Proposed Registration Document PRD2014-12

Halauxifen-Methyl

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Publications
Pest Management Regulatory Agency
Health Canada
2720 Riverside Drive
A.L. 6604-E2
Ottawa, Ontario K1A 0K9

Internet: pmra.publications@hc-sc.gc.ca
healthcanada.gc.ca/pmra
Facsimile: 613-736-3758
Information Service:
1-800-267-6315 or 613-736-3799
pmra.infoserv@hc-sc.gc.ca

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Overview

Proposed Registration Decision for Halauxifen-Methyl

Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act* and Regulations, is proposing full registration for the sale and use of XDE-729 Methyl Technical Herbicide and its end-use products, GF-2685 Herbicide, Paradigm Herbicide and Pixxaro A Herbicide, containing the technical grade active ingredient halauxifen, present as methyl ester, for control of annual broadleaf weeds in cereal crops (spring wheat, winter wheat, durum wheat and spring barley). Halauxifen, present as methyl ester, is referred to as halauxifen-methyl in this consultation document.

GF-2685 Herbicide is formulated with halauxifen-methyl and the safener, cloquintocet-mexyl. Paradigm Herbicide contains halauxifen-methyl and florasulam. Pixxaro A Herbicide is formulated with halauxifen-methyl, fluroxypyr and the safener cloquintocet-mexyl.

An evaluation of available scientific information found that, under the approved conditions of use, the product has value and does not present an unacceptable risk to human health or the environment.

This Overview describes the key points of the evaluation, while the Science Evaluation provides detailed technical information on the human health, environmental and value assessments of XDE-729 Methyl Technical Herbicide and its end-use products, GF-2685 Herbicide, Paradigm Herbicide and Pixxaro A Herbicide.

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 (for example, those

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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."

most sensitive to environmental contaminants). 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 PMRA regulates pesticides, the assessment process and risk-reduction programs, please visit the Pesticides and Pest Management portion of Health Canada's website at healthcanada.gc.ca/pmra.

Before making a final registration decision on halauxifen-methyl, the PMRA will consider all comments received from the public in response to this consultation document[3]. The PMRA will then publish a Registration Decision[4] on halauxifen-methyl, which will include the decision, the reasons for it, a summary of comments received on the proposed final registration decision and the PMRA's response to these comments.

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

What Is Halauxifen-Methyl?

Halauxifen-methyl is the first member of a new chemical class of synthetic auxin herbicides, the arylpicolinates. It belongs to the Weed Science Society of America (WSSA) Group 4 herbicides and to the Herbicide Resistance Action Committee (HRAC) Group O. Halauxifen-methyl mimics the effect of a persistent high dose of the natural plant hormone auxin, causing over-stimulation of specific auxin-regulated genes which result in the disruption of several growth processes in susceptible plants. Tissues that are undergoing active cell division and growth are particularly susceptible to injury.

Health Considerations

Can Approved Uses of Halauxifen-Methyl Affect Human Health?

Products containing halauxifen-methyl are unlikely to affect your health when used according to label directions.

Potential exposure to halauxifen-methyl may occur through the diet (food and water) or when handling and applying end-use products. 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). 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 where no effects are observed. The health effects noted in animals occur at doses more than 100-times higher (and often much higher) than levels

[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*.

to which humans are normally exposed when pesticide products are used according to label directions.

Halauxifen-methyl is the active proposed for registration. The majority of the toxicology data was conducted with its acid form, herein referred to as halauxifen acid. Acceptable bridging data were provided and halauxifen acid was considered to be the relevant compound for risk assessment purposes.

In laboratory animals, the technical grade active ingredient halauxifen-methyl was of low acute toxicity by the oral and dermal routes of exposure. It was non-irritating to the eyes and skin, and did not cause allergic skin reactions. Consequently, hazard signal words are not required on the label.

The associated end-use products, GF-2685 Herbicide, Paradigm Herbicide and Pixxaro A Herbicide, were of low acute toxicity via the oral, dermal and inhalation routes of exposure. Paradigm Herbicide was minimally irritating to eyes and skin. Pixxaro A Herbicide was moderately irritating to the eye and mildly irritating to the skin. Therefore, the hazard signal words "WARNING EYE AND SKIN IRRITANT" are required on the label. GF-2685 Herbicide was minimally irritating to the eye, but mildly irritating to the skin; consequently, the hazard signal words "CAUTION SKIN IRRITANT" must appear on the label. All of the end-use products caused allergic skin reactions and therefore, the hazard signal words "POTENTIAL SKIN SENSITIZER" are required on all the labels.

Health effects in animals given repeated doses of halauxifen-methyl included effects on the liver and thyroid. In animals given repeated doses of halauxifen acid, treatment-related effects were observed in the kidneys and urinary bladder.

Halauxifen acid did not cause cancer in animals and there was no evidence that halauxifen-methyl or halauxifen acid damages genetic material. There was no indication that halauxifen acid caused damage to the nervous system and halauxifen-methyl did not affect the immune system. There were no treatment-related effects on the ability to reproduce after treatment with halauxifen acid.

When halauxifen-methyl or halauxifen acid was given to pregnant animals, resorptions were observed in rats at doses that were toxic to the mother, indicating that the young do not appear to be more sensitive than the adult animal; however, some fetal loss occurred in rabbits at a dose considered to be only marginally toxic to the mother.

The risk assessment protects against the effects of halauxifen-methyl and halauxifen acid by ensuring that the level of human exposure is well below the lowest dose at which these effects occurred in animal tests.

Residues in Water and Food

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

Aggregate dietary intake estimates (food plus drinking water) revealed that the general population and all subpopulations are expected to be exposed to <1% of the acceptable daily intake. Based on these estimates, the chronic dietary risk from halauxifen-methyl is not of health concern for all population subgroups.

Halauxifen-methyl is not carcinogenic; therefore, a cancer dietary risk assessment is not required.

An acute dietary exposure assessment was not conducted since an acute reference dose (ARfD) was not established.

The *Food and Drugs Act* prohibits the sale of adulterated food, that is, food containing a pesticide residue that exceeds the established maximum residue limit (MRL). Pesticide MRLs are established for *Food and Drugs Act* purposes through the evaluation of scientific data under the *Pest Control Products Act* . Food containing a pesticide residue that does not exceed the established MRL does not pose an unacceptable health risk.

Residue trials conducted throughout the United States and Canada using halauxifen-methyl on wheat (spring and winter varieties) and barley are acceptable. The MRLs for this active ingredient can be found in the Science Evaluation section of this consultation document.

The end-use products are also formulated with fluroxypyr, or florasulam, and/or with the safener cloquintocet-mexyl. Fluroxypyr, florasulam and cloquintocet-mexyl are already registered for foliar treatment use in Canada on wheat and barley.

Occupational Risks from Handling GF-2685 Herbicide, Paradigm Herbicide and Pixxaro A Herbicide

Occupational risks are not of concern when GF-2685 Herbicide, Paradigm Herbicide or Pixxaro A Herbicide is used according to the proposed label directions, which include protective measures.

Farmers and custom applicators who mix, load or apply GF-2685 Herbicide, Paradigm Herbicide or Pixxaro A Herbicide, as well as field workers re-entering freshly treated fields, can come into direct contact with halauxifen-methyl residues on the skin or through inhalation of spray mists. Therefore, the label specifies that anyone mixing/loading and applying Pixxaro A Herbicide, Paradigm Herbicide, or GF-2685 Herbicide must wear a long-sleeved shirt, long pants, shoes, socks and chemical-resistant gloves (gloves are not required during application). Mixer/loaders of Pixxaro A Herbicide must also wear eye protection. The label also requires that workers do not enter treated fields for 12 hours after application. Taking into consideration these label statements, the number of applications and the expectation of the exposure period for handlers and workers, the risk to these individuals are not expected to be of concern.

Paradigm Herbicide is a co-formulation with florasulam, and Pixxaro A Herbicide is a co-formulation with fluroxypyr. In addition, the safener cloquintocet-mexyl is co-formulated in GF-2685 and Pixxaro A Herbicide. Florasulam, fluroxypyr and cloquintocet-mexyl are registered for use on wheat and barley. The precautions required to mitigate risk from the exposure of halauxifen-methyl are also adequate for the co-formulated active ingredients and safener. Florasulam, fluroxypyr and cloquintocet-mexyl will not be further discussed herein.

For bystanders, exposure is expected to be much less than that for workers and is considered negligible. Therefore, health risks to bystanders are not of concern.

Environmental Considerations

What Happens When Halauxifen-Methyl Is Introduced Into the Environment?

Halauxifen-methyl can pose a risk to non-target terrestrial plants and aquatic vascular plants; therefore, statements on the product labels are required to inform users of the potential risks, and spray buffer zones are required during application.

Halauxifen-methyl enters the environment when applied to control broadleaf weeds on certain cereal crops. Halauxifen-methyl can break down by reacting with water or in the presence of soil microbes and is unlikely to persist in terrestrial systems. The properties of halauxifen-methyl and its transformation products, XDE-729 acid (X11393729) and X11449757, indicate some potential for movement through the soil. In field studies, the majority of halauxifen-methyl and its transformation products were measured in the top 30 cm of soil. Conservative modelling data indicates that levels of halauxifen-methyl and its transformation products that may reach groundwater are very low. In aquatic environments, halauxifen-methyl is rapidly broken down in the presence of sunlight, in the presence of microbes or by reacting with water. It is not expected to move into the sediment to a great extent or accumulate in aquatic organisms. Halauxifen-methyl is not expected to enter the atmosphere.

When used according to label directions, halauxifen-methyl is expected to pose a negligible risk to earthworms, bees, birds, small mammals, aquatic invertebrates, amphibians, algae and fish. Halauxifen-methyl may pose a risk to non-target terrestrial and aquatic plants. Risks to non-target terrestrial and aquatic plants can be mitigated with label statements and spray buffer zones to protect sensitive terrestrial and aquatic habitats. Label statements are required on the product labels to inform the users of the potential risks.

The use of the end-use product Paradigm Herbicide contains the active ingredients halauxifen-methyl and florasulam. Florasulam and its major soil transformation product, 5-hydroxy-XDE-570, have the potential to leach. Also, 5-hydroxy-XDE-570 has the potential to carry over into the next growing season. Label statements are required on the label for Paradigm Herbicide to inform users of the potential risks of leaching and carry-over.

The use of the end-use product Pixxaro A Herbicide contains aromatic petroleum distillates which are toxic to aquatic organisms. Label statements are required on the label for Pixxaro A Herbicide to inform users of the potential risks.

Value Considerations

What Is the Value of GF-2685 Herbicide, Paradigm Herbicide or Pixxaro A Herbicide?

Halauxifen-methyl is a postemergence herbicide that can be used at different rates of application to target specific weeds.

GF-2685 Herbicide, Paradigm Herbicide and Pixxaro A Herbicide provide control of important broadleaf weeds and may enable growers to control both broadleaf and grass weeds with a single pass in spring wheat, winter wheat, durum wheat, and barley when tank-mixed with various herbicides listed on the end-use product labels. Halauxifen-methyl has little residual activity following a postemergence application which allows for flexibility in crop rotation with numerous crops that can be seeded after an interval of 10 months following an application of any of the three end-use products.

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 GF-2685 Herbicide, Paradigm Herbicide or Pixxaro A Herbicide 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 halauxifen-methyl on the skin or through inhalation of spray mists, anyone mixing, loading and applying Pixxaro A Herbicide, Paradigm Herbicide or GF-2685 Herbicide must wear long-sleeved shirt, long pants, shoes, socks and chemical-resistant gloves (gloves are not required during application). Mixer/loaders of Pixxaro A Herbicide must also wear eye protection. In addition, standard label statements to protect against drift during application were added to the label.

Environment

Halauxifen-methyl can pose a risk to non-target terrestrial and aquatic plants. The use of the end-use products Paradigm Herbicide, containing the active ingredients halauxifen-methyl and florasulam, and Pixxaro A Herbicide, containing halauxifen-methyl and fluroxypyr present as

methylheptyl ester, can also pose a risk to non-target terrestrial and aquatic plants. Label statements and spray buffer zones to protect sensitive terrestrial and aquatic habitats are to be specified on the labels.

To mitigate potential exposures to halauxifen-methyl via spray drift, spray buffer zones of 1 to 100 metres are required to protect sensitive terrestrial habitats, and spray buffer zones of 1 to 10 metres are required to protect sensitive aquatic habitats, depending on the end-use product and the method of application. These spray buffer zones are to be specified on the product labels.

Label statements are required on the label for Paradigm Herbicide to inform users of the potential risks of leaching of florasulam and its major soil transformation product, 5-hydroxy-XDE-570, and the potential for carry-over of 5-hydroxy-XDE-570.

Label statements are required on the label for Pixxaro A Herbicide to inform users of the potential risks to aquatic organisms from the aromatic petroleum distillates contained in the end-use product.

Next Steps

Before making a final registration decision on halauxifen-methyl, the PMRA will consider all comments received from the public in response to this consultation document. The PMRA will accept written comments on this proposal up to 45 days from the date of publication of this document. Please note that, to comply with Canada's international trade obligations, consultation on the proposed MRLs will also be conducted internationally via a notification to the World Trade Organization. Please forward all comments to Publications (contact information on the cover page of this document). The PMRA will then publish a Registration Decision, which will include its decision, the reasons for it, a summary of comments received on the proposed final decision and the Agency's response to these comments.

Other Information

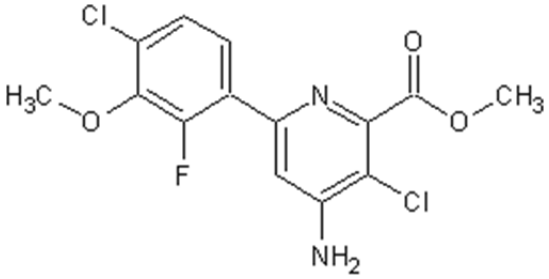
When the PMRA makes its registration decision, it will publish a Registration Decision on halauxifen-methyl (based on the Science Evaluation of this consultation document). In addition, the test data referenced in this consultation document will be available for public inspection, upon application, in the PMRA's Reading Room (located in Ottawa).

Science Evaluation

Halauxifen-Methyl

1.0 The Active Ingredient, Its Properties and Uses

1.1 Identity of the Active Ingredient

Active substance	Halauxifen-methyl
Function	Herbicide
Chemical name	
1. International Union of Pure and Applied Chemistry (IUPAC)	methyl 4-amino-3-chloro-6-(4-chloro-2-fluoro-3-methoxyphenyl)pyridine-2-carboxylate
2. Chemical Abstracts Service (CAS)	methyl 4-amino-3-chloro-6-(4-chloro-2-fluoro-3-methoxyphenyl)-2-pyridinecarboxylate
CAS number	943831-98-9
Molecular formula	$C_{14}H_{11}Cl_2FN_2O_3$
Molecular weight	347.17 g/mol
Structural formula	
Purity of the active ingredient	92.0% (as halauxifen moiety)

1.2 Physical and Chemical Properties of the Active Ingredients and End-Use Product

Technical Product — XDE-729 Methyl Technical Herbicide

Property	Result
Colour and physical state	Off-white powder
Odour	Mild
Melting range	145.50°C
Boiling point or range	Decomposes before boiling
Density	1.5 g/cm^3
Vapour pressure at 20°C	5.9×10^{-9} Pa
Henry's law constant at 20°C	1.2×10^{-11} atm•m^3/mol at 20°C

Property	Result
Ultraviolet (UV)-visible spectrum	medium — λ_{max}, nm neutral — 212, 249 acidic — 215, 256 basic — 212, 247
Solubility in water at 20°C	pH — solubility (mg/L) purified water — 1.83 5 — 1.66 7 — 1.67 9 — 1.69
Solubility in organic solvents at 20°C	solvent — solubility (g/L) methanol — 38.1 acetone — >250 xylene — 9.13 1,2-dichloroethane — 65.9 ethyl acetate — 129 n-heptane — 0.0361 n-octanol — 9.83
n-Octanol-water partition coefficient (K_{ow}) at 20°C	pH — log K_{ow} 5 — 3.75 7 — 3.76 9 — 3.92
Dissociation constant (pK_a)	2.84 ± 0.04 for the conjugate base
Stability (temperature, metal)	Stable for 2 weeks at 20°C and 54°C in the presence of metals and metal ions: copper, brass, 304 stainless steel, 316 stainless steel, aluminum, copper (I) chloride, nickel (II) chloride and iron (III) chloride

End-Use Products – GF-2685 Herbicide, Paradigm Herbicide and Pixxaro A Herbicide

Property	GF-2685 Herbicide	Paradigm Herbicide	Pixxaro A Herbicide
Colour	Tan	Tan	Yellow
Odour	Musty	Mild	
Physical state	Solid	Solid	Liquid
Formulation type	Wettable granule	Water-dispersible granule	Emulsifiable concentrate
Guarantee	10% halauxifen, present as methyl ester	20% halauxifen, present as methyl ester 20% florasulam	16.25 g/L halauxifen, present as methyl ester 250 g/L fluroxypyr, present as 1-methylheptyl ester
Container material and description	HDPE 1 kg to bulk	HDPE 1 kg to bulk	HDPE 1 L to bulk
Density	0.57 g/mL	0.59 g/mL	1.0252 g/mL

Property	GF-2685 Herbicide	Paradigm Herbicide	Pixxaro A Herbicide
pH of 1% dispersion in water	5.80	5.62	4.95
Oxidizing or reducing action	Not an oxidizing or reducing agent		
Storage stability	Stable over 1 year's storage at ambient warehouse conditions in HDPE	Stable over 1 year's storage at ambient warehouse conditions in HDPE bottles and foil laminate sachets	Not yet provided
Corrosion characteristics	Not corrosive to commercial packaging over 1 year's storage		Not yet provided
Explodability	Not considered to be explosive when exposed to impact or heat		

1.3 Directions for Use

1.3.1 GF-2685 Herbicide

GF-2685 Herbicide, containing halauxifen-methyl at 100 grams per kilogram of product, is a postemergence herbicide that will provide control and suppression of select annual broadleaf weeds in spring wheat, durum wheat, winter wheat and spring barley from the 1-leaf stage to just prior to flag leaf emergence, except for winter wheat which is from the 3-leaf stage to just prior to flag leaf emergence, in the Prairie provinces and the Peace River region of British Columbia and in Eastern Canada (Table 1.3.1.1). GF-2685 Herbicide may be applied once per year at a rate of 2.5 to 10 g acid equivalents (a.e.)/ha with ground or aerial application equipment. GF-2685 Herbicide is to be applied post emergence to the target weed species. GF-2685 Herbicide is formulated with the safener cloquintocet-mexyl in a 1:1 ratio with halauxifen-methyl.

Table 1.3.1.1 Weed claims for GF-2685 Herbicide (when applied postemergent in spring wheat, durum wheat, winter wheat and barley)

Rate of Application of GF-2685	Rate of Application for the Turbocharge Adjuvant	Weeds Controlled*
halauxifen-methyl at 2.5 g a.e./ha	0.5 % v/v (0.5 L per 100 L of spray volume)	• Cleavers (1-9 whorl stage) • Lamb's quarters (1-8 leaf stage) • Hemp-nettle (suppression) (1-8 leaf stage) • Flax, volunteer (up to 15 cm in height) • Redroot pigweed (suppression) (1-8 leaf stage)

Rate of Application of GF-2685	Rate of Application for the Turbocharge Adjuvant	Weeds Controlled*
halauxifen-methyl at 5.0 g a.e./ha	0.5 % v/v (0.5 L per 100 L of spray volume)	• Cleavers (1-9 whorl stage) • Lamb's quarters (1-8 leaf stage) • Chickweed (1-8 leaf stage) • Flax, volunteer (up to 15 cm in height) • Hemp-nettle (1-8 leaf stage) • Redroot pigweed (1-8 leaf stage) • Buckwheat, wild (suppression) (1-8 leaf stage) • Kochia ** (suppression)
halauxifen-methyl at 10.0 g a.e./ha	0.5 % v/v (0.5 L per 100 L of spray volume)	• Cleavers (1-9 whorl stage) • Lamb's quarters (1-8 leaf stage) • Chickweed (1-8 leaf stage) • Flax, volunteer (up to 15 cm in height) • Hemp-nettle (1-8 leaf stage) • Redroot pigweed (1-8 leaf stage) • Buckwheat, wild (1-6 leaf stage) • Kochia ** (suppression)

* Including Group 2 resistant biotypes.
** Light to moderate infestations (up to 150 plants/m^2; up to 15 cm in height).

1.3.2 Paradigm Herbicide

Paradigm Herbicide, containing halauxifen-methyl at 200 grams per kilogram of product and florasulam at 200 grams per kilogram of product, is a postemergence herbicide that will provide control and suppression of select annual and perennial broadleaf weeds in spring wheat, durum wheat, winter wheat and spring barley from the 1-leaf stage to just prior to flag leaf emergence, except for winter wheat which is from the 3-leaf stage to just prior to flag leaf emergence, in the Prairie provinces and the Peace River region of British Columbia (Table 1.3.2.1). Paradigm Herbicide may be applied once per year at a rate of 10 g a.e./ha (5.0 g a.e./ha of halauxifen-methyl + 5.0 g a.i./ha of florasulam) with ground application equipment only. Paradigm Herbicide is to be applied post emergence to the target weed species.

Table 1.3.2.1 Weed claims for Paradigm Herbicide (when applied postemergent in spring wheat, durum wheat, winter wheat and barley)

Rate of Application of Paradigm Herbicide 25 g of product/ha	Rate of Application for the Turbocharge Adjuvant	Weeds Controlled
halauxifen-methyl at 5.0 g a.e./ha + florasulam at 5.0 g	0.5 % v/v (0.5 L per 100 L of spray volume)	**Control:** • Buckwheat, wild (1-8 leaf stage) • Volunteer canola (1-8 leaf stage)**

Rate of Application of Paradigm Herbicide 25 g of product/ha	Rate of Application for the Turbocharge Adjuvant	Weeds Controlled
a.i./ha		• Chickweed (1-8 leaf stage)*** • Cleavers (1-9 whorl stage)*** • Flax, volunteer (up to 15 cm in height) • Lamb's quarters (1-8 leaf stage)*** • Wild mustard (1-8 leaf stage)**** • Redroot pigweed (1-8 leaf stage) • Shepherd's purse (1-8 leaf stage)**** • Smartweed (green smartweed, lady's thumb) (1-8 leaf stage) • Stinkweed (1-8 leaf stage)**** **Suppression:** • Hemp-nettle (1-8 leaf stage)*** • Kochia * • Annual sowthistle (1-8 leaf stage)**** • Perennial sowthistle (1-8 leaf stage)****

* Light to moderate infestations (up to 150 plants/m^2; up to 15 cm in height), including Group 2 resistant biotypes.
** Will not control volunteer imidazolinone-tolerant canola (Clearfield varieties).
*** Including Group 2 resistant biotypes.
**** Best results are obtained when applied to actively growing weeds in the 1 to 4 leaf (seedling) stage.

1.3.3 Pixxaro A Herbicide

Pixxaro A Herbicide, containing halauxifen-methyl at 16.25 grams per kilogram of product and fluroxypyr at 250 grams per kilogram of product, is a postemergence herbicide that will provide control and suppression of select annual broadleaf weeds in spring wheat, durum wheat, winter wheat and spring barley from the 1-leaf stage to just prior to flag leaf emergence, except for winter wheat which is from the 3-leaf stage to just prior flag leaf emergence, in the Prairie provinces and the Peace River region of British Columbia (Table 1.3.3.1). Pixxaro A Herbicide may be applied once per year at a rate of 82.0 g a.e./ha (5.0 g a.e./ha of halauxifen-methyl + 77.0 g a.e./ha of fluroxypyr) with ground or aerial application equipment. Pixxaro A Herbicide is to be applied post emergence to the target weed species. Pixxaro A Herbicide is formulated with the safener cloquintocet-mexyl in a 1:1 ratio with halauxifen-methyl.

Table 1.3.3.1 Weed claims for Pixxaro A Herbicide (when applied postemergent in spring wheat, durum wheat, winter wheat and barley)

Rate of Application of Pixxaro A Herbicide 308 mL of product/ha	Rate of Application for the Turbocharge Adjuvant	Weeds Controlled*
halauxifen-methyl at 5.0 g a.e./ha + fluroxypyr at 77.0 g a.e./ha	0.5 % v/v (0.5 L per 100 L of spray volume)	**Control:** • Buckwheat, wild (1-8 leaf stage) • Chickweed (1-8 leaf stage) • Cleavers (1-9 whorl stage) • Flax, volunteer (up to 15 cm in height) • Hemp-nettle (1-8 leaf stage) • Kochia (up to 15 cm in height) • Lamb's quarters (1-8 leaf stage) • Redroot pigweed (1-8 leaf stage) **Suppression:** • Wild mustard (1-4 leaf stage, up to 10 cm in height)

* Including Group 2 resistant biotypes.

1.4 Mode of Action

Halauxifen-methyl is the first member of a new chemical class of synthetic auxin herbicides, the arypicolinates. It belongs to the Weed Science Society of America Group 4 herbicides and to the Herbicide Resistance Action Committee Group O. Halauxifen-methyl is a systemic herbicide that can be absorbed through the leaves, shoots and roots of plants at which point it will be symplastically translocated throughout the plant and will accumulate in meristematic tissue. Halauxifen-methyl mimics the effect of a persistent high dose of the natural plant hormone auxin causing over-stimulation of specific auxin-regulated genes which result in the disruption of several growth processes in susceptible plants. Tissues that are undergoing active cell division and growth are particularly susceptible to injury.

Symptoms of halauxifen-methyl herbicide injuries include: cessation of growth, stem and petiole twisting (epinasty), leaf malformation (parallel venation, leaf strapping and cupping), chlorosis, swelling, thickening and splitting of stems, callus tissue formation, and stunted root growth.

2.0 Methods of Analysis

2.1 Methods for Analysis of the Active Ingredient

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

2.2 Method for Formulation Analysis

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

2.3 Methods for Residue Analysis

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

Liquid chromatography methods with tandem mass spectroscopic detection (LC-MS/MS) were developed and proposed for data generation and enforcement purposes in both plant and animal matrices. The plant methods fulfilled the requirements with regards to specificity, accuracy and precision at the respective method limits of quantitation. Acceptable recoveries (70–120%) were obtained in plant matrices. The proposed plant enforcement method was successfully validated in plant matrices by an independent laboratory. Adequate extraction efficiencies were demonstrated using radiolabelled samples of crops from the plant metabolism studies with the enforcement method.

The proposed animal method was adequately validated for halauxifen-methyl and halauxifen acid. However, this method has not been adequately validated for the metabolite X11449757, which is a component of the residue definition in livestock matrices for both enforcement and dietary exposure assessment purposes. Therefore, there is currently no animal method available for enforcement purposes. An enforcement method for edible livestock commodities is currently not required given that maximum residue limits (MRLs) are not being established due to the low potential for residue transfer to these matrices. However, in the event that MRLs are needed for livestock commodities with future use expansion requests, an adequate enforcement method for X11449757 and an acceptable independent laboratory validation of the enforcement method will be required.

Methods for residue analysis are summarized in Appendix I, Tables 1a and 1b.

3.0 Impact on Human and Animal Health

3.1 Toxicology Summary

Extensive toxicokinetic data in laboratory animals indicate that halauxifen-methyl is rapidly and nearly completely hydrolyzed to its acid form in vivo. Both forms were assessed for acute and short-term toxicity in rats, as well as for mutagenic potential and developmental toxicity in rodent and non-rodent species. Mammalian metabolism and toxicokinetic studies, reproductive toxicity studies in rats, and chronic toxicity and oncogenicity studies in rats and mice were conducted using the acid form.

High quality bridging studies were provided including extensive complementary toxicokinetic data on mice, rats and dogs demonstrating a rapid and almost 100% conversion of halauxifen-methyl to its acid form, hereafter referred to as halauxifen acid. Halauxifