift and through the movement of soil particles in surface runoff. Once in water, fluxapyroxad is expected to move to the sediment. When fluxapyroxad is used in accordance with the label and the required precautions, the resulting environmental risk is considered to be acceptable.

Value Considerations

What Is the Value of Xzemplar?

Fluxapyroxad is the active ingredient in Xzemplar. The registration of Xzemplar will provide Canadian users with a new product to manage dollar spot, an important fungal disease on golf course turf grass.

Xzemplar contains fluxapyroxad as its active ingredient. Xzemplar, applied as a foliar spray, is effective against dollar spot, an economically important fungal disease of cool-season turf grass on golf courses.

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 label of Xemium Technical Fungicide and Xzemplar to address the potential risks identified in this assessment are as follows.

Key Risk-Reduction Measures

Human Health

Because there is a concern with users coming into direct contact with fluxapyroxad on the skin or through inhalation of spray mists, any users must wear a long-sleeved shirt, long pants, chemical-resistant gloves, shoes and socks during mixing, loading, application, clean-up and repair.

The Xzemplar label also requires that workers and the general public do not enter treated areas in golf courses until sprays have dried. In addition, standard label statements to protect against drift during application are present on the label.

Environment

To protect the environment, the following proposed risk mitigation measures are required:

- Spray buffer zones of 1 metre for the protection of sensitive aquatic and terrestrial habitats.
- A statement indicating that fluxapyroxad may leach in soil.
- Advisory statements informing users of potential risk to non-target terrestrial plants and aquatic organisms.
- Recommendations to reduce runoff to further protect the aquatic environment.

Next Steps

Before making a final registration decision on fluxapyroxad and Xzemplar, 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 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 the Health Canada makes its registration decision, it will publish a Registration Decision on fluxapyroxad and Xzemplar (based on the Science Evaluation section 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 (located in Ottawa).

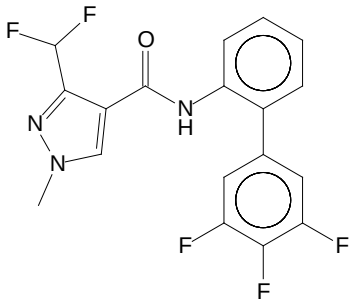
Science Evaluation

Fluxapyroxad and Xzemplar

1.0 The Active Ingredient, Its Properties and Uses

1.1 Identity of the Active Ingredient

Active substance

Function	**Fungicide**
Chemical name	
1. International Union of Pure and Applied Chemistry (IUPAC)	**3-(difluoromethyl)-1-methyl-*N*-(3′,4′,5′-trifluorobiphenyl-2-yl)pyrazole-4-carboxamide**
2. Chemical Abstracts Service (CAS)	**3-(difluoromethyl)-1-methyl-*N*-(3′,4′,5′-trifluoro[1,1′-biphenyl]-2-yl)-1*H*-pyrazole-4-carboxamide**
CAS number	**907204-31-3**
Molecular formula	**$C_{18}H_{12}F_5N_3O$**
Molecular weight	**381.31**
Structural formula	
Purity of the active ingredient	**98.9 % nominal**

1.2 Physical and Chemical Properties of the Active Ingredient and End-use Product

Technical Product—Xemium Technical Fungicide

Property	Result
Colour and physical state	White solid
Odour	Odourless
Melting point	~ 157 °C

Boiling point or range	Decomposes at ~ 230 °C
Relative Density	1.471
Vapour pressure at 20 °C	2.7×10^{-9} Pa (estimated)
Henry's law constant at 20 °C	3.028×10^{-7} Pa*m3/mol @ 20ºC 8.13×10^{9} (1/H)
Ultraviolet (UV)-visible spectrum	Methanol pure, pH 6.7 λ = 203 nm ε = 3.16×10^{4} M^{-1} cm^{-1} λ = 229 nm ε = 2.39×10^{4} M^{-1} cm^{-1} λ = 290 nm ε = 1.60×10^{3} M^{-1} cm^{-1} Methanol : Water = 1 : 99, pH 5.9 λ = 193 nm ε = 4.41×10^{4} M^{-1} cm^{-1} λ = 230 nm ε = 2.40×10^{3} M^{-1} cm^{-1} λ = 290 nm ε = 9.78×10^{2} M^{-1} cm^{-1} Methanol : 1M HCl : Water = 10 : 5 : 85, pH 1.4 λ = 199 nm ε = 3.59×10^{4} M^{-1} cm^{-1} λ = 230 nm ε = 2.41×10^{4} M^{-1} cm^{-1} λ = 290 nm ε = 1.15×10^{3} M^{-1} cm^{-1} Methanol : 1M NaOH : Water = 10 : 5 : 85, pH 12.2 λ = 215 nm ε = 2.32×10^{4} M^{-1} cm^{-1} λ = 229 nm ε = 2.35×10^{4} M^{-1} cm^{-1} λ = 290 nm ε = 2.41×10^{3} M^{-1} cm^{-1}
Solubility in water at 20 °C	3.88 mg/L
Solubility in organic solvents at 20 °C (g/100 mL)	Solvent — Solubility (g/100 mL) acetone — > 25 acetonitrile — 16.76 dichloromethane — 14.61 ethylacetate — 12.33 methanol — 5.34 toluene — 2.00 n-octanol — 0.469 n-heptane — 0.0106
n-Octanol-water partition coefficient (K_{ow})	pH — log K_{ow} 4 — 3.09 7 — 3.13 9 — 3.09 deionized water — 3.08

Dissociation constant (pK_a)	12.58 (calculated)
Stability (temperature, metal)	Stable in the presence of metal and metal ions at normal and elevated temperatures

End-use Product—Xzemplar

Property	Result
Colour	Off white/light rose
Odour	Faintly fruity
Physical state	Opaque liquid
Formulation type	SU (Suspension)
Guarantee	Fluxapyroxad 300 g/L nominal
Container material and description	HDPE jugs or totes
Density	1.12 – 1.14 g/mL
pH of 1% dispersion in water	6.0 – 8.0
Oxidizing or reducing action	Not an oxidizing agent, a weak reducing agent
Storage stability	No degradation of active ingredient was observed after accelerated storage stability testing; a long-term study at ambient temperature is underway.
Corrosion characteristics	No corrosion observed to storage container
Explodability	The product is not explosive

1.3 Directions for Use

Xzemplar is applied prior to or in the early stages of disease development at 6.7 mL/100 m^2 on a 14 to 21 day interval, or at 8.3 mL/100 m^2 on a 21–28 day interval, and in accordance with the label, for the control of dollar spot on golf course turf grass.

1.4 Mode of Action

Fluxapyroxad is classified as a Group 7 fungicide by the Fungicide Resistance Action Committee (FRAC). Fluxapyroxad is a succinate-dehydrogenase inhibitor (SDHI) fungicide. It inhibits spore germination, mycelial growth, and sporulation of the fungus on the leaf surface.

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 the impurities in Xemium Fungicide Technical have been validated and assessed to be acceptable.

2.2 Method for Formulation Analysis

The method provided for the analysis of the active ingredient in Xzemplar has been validated and assessed to be acceptable for use as an enforcement analytical method.

3.0 Impact on Human and Animal Health

3.1 Toxicology Summary

Fluxapyroxad belongs to the SDHI fungicide class of pesticides. These fungicides work by blocking an enzyme within the fungus, which inhibits cellular respiration.

A detailed review of the toxicity studies conducted previously with fluxapyroxad was published in PRD2012-09, *Fluxapyroxad*. No new toxicological data were submitted and the public literature was searched for any new information. The scientific quality of the data is acceptable and the database is considered adequate to characterize the potential health hazards associated with fluxapyroxad. The toxicological reference values that were previously established in PRD2012-09 remain unchanged. Only consideration for aggregate and cumulative risk assessments were required in the context of this major new use review.

The results of acute toxicity studies conducted with the end-use product BAS 700 04 F, and summarized in Appendix I, Table 2d of PRD2012-09, were considered adequate to characterize the acute hazards of the end-use product Xzemplar. Based on the acute hazard profile of BAS 700 04 F, Xzemplar was considered to be of low acute toxicity via the oral, dermal and inhalation routes of exposure. It was minimally irritating to the skin, non-irritating to eyes and was not considered to be a dermal sensitizer.

After repeated oral dosing with fluxapyroxad, the liver and thyroid were the primary targets in all species tested. In rats and mice, the key treatment-related effects were changes in liver metabolism, which led to increased hypertrophy and hyperplasia in the liver and thyroid. Hepatocellular necrosis was also observed at higher dose levels in rats and mice in subchronic studies. In rats, oncogenicity was observed in the liver and thyroid. The available data supported a non-genotoxic, threshold mode of action for the development of these tumours. In dogs, damage to the liver was reflected by adverse clinical chemistry effects and, as the duration of treatment increased, fibrosis and cirrhosis of the liver. Other key treatment-related effects consisted of siderosis and impaired iron storage in rats and dogs as well as teeth whitening and shortened prothrombin time in rats only. While adverse effects in the liver were observed in all of the species tested, the thyroid effects were observed only in rats.

Results of the toxicology studies conducted on laboratory animals with fluxapyroxad are summarized in Appendix I, Table 2g of PRD2012-09. The toxicological reference values for use in the human health risk assessment are summarized in Appendix I, Table 3 of PRD2012-09.

Human Incident Reports

As of 19 July 2019, no human, domestic animal or environmental incident reports involving fluxapyroxad had been reported to the PMRA.

Aggregate Toxicology Reference Value

Aggregate exposure is the total exposure to a single pesticide that may occur from dietary, 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 fluxapyroxad is comprised of food, drinking water and residential exposure via the dermal route. No endpoint was selected for short- to intermediate-term aggregate risk assessment as there was no evidence of systemic toxicity in the repeat-dose dermal toxicity study, up to the limit dose. Therefore, the aggregate risk assessment for fluxapyroxad consisted of combining food and drinking water exposure only. The most relevant toxicological endpoint and uncertainty factors for acute and chronic dietary aggregate exposure are the same as those selected for the acute reference dose (ARfD) and acceptable daily intake (ADI), respectively (summarized in Appendix I, Table 3 of PRD2012-09).

3.2 Occupational and Residential Risk Assessment

Occupational exposure to fluxapyroxad is characterized as short- to intermediate-term in duration, and is predominantly by the dermal and inhalation routes. Exposure to fluxapyroxad when golfing on treated turf is characterized as short- to intermediate-term in duration, and is predominantly by the dermal route.

3.2.1 Dermal Absorption

A dermal absorption value was not required in the calculation of dermal exposure, since the short- to intermediate-term dermal endpoint is based on a dermal toxicity study.

3.2.2 Occupational Exposure and Risk

3.2.2.1 Mixer/loader/applicator Exposure and Risk Assessment

Individuals have potential for exposure to fluxapyroxad when mixing/loading and application. Exposure to workers mixing, loading and applying Xzemplar is expected to be short- to intermediate-term in duration and to occur primarily by the dermal and inhalation routes. Exposure estimates were derived for mixers/loaders/applicators applying Xzemplar at the maximum rate in golf courses using groundboom, backpack sprayer or turf gun.

The exposure estimates are based on mixers/loaders/applicators with the following personal protective equipment (PPE):

- long-sleeved shirt, long pants, chemical-resistant gloves, shoes and socks during mixing, loading, application, clean-up and repair.

As chemical-specific data for assessing human exposures were not submitted, dermal and inhalation exposures were estimated using the Agricultural Handlers Exposure Task Force (AHETF) data for groundboom application, the Outdoor Residential Exposure Task Force (ORETF) for turf gun/low pressure handgun application, and PHED version 1.1 values for backpack application. PHED is a compilation of generic mixer/loader and applicator passive dosimetry data with associated software which facilitates the generation of scenario-specific exposure estimates.

Dermal exposure was estimated by coupling the unit exposure values with the amount of product handled per day. A dermal absorption value was not required in the calculation of dermal exposure, since the short- to intermediate-term dermal endpoint is based on a dermal toxicity study. Inhalation exposure was estimated by coupling the unit exposure values with the amount of product handled per day with 100% inhalation absorption. Exposure was normalized to mg/kg bw/day by using 80 kg adult body weight. The dermal and inhalation exposure estimates were not combined since they do not share common toxicological effects.

Exposure estimates were compared to the toxicological reference values to obtain the margin of exposure (MOE); the target MOE is 100 for both exposure routes and all durations. Table 3.2.2.1.1 presents the AHETF, ORETF and PHED unit exposure values used and the estimates of exposure and risk for Xzemplar. Calculated MOEs are above the target MOE of 100 for workers who wear the PPE stated on the product label, and are, therefore, not of health concern.

Table 3.2.2.1.1 Mixer/Loader/Applicator Risk Assessment for Workers Handling Xzemplar

Exposure scenario	AHETF/ORETF/ PHED unit exposure (µg/kg a.i.)[1]		ATPD (ha/day)[2]	Maximum application rate (kg a.i./ha)	Exposure (mg/kg bw/day)		Calculated MOE[5]		
	Dermal	Inhalation			Dermal[3]	Inhalation[4]	Dermal	Inhalation	
								Short-term	Intermediate-term
Groundboom golf course	83.90	2.31	16	0.249	4.18×10^{-3}	1.15×10^{-4}	239 336	78 235	63 457
Turf gun	785	4.0	2	0.249	4.89×10^{-3}	2.49×10^{-5}	204 640	361 445	293 172
Backpack sprayer	5445.85	62.10	0.3	0.249	5.08×10^{-3}	5.80×10^{-5}	196 654	155 210	125 892

[1] Exposure was estimated for workers handling liquids and wearing a single layer plus gloves.
[2] Default area treated per day (ATPD) values for all but backpack sprayer; using the default 150 L/day from USEPA Policy No. 9 and a minimum application volume of 500 L/ha, the ATPD for backpack sprayers is calculated as follows: 150 L/day ÷ 500 L/ha = 0.3 ha/day.
[3] Dermal exposure = (unit-exposure × rate × ATPD × 0.001 mg/µg) / 80 kg bw
[4] Inhalation exposure = (unit-exposure × rate × ATPD × 0.001 mg/µg × 100% inhalation absorption) / 80 kg bw
[5] Margin of Exposure (MOE) = $NOAEL_{(route\text{-}specific)}$ / Exposure
Based on dermal NOAEL of 1000 mg/kg bw/day, and on inhalation NOAELs of 9 mg/kg bw/day for short-term exposure and 7.3 mg/kg bw/day for intermediate-term exposure; target MOE = 100 for all routes and durations.

3.2.2.2 Exposure and Risk Assessment for Workers Entering Treated Areas

There is potential for exposure to workers entering golf courses treated with Xzemplar when conducting various activities. The duration of exposure is expected to be short-term for all postapplication activities. The primary route of exposure for workers entering treated areas would be through the dermal route. Inhalation exposure is not considered to be a significant route of exposure for people entering treated areas compared to the dermal route, since fluxapyroxad is relatively non-volatile (8.1×10^{-9} kPa at 25 °C) and as such, an inhalation risk assessment was not required.

No chemical-specific transferable turf residue (TTR) data were submitted. Postapplication risk assessments were conducted with the maximum rate of Xzemplar. Dermal exposure to workers entering treated areas was estimated by coupling default TTR values (1% dislodgeable on the day of application, 10% dissipation per day) with activity-specific transfer coefficients and an exposure duration of 8 hours per day.

For postapplication risk, the dermal exposure estimates were compared to the toxicological reference value to obtain the MOE; the target MOE is 100. Table 3.2.2.2.1 presents the calculated MOEs on the day of application and the resulting restricted-entry interval (REI), which are not of concern.

Table 3.2.2.2.1 Postapplication Exposure and Risk Estimates on the Day of Application for Golf Courses Treated with Xzemplar

Re-entry activity	Peak DFR/TTR (µg/cm^2)[1]	Transfer coefficient (cm^2/hr)[2]	Dermal exposure (mg/kg bw/day)[3]	Calculated MOE[4]	REI[5]
Transplanting/Planting	0.0279	6700	0.0187	53 453	Until sprays have dried
Mowing, watering, and irrigation repair (and cup changing and miscellaneous grooming)		3500	0.00980	102 323	
Aerating, fertilizing, hand pruning, mechanical weeding, scouting, seeding		1000	0.00280	358 132	

[1] Calculated using the default for turf of 1% dislodgeable on the day of application and 10% dissipation per day
[2] Transfer coefficients (TCs) from the Agricultural Re-entry Task Force (ARTF)
[3] Exposure = (Peak DFR/TTR [µg/cm^2] × TC [cm^2/hr] × Exposure Duration (8 hours for workers) / (80 kg bw × 1000 µg/mg)
[4] Based on NOAEL of 1000 mg/kg bw/day, target MOE = 100
[5] Restricted-entry interval

3.2.3 Residential Exposure and Risk Assessment

3.2.3.1 Handler Exposure and Risk

Xzemplar is not a domestic class product; therefore, a residential handler assessment was not required.

3.2.3.2 Postapplication Exposure and Risk

Since Xzemplar is for use on turf grass on golf courses, there is potential for recreational postapplication exposure to the general population entering treated areas. The duration of exposure for golfing is considered to be short- to intermediate-term. The primary route of exposure for these individuals would be through the dermal route. Fluxapyroxad is considered non-volatile and it is not an inhalation concern for postapplication exposure.

Exposure was assessed according to equations and parameters stated in the 2012 US EPA Residential Standard Operating Procedures. Dermal exposure from golfing was assessed for adults (16 years plus), youth (11-<16 years) and children (6-<11 years) using default TTR values (1% dislodgeable on the day of application, 10% dissipation per day) and the toxicological reference value for short- to intermediate-term dermal exposure. Table 3.2.3.2.1 presents the calculated MOEs on the day of application for recreational dermal exposure, which are above the target MOE of 100, and therefore, not of health concern.

Table 3.2.3.2.1 Exposure and Risk Assessment for Golfers Entering Treated Turf Areas

Re-entry activity	Rate (kg a.i./ha)	Number of Applications (min RTI)	Age (Years)	Peak TTR (µg/cm^2)[1]	Transfer coefficient (cm^2/hr)[2]	Dermal exposure (mg/kg bw/day)[3]	MOE[4]
Golfing	0.249	3 (21 days)	16+	0.0279	5300	0.00740	140 000
			11<16		4400	0.00862	120 000
			6<11		2900	0.0101	99 000

[1] Calculated based on default values (1% TTR on the day of application, 10% dissipation per day)
[2] TC = Transfer coefficients from ARTF
[3] Exposure = (Peak TTR × TC × ED)/(body weight [bw] × 1000 µg/mg); ED = exposure duration (4 hours default)
[4] Based on NOAEL= 1000 mg/kg bw/day, target MOE = 100

3.2.3.3 Bystander Exposure and Risk

For Xzemplar applied to turf in golf courses, the risk to bystanders is considered negligible as exposure to spray drift is expected to be well below the exposure for mixers/loaders and applicators.

3.3 Exposure from Drinking Water

Concentrations in Drinking Water

The residue definition for drinking water included fluxapyroxad and its major transformation products M700F001 and M700F002. Estimated environmental concentrations (EECs) in potential sources of drinking water were calculated for the combined residues using the Pesticide in Water Calculator (PWC, version 1.52). For the human health assessment, EECs are calculated for both surface water and groundwater.

For surface water, PWC simulates pesticide runoff from a treated field into an adjacent water body and the fate of a pesticide within that water body. Pesticide concentrations in surface water were estimated in one type of vulnerable drinking water source, a small reservoir. For groundwater, PWC simulates leaching of the pesticide through a layered soil profile. The concentration is based on the movement of pesticide into shallow groundwater with time.

In order to capture the entire fluxapyroxad use pattern, separate modelling was conducted for the existing uses on crops and for the proposed use on turf. It is noted that crop uses were previously modelled to support the fluxapyroxad registration (PRD2012-09); however, given that modelling approaches have since evolved, crop uses were modelled again based on current standards to facilitate the comparison of results.

Drinking water modelling follows a tiered approach consisting of progressive levels of refinement. Level 1 EECs are conservative values intended to screen out pesticides that are not expected to pose any concern related to drinking water. These are calculated using conservative inputs with respect to application rate, application timing, and geographic scenario. Level 2 EECs are based on a narrower range application timing, methods, or geographic scenarios.

Uses on crops were modelled at Level 1 using the highest currently registered rates on crops. The surface water modelling was based on a single standard Level 1 scenario. Groundwater modelling considered several scenarios representing different regions of Canada; only the highest EECs from across these scenarios are reported. Uses on turf were modelled at Level 2 using turf-specific use information and turf-specific modelling scenarios for both surface water and groundwater.

Application information and the main environmental fate characteristics used in the models are summarized in Appendix I, Table 2. Resulting EECs in potential sources of drinking water are reported in Appendix I, Table 3. The Level 1 EECs on crops were found to be the most appropriate input values for the dietary exposure assessment, as a cover both the registered uses on crops and the proposed use on turf grass.

3.4 Food Residues Exposure Assessment

3.4.1 Residues in Plant and Animal Foodstuffs

Please refer to PRD2012-09 for summaries of the previously reviewed data. The information captured herein only relates to the changes in dietary exposure due to the modification in the drinking water assessments to support the registration of fluxapyroxad for use on golf course turf grass in Canada

3.4.2 Dietary Risk Assessment

Acute and chronic (cancer and non-cancer) dietary risk assessments were conducted using the Dietary Exposure Evaluation Model (DEEM–FCID™ Version 4.02).

3.4.2.1 Chronic Dietary Exposure Results and Characterization

The following criteria were applied to the intermediate refined chronic (cancer and non-cancer) analysis for fluxapyroxad: 100% percent crop treated, residues of treated crops based on supervised trial median residue (STMdR) values (for combined residues of fluxapyroxad plus metabolite M700F008), experimental processing factors for fluxapyroxad where available, and the Level I yearly EECs for groundwater based on the highest application rates for registered crop uses, which also covers the golf course turf use. The intermediate refined chronic dietary aggregate exposure from all supported fluxapyroxad food uses and drinking water is considered acceptable. The PMRA estimates that chronic dietary exposure to fluxapyroxad from food and drinking water is 33.5% (0.00704 mg/kg bw/day) of the ADI for the total population. The highest exposure and risk estimate is for all infants less than 1 year of age at 103.8% (0.0218 mg/kg bw/day) of the ADI. Although exposure to fluxapyroxad residues for the most susceptible subpopulation (all infants <1 year of age) exceeds the ADI, exposure is nevertheless considered to be acceptable given that drinking water accounted for 83.1% of the total exposure and the EEC values were calculated using the most conservative inputs with respect to application rate, application timing, and geographic scenario; as such, these values are considered protective.

3.4.2.2 Acute Dietary Exposure Results and Characterization

The following assumptions were applied in the basic acute analysis for fluxapyroxad: 100% percent crop treated, default processing factors (where applicable), MRLs for crops and all edible animal commodities, and the Level I daily EECs for groundwater based on the maximum application rate on all registered crops. The basic acute dietary aggregate exposure for food and drinking water for all supported fluxapyroxad registered commodities is estimated to be 6.7% (0.0833 mg/kg bw) of the ARfD for the total population (95^{th} percentile, deterministic). The highest exposure and risk estimate is for children 1–2 years of age at 12.6% (0.158 mg/kg bw) of the ARfD.

3.4.3 Aggregate Exposure and Risk

Although golf course turf grass can be treated with Xzemplar leading to potential exposure to fluxapyroxad through the diet as well as activities related to golfing, an aggregate risk assessment for fluxapyroxad was not conducted to include the dietary exposure from food and drinking water sources and the dermal exposure from the use on golf courses since there was no evidence of systemic toxicity in the repeat-dose dermal toxicity study, up to the limit dose.

3.4.4 Maximum Residue Limits

Please refer to the Maximum Residue Limit Database in the Pesticides and Pest Management section of Health Canada's website for the established MRLs for fluxapyroxad.

The nature of the residues in animal and plant matrices, analytical methodology and residue trial data were reported in PRD2012-09. The chronic (cancer and non-cancer) and acute dietary risk estimates are summarized in Appendix I, Table 4.

3.4.5 Cumulative Assessment

The *Pest Control Products Act* requires that the PMRA consider the cumulative exposure to pesticides with a common mechanism of toxicity. Accordingly, an assessment of a potential common mechanism of toxicity with other pesticides was undertaken for fluxapyroxad. Fluxapyroxad is an SDHI fungicide. Currently, there are approximately 22 SDHI pesticides approved for use worldwide. More than half of these SDHI pesticides, including fluxapyroxad, are registered for use in Canada. There is evidence of a similar spectrum of toxicological effects among SDHI pesticides, such as decreased body weight, and effects on the liver and thyroid gland. Additionally, oncogenicity in the liver and thyroid appears in multiple SDHI toxicological databases. Investigations into the mode of action for tumour formation have determined that the oncogenicity, in addition to the thyroid and liver toxicity related to the mode of action, are based on metabolic pathways in the laboratory animals that are not relevant to humans. Other effects on the liver and body weight are considered to represent a more generalized toxicity, and a common mechanism of toxicity has not been identified. Therefore, a cumulative health risk assessment is not required at this time.

4.0 Impact on the Environment

The environmental fate and ecotoxicology of fluxapyroxad were previously reviewed to support uses of fluxapyroxad on crops; please refer to PRD2012-09. The endpoints determined in the previous review were the basis of the current assessment for the proposed new use on golf course turf. A summary of the data is provided below. A revised environmental risk assessment was warranted since application rates on turf are higher than currently registered rates on crops.

4.1 Fate and Behaviour in the Environment

Fluxapyroxad exhibits low volatility and low aqueous solubility. Fluxapyroxad does not readily break down when it comes into contact with water or light, but will breakdown from the action of microbes.

Laboratory studies show that fluxapyroxad is moderately persistent to persistent in aerobic soils (DT_{50} from 89–2690 days), and slowly transforms into two major transformation products, M700F001 and M700F002. In aerobic soils, M700F001 is non-persistent (DT_{50} from 2.7–9.3 days) and M700F002 is moderately persistent (DT_{50} from 94–158 days). Fluxapyroxad was also shown to persist under terrestrial field conditions (DT_{50} from 338–366 days).

Fluxapyroxad adsorbs to soil. Conversely, the major transformation products M700F001 and M700F002 have very low adsorption. While the high sorption and low solubility of fluxapyroxad could suggest a low potential for leaching, this pesticide may still reach groundwater due to its persistence. The GUS (Groundwater Ubiquity Score) classifies fluxapyroxad as borderline leacher to leacher. In field dissipation studies, fluxapyroxad was found in soil up to a depth of 105 cm and M700F002 up to a depth of 75 cm one year after application, confirming the leaching potential.

Fluxapyroxad can enter the aquatic environment through spray drift, runoff or through the movement of soil particles to which fluxapyroxad is bound. Once it has entered a surface water system, fluxapyroxad is expected to partition to sediments due to its high sorption. Fluxapyroxad is persistent in both aerobic (DT_{50} of 713 days) and anaerobic water/sediment systems (DT_{50} of 1042 days).

In addition to the previously reviewed studies discussed above, one field dissipation study was provided specifically to support the proposed use on turf. In this study, fluxapyroxad was applied to both bare soil and turf covered plots, at a yearly rate of 900 g a.i. per hectare. Environmental conditions at the test site (in Georgia, United States) were not relevant to Canadian field conditions, and therefore, dissipation rates were not considered in the assessment. However, results pertaining to the leaching were found to be informative given the layout of the study, which allowed a side-by-side comparison of the behaviour of the pesticide in bare soil and turf covered plots. Results show that the leaching behaviour of fluxapyroxad is similar in turf than it is in bare soil. Quantifiable levels of fluxapyroxad were found up to depths of 12–18 inches (turf plots) and 6–12 inches (bare soil plots). Residues of M700F001 were not detected at any soil depth throughout the study period, and residues of M700F002 remained above 12 inches in the turf plot and above 3 inches in the bare ground plot.

4.2 Environmental Risk Characterization

The environmental risk assessment integrates the environmental exposure and ecotoxicology information to estimate the potential for adverse effects on non-target species. This integration is achieved by comparing exposure concentrations with concentrations at which adverse effects occur. The EECs are concentrations of pesticide in various environmental media, such as food, water, soil and air. The EECs are estimated using standard models which take into consideration the application rate(s), chemical properties and environmental fate properties, including the dissipation of the pesticide between applications. Ecotoxicology information includes acute and chronic toxicity data for various organisms or groups of organisms from both terrestrial and aquatic habitats including invertebrates, vertebrates, and plants. Toxicity endpoints used in risk assessments may be adjusted to account for potential differences in species sensitivity as well as varying protection goals (in other words, protection at the community, population, or individual level).

Initially, a screening level risk assessment is performed to identify pesticides and/or specific uses that do not pose a risk to non-target organisms, and to identify those groups of organisms for which there may be a potential risk. The screening level risk assessment uses simple methods, conservative exposure scenarios (for example, direct application at a maximum cumulative application rate) and sensitive toxicity endpoints. A risk quotient (RQ) is calculated by dividing the exposure estimate by an appropriate toxicity value (RQ = exposure/toxicity), and the risk quotient is then compared to the level of concern (LOC = 1). If the screening level risk quotient is below the level of concern, the risk is considered negligible and no further risk characterization is necessary. If the screening level risk quotient is equal to or greater than the level of concern, then a refined risk assessment is performed to further characterize the risk.

A refined assessment takes into consideration more realistic exposure scenarios (such as drift to non-target habitats) and might consider different toxicity endpoints. Refinements to the risk assessment may continue until the risk is adequately characterized or no further refinements are possible.

4.2.1 Risks to Terrestrial Organisms

A risk assessment of fluxapyroxad was undertaken for terrestrial organisms based on the proposed use pattern on turf and using the same toxicological endpoints as in PRD2012-09 for fluxapyroxad and relevant formulations.

Pollinators (bees): A quantitative assessment was not conducted for pollinators given the low attractiveness of golf course turf to pollinators, which would result in negligible exposure and risk to bees on the treated area. The risk to pollinators in habitats adjacent to the treated area is also expected to be negligible considering results of the previous assessment conducted for crop uses; given that the risk to bees on the treated field was found acceptable for crop uses, risk from spray drift resulting from ground application on turf (6% drift one meter from the treated area using ground application equipment) would be negligible despite the higher rate on turf than on crops.

Beneficial insects: Beneficial arthropods living in leafy foliage are not found in golf course turf and are not expected to be exposed to fluxapyroxad on the treated area. As is the case for bees, beneficial foliar invertebrates in habitats adjacent to the treated area are not expected to be at risk based on the previous assessment for crop uses. Results of the previous on-field assessment show refined risk quotients below the level of concern for BASF 700 04 F (a formulation comparable to Xzemplar), and the screening level risk quotients associated with the most conservative data (for BASF 700 01 F, which is similar but not the same as Xzemplar) only slightly exceeded the level of concern. Considering the low off-field drift rate of 6% using ground sprayer application, risks from spray drift would not be expected from turf uses despite the higher use rate.

Soil invertebrates: Laboratory studies conducted with technical grade fluxapyroxad, fluxapyroxad formulations and major soil transformation products showed low acute and chronic toxicity in soil-dwelling species such as earthworms and springtails. Screening level risk quotients, calculated assuming direct applications on bare soil, are below the level of concern (Appendix I, Table 5). Earthworms and other soil invertebrates are not at risk from the use of fluxapyroxad on turf.

Birds and mammals: Fluxapyroxad exhibits low acute toxicity to birds and mammals, while some effects are observed in chronic tests at high doses. The risk assessment considers the ingestion of food items contaminated with fluxapyroxad. At the screening level, food items representing the most conservative exposure levels are used. Screening level risk quotients do not exceed the level of concern for both birds and mammals (Appendix I, Table 7). Given results of the screening level assessment, no risks are expected for birds and mammals feeding off the treated area.

Non-target plants: No treatment-related adverse effects (> 25% effect) were observed in any plant species in either the vegetative vigour or seedling emergence assays. Some adverse effects were noted at the highest level tested for seedling emergence. At the screening level, the risk is assessed using exposure levels that would be expected directly on the treated area. Results indicate that non-target plants are not at risk for vegetative vigour. However, non-target plants located on the treated area may be expected to be at risk for seedling emergence (Appendix I, Table 5). Given that few non-target plants would be found on maintained turf areas, the risk is considered minimal. When risk quotients are calculated with drift one meter downwind from the site of application, the level of concern is no longer exceeded. A buffer zone of one meter will adequately mitigate potential risks to non-target terrestrial habitats located on the margins of the treated area.

4.2.2 Risks to Aquatic Organisms

The aquatic assessment for the use expansion on turf focused on refined exposure scenarios based on surface runoff and drift given that potential risks for certain aquatic species were identified in the original environmental assessment (PRD2012-09). The aquatic assessment considered fluxapyroxad only given the lower toxicity of the transformation products to aquatic organisms. Also, only species for which the level of concern was exceeded in the previous screening level assessment were considered in the current assessment for turf.

The EECs of fluxapyroxad from runoff into a receiving water body were simulated using the Pesticide in Water Calculator (v1.52). The PWC model calculates the amount of pesticide entering the water body and the subsequent degradation of the pesticide in the water and sediment. The modelling was conducted using turf specific scenarios. The most conservative EECs obtained from the modelling, in water bodies of 80 cm and 15 cm, are reported in Appendix I, Table 8.

Risk quotients calculated for runoff are below the level of concern for all non-target species, except amphibians on an acute basis (Appendix I, Table 9). Given that the level of concern is only slightly exceeded for amphibians using the most conservative EECs, the overall risks from runoff are considered acceptable.

To calculate potential risks from spray drift, the screening level EECs expected from a direct overspray (0.588 and 0.110 mg a.i./L in bodies of water of 15 cm and 80 cm, respectively) were adjusted according to the amount of drift expected at a distance of 1 metre from the treated area (6% drift with a field sprayer and a medium spray quality), resulting in an estimated exposures of 0.0353 mg a.i./L in 15 cm and 0.0066 mg a.i./L in 80 cm of water. With these exposure levels, the level of concern is slightly exceeded only for amphibians on an acute basis. These risks will be mitigated with a spray buffer zone of 1 metre.

5.0 Value

Fluxapyroxad is a new conventional active ingredient for disease management on turf grass in Canada. There are multiple products registered in Canada for control, suppression or partial suppression of dollar spot on turf grass. The registration of Xzemplar will provide users with a

new FRAC group 7 option to manage this widespread and destructive fungal disease on golf course turf grass. Efficacy data from field trials, use history information and published articles confirmed that Xzemplar is effective against dollar spot.

As no phytotoxicity or other adverse effects were observed on turf grass in the trial studies, application of Xzemplar is not expected to result in any injury to golf course turf grass when used according to label directions. Details of the supported uses are provided in Appendix I, Table 10.

6.0 Pest Control Product Policy Considerations

6.1 Toxic Substances Management Policy Considerations

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, such as, 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, fluxapyroxad and its transformation products were assessed in accordance with the PMRA Regulatory Directive DIR99-03[5] and evaluated against the Track 1 criteria. The PMRA has reached the conclusion that fluxapyroxad technical fungicide and its transformation products do not meet all of the TSMP Track-1 criteria.

Please refer to PRD2012-09, *Fluxapyroxad,* for further information on the TSMP assessment.

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*.[6] The list is used as described in the PMRA Notice of Intent NOI2005-01[7] and is based on existing policies and regulations, including the Toxic Substances Management Policy and Formulants Policy,[8] and taking into consideration the Ozone-depleting Substance Regulations, 1998, of the *Canadian Environmental Protection Act* (substances designated under the Montreal Protocol).

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

6 SI/2005-114, last amended on 25 June 2008. See Justice Laws website, Consolidated Regulations, *List of Pest Control Products Formulations and Contaminants of Health or Environmental Concern*.

7 PMRA's Notice of Intent NOI2005-01, *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern* under the New *Pest Control Products Act*.

8 DIR2006-02, *Formulants Policy and Implementation Guidance Document.*

- The PMRA has reached the conclusion that technical grade fluxapyroxad and its end-use product Xzemplar 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 the PMRA formulant initiatives and Regulatory Directive DIR2006-02.

7.0 Summary

7.1 Human Health and Safety

The toxicology database submitted for fluxapyroxad is adequate to define the majority of toxic effects that may result from exposure. There was no evidence of increased susceptibility of the young in reproduction or developmental toxicity studies. Fluxapyroxad is not neurotoxic. In short-term and chronic studies on laboratory animals, the primary targets were the liver and thyroid. The key effects were: changes in clinical chemistry and liver histopathology as dose and duration of exposure increased, as well as iron deposition and teeth whitening, thyroid gland effects, and decreased prothrombin time. There was also evidence of liver and thyroid carcinogenicity in rats after longer-term dosing. A non-genotoxic, threshold mode of action for the development of these tumours was supported and consequently a threshold approach was applied for the cancer risk assessment. The risk assessment protects against the toxic effects noted above by ensuring that the level of human exposure is well below the lowest dose at which these effects occurred in animal tests.

Mixers, loaders and applicators handling Xzemplar and workers re-entering treated turf in golf courses are not expected to be exposed to levels of fluxapyroxad that will result in health risks of concern when Xzemplar is used according to label directions. The PPE on the product label is adequate to protect workers.

Exposure to the general public entering treated golf courses is not expected to result in health risks of concern when Xzemplar is used according to label directions.

Please refer to PRD2012-09, for previously reviewed data regarding the food residue exposure assessment. The use of fluxapyroxad on golf course turf grass does not constitute a health risk of concern for chronic dietary exposure (food and drinking water) to any segment of the population, including infants, children, adults and seniors.

7.2 Environmental Risk

The use of Xzemplar, containing the active ingredient fluxapyroxad, is not expected to pose risks of concern to non-target terrestrial and aquatic organisms when used in accordance with the label directions. Precautionary label statements to advise users that fluxapyroxad is toxic to terrestrial plants and aquatic organisms are required.

7.3 Value

Fluxapyroxad, the active ingredient of Xzemplar, is effective against dollar spot, an important fungal disease of cool-season turf grass when used as a preventative foliar treatment. The availability of Xzemplar will provide Canadian users with a new FRAC group 7 option to manage dollar spot on golf course turf grass.

8.0 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 Xemium Technical Fungicide and Xzemplar, containing the technical grade active ingredient fluxapyroxad, to control dollar spot on golf course turf grass.

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.

List of Abbreviations

<	less than
>	greater than
ε	Molar Absorption coefficient
λ	wavelength
µg	micrograms
°C	degree centigrade
a.i.	active ingredient
ADI	acceptable daily intake
AHETF	Agricultural Handlers Exposure Task Force
ARfD	acute reference dose
ARTF	Agricultural Reentry Task Force
ATPD	Area Treated per Day
bw	body weight
CAS	Chemical Abstracts Service
cm	centimetres
d	day
DEEM-FCID	Dietary Exposure Evaluation Model
DFR	dislodgeable entry interval
DIR	Regulatory Directive
DNA	deoxyribonucleic acid
DT_{50}	dissipation time 50% (the dose required to observe a 50% decline in concentration)
dw	dry weight
EC_{25}	effective concentration on 25% of the population
ECO	ecological water modelling
ED	exposure duration
EDE	estimated daily exposure
EEC	estimated environmental concentration
ELS	early life stage
FRAC	Fungicide Resistance Action Committee
g	gram
GUS	Groundwater Ubiquity Score
GW	groundwater (drinking water) modelling
ha	hectare(s)
HDPE	high density polyethylene
HPLC-MS/MS	high performance liquid chromatography with tandem mass spectrometry
hr	hour(s)
IUPAC	International Union of Pure and Applied Chemistry
kg	kilogram
K_{oc}	organic-carbon partition coefficient
K_{ow}	*n*–octanol-water partition coefficient
kPa	kiloPascal
L	litre
LC_{50}	lethal concentration 50%
LD_{50}	lethal dose 50%

LOC	level of concern
LOQ	limit of quantitation
LR_{50}	lethal rate 50%
M	mole
m	metre(s)
m^2	metre squared
mg	milligram
mL	millilitre
min	minimum
MOE	margin of exposure
MRL	maximum residue limit
MS	mass spectrometry
MS-MS	tandem mass spectrometry
nm	nanometre
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
NOEL	no observed effect level
ORETF	Outdoor Residential Exposure Task Force
Pa	Pascal
PHED	Pesticide Handlers Exposure Database
pH	measure of the acidity or basicity of an aqueous solution
p*K*a	dissociation constant
PMRA	Pest Management Regulatory Agency
PPE	personal protective equipment
ppm	parts per million
PRD	Proposed Registration Decision
PWC	Pesticide Water Calculator
REI	restricted-entry interval
RQ	risk quotient
RTI	retreatment interval
SDHI	succinate-dehydrogenase inhibiting
STMdR	supervised trial median residue
SW	surface water (drinking water) modelling
$t_{1/2}$	half-life
T3	tri-iodothyronine
T4	thyroxine
TC	transfer coefficient
TRR	total radioactive residue
TSMP	Toxic Substances Management Policy
TTR	transferable turf residue
USEPA	United States Environmental Protection Agency
UV	ultraviolet

Appendix I Tables and Figures

Table 1 Residue Analysis

Matrix	Method ID	Analyte	Method Type	MS-MS transition monitored	LOQ	Reference
Soil	D0903, L0092	Active	HPLC-MS/MS	382 → 362[1] 382 → 342[2]	0.001 mg/kg	1883545 1883543 1883541
		M700F001		175 → 91[1]		
		M700F002		161 → 141[1]		
Water	L0143/01	Active	HPLC-MS/MS	382 → 362[1] 382 → 342[2]	0.03 µg/L	1883548
		M700F001		175 → 91[1] 175 → 111[2]		
		M700F002		161 → 141[1] 161 → 97[2]		
		M700F007		176 → 156[1] 176 → 136[2]		

[1]Primary transition
[2]Secondary transition

Table 2 Major Inputs for the Water Modelling of Fluxapyroxad

Type of Input	Parameter	Value
Application Information	Modelled use pattern	Crops: 200 + 200 + 200 g a.i./ha with an interval of 7 days; maximum seasonal rate of 600 g a.i./ha Turf: 249 + 249 + 201 + 201 g a.i./ha at intervals of 21, 21 and 14 days; maximum seasonal rate of 900 g a.i./ha
	Modelled method of application	Crops: aerial Turf: ground foliar
Environmental Fate Characteristics	Hydrolysis half-life at pH 7 (days)	Stable
	Photolysis half-life in water (days)	Stable
	Adsorption K_{oc} (mL/g)	Fluxapyroxad: 721.6 (SW, ECO, GW) M700F001: 0.62 (GW) M700F002: 6.9 (GW) (20^{th} percentile of K_{OC} values)

	Aerobic soil biotransformation half-life (days) at 20 ºC	Combined: 2138 (SW) Fluxapyroxad: 1364 (GW and ECO) M700F001: 6.9 (GW) M700F002: 136.0 (GW) (90th percentile confidence on the mean of 11, 11, 3 and 4 values, respectively)
	Aerobic aquatic biotransformation half-life (days) at 20 ºC	929 (SW) and 820 (ECO) (longest of two values)
	Anaerobic aquatic biotransformation half-life (days) at 20 ºC	1042 (SW and ECO) (single value)

ECO = ecological water modelling; SW = surface water (drinking water) modelling; GW = groundwater (drinking water) modelling

Table 3 EECs of the Combined Residue of Fluxapyroxad, M700F001 and M700F002 in Potential Sources of Drinking Water, Reported as Parent Equivalent

Use pattern	Groundwater (µg a.i./L)		Surface Water (µg a.i./L)	
	Daily[1]	Yearly[2]	Daily[3]	Yearly[4]
Level 1 Crops: 200 + 200 + 200 g a.i./ha at 7 day intervals	240	240	28	6.2
Level 2 Turf: 249 + 249 + 201 + 201 g a.i./ha at intervals of 21, 21 and 14 days	205	205	14	7.3

1 90th percentile of daily average concentrations
2 90th percentile of 365-day moving average concentrations
3 90th percentile of 1-day concentrations from each year
4 90th percentile of yearly average concentrations

Table 4 Food Residue Chemistry Overview of Metabolism Studies and Risk Assessment

DIETARY RISK FROM FOOD AND DRINKING WATER		
	POPULATION	**ESTIMATED RISK % OF ACUTE REFERENCE DOSE (ARfD)**
		Food and Drinking Water
Basic acute dietary exposure analysis, 95th percentile **ARfD = 1.25 mg/kg bw** **Level I Estimated acute drinking water concentration [EEC] = 0.240 ppm**	All infants <1 year	6.7
	Children 1–2 years	9.3
	Children 3–5 years	12.6
	Children 6–12 years	10.5
	Youth 13–19 years	6.5
	Adults 20–49 years	5.1
	Adults 50+ years	6.0

DIETARY RISK FROM FOOD AND DRINKING WATER		
	Females 13–49 years	5.9
	Total population	6.1
	POPULATION	**ESTIMATED RISK % OF ACCEPTABLE DAILY INTAKE (ADI)**
		Food and Drinking Water
Intermediate refined chronic [non-cancer and cancer] dietary exposure analysis **ADI = 0.021 mg/kg bw/day** **Level I estimated chronic drinking water concentration [EEC] = 0.240 ppm**	All infants <1 year	33.5
	Children 1–2 years	103.8
	Children 3–5 years	61.1
	Children 6–12 years	47.4
	Youth 13–19 years	31.2
	Adults 20–49 years	23.0
	Adults 50+ years	31.8
	Females 13–49 years	32.0
	Total population	31.6

Table 5 Screening Level Risk Assessment for Non-Target Terrestrial Species Other Than Birds and Mammals

Organism	Exposure	Test Substance	Endpoint	EEC	RQ
Invertebrates					
Earthworm *(Eisenia fetida)*	Acute, 14 days	BAS 700 F	1/2 LC_{50} > 1000 mg a.i./kg soil dw	0.3948 mg a.i./kg soil dw	<0.01
		BAS 700 01 F	1/2 LC_{50} > 59.58 mg a.i./kg soil dw	0.3948 mg a.i./kg soil dw	<0.01
	Chronic, 56-days (28-day exposure)	BAS 700 F	NOEC = 21.22 mg a.i./kg soil dw	0.3948 mg a.i./kg soil dw	0.02
		M700F002	NOEC = 2.56 mg/kg soil dw (high test concentration)	0.169 mg a.i./kg soil dw	0.066
Rove beetle (*Aleochara bilineata*)	35-day exposure (residues on natural soil)	BAS 700 01 F	LR_{50} = 906.3 g a.i./ha	888.2 g a.i./ha	0.98
Springtail (*Folsomia candida*)	Chronic, 28-day	BAS 700 01 F	NOEC = 2.98 mg a.i./kg soil dw	0.3948 mg a.i./kg soil dw	0.13
		M700F002	NOEC = 1000 mg a.i./kg soil dw	0.169 mg a.i./kg soil dw	<0.01

Vascular Plants					
Cabbage, carrot lettuce and other crops	Vegetative vigour (21 days observation)	BAS 700 01 F	EC_{25} > 400 g a.i./ha	249 g a.i./ha	0.62
	Seedling emergence (21 days observation)	BAS 700 01 F	EC_{25} > 400 g a.i./ha	888.2 g a.i./ha	**<2.2**

Endpoints from PRD2012-09. Bolded values indicate that the LOC is exceeded (LOC = 1).

Table 6 Toxicity Data for the Bird and Mammal Assessment

Study type	Dose-based endpoint	Toxicity dose (mg a.i./kg bw/day)	Uncertainty factor	Value used for the risk assessment
Birds				
Acute oral	LD_{50}	2000	10	200
Acute dietary	5-d LD_{50}	561	10	56.1
Reproduction	NOEL	31.9	1	31.9
Mammals				
Acute oral	LD_{50}	2000	10	200
Reproduction	NOEL	285.4	1	285.4

Endpoints from PRD2012-09.

Table 7 Screening Level Risk Assessment for Birds and Mammals

	Toxicity (mg a.i./kg bw/d)	Feeding Guild (food item)	EDE (mg a.i./kg bw)	RQ
Birds				
Small-sized Bird (0.02 kg)				
Acute	200	Insectivore	28.81	0.14
Reproduction	31.9	Insectivore	28.81	0.90
Medium-sized Bird (0.1 kg)				
Acute	200	Insectivore	22.48	0.11
Reproduction	31.9	Insectivore	22.48	0.70
Large-sized Bird (1 kg)				
Acute	200	Herbivore (short grass)	14.52	0.07
Reproduction	31.9	Herbivore (short grass)	14.52	0.46
Mammals				
Small-sized Mammal (0.015 kg)				
Acute	200	Insectivore	16.57	0.08
Reproduction	285.4	Insectivore	16.57	0.06
Medium-sized Mammal (0.035 kg)				
Acute	200	Herbivore (short grass)	32.14	0.16
Reproduction	285.4	Herbivore (short grass)	32.14	0.11

	Toxicity (mg a.i./kg bw/d)	Feeding Guild (food item)	EDE (mg a.i./kg bw)	RQ
Large-sized Mammal (1 kg)				
Acute	200	Herbivore (short grass)	17.17	0.09
Reproduction	285.4	Herbivore (short grass)	17.17	0.06

Table 8 EECs in Surface Water Due to Runoff

Use pattern	Depth of water body	EECs (µg a.i./L)		
		Peak	4 day	21 day
Turf: 249 + 249 + 201 + 201 g a.i./ha at intervals of 21, 21 and 14 days	15 cm	44	33	21
	80 cm	16	15	14

Table 9 Refined Risk Assessment for Aquatic Organisms Based on Surface Runoff and Drift

Organism	Exposure	Test Substance	Endpoint Value	Runoff		Drift	
				EEC (mg a.i./L)	RQ	EEC (mg a.i./L)	RQ
Common carp *(Cyprinus carpio)*	Acute 96-hour flow-through	BAS700 F	1/10 LC_{50} = 0.029 mg a.i./L	0.015	0.52	0.0066	0.23
Fathead minnow *(Pimephales promelas)*	Acute 96-hour flow-through	BAS 700 F	1/10 LC_{50} = 0.0466 mg a.i./L	0.015	0.32	0.0066	0.14
	Chronic (ELS) 33-days flow-through	BAS 700 F	NOEC = 0.036 mg a.i./L (mean length)	0.014	0.39	0.0066	0.18
Amphibians (using fish as a surrogate)	Acute 96-hour flow-through	BAS700 F	1/10 LC_{50} = 0.029 mg a.i./L	0.033	**1.14**	0.035	**1.22**
	Chronic (ELS) 33-days flow-through	BAS 700 F	NOEC = 0.036 mg a.i./L (mean length)	0.021	0.58	0.035	0.98

Runoff EECs were generated from modelling. Drift EECs were calculated by adjusting screening level EECs with 6% drift. Endpoints from PRD2012-09. Bolded values indicate that the LOC is exceeded (LOC = 1).

Table 10 List of Supported Uses

Supported use claims for Xzemplar
Use Xzemplar for the control of dollar spot (*Sclerotinia homoeocarpa*) on golf course turf grass at 6.7 mL/100 m^2 (200 g a.i./ha) on a 14–21 day interval, or at 8.3 mL/100 m^2 (250 g a.i./ha) on a 21–28 day interval. Apply prior to or in early stages of disease development. Use the shorter application interval and/or the higher rate when prolonged favourable disease conditions exist. Do not apply more than two (2) sequential applications. No more than 3.0 L product/ha may be applied annually.

References

A. List of Studies/Information Submitted by Registrant

PMRA Document Number **References**

1.0 Chemistry

None

2.0 Human and Animal Health

None

3.0 Environment

2875388 2012, Terrestrial Field Dissipation of BAS 700 F Following Broadcast Applications of BAS 700 AC F in Turf, DACO: 8.3.2.1

4.0 Value

2875377 2018, Part 10 Value Assessment, DACO: 10.1,10.2.1,10.2.2,10.2.3,10.2.3.1,10.3, 10.3.2(B),10.4,10.5,10.5.1,10.5.2,10.5.3,10.5.4
2875378 2017, DACO 10.2.4 History of Use table, DACO: 10.2.4
2875379 2018, Trial Reports, DACO: 10.2.3.3(D),10.3.2(B)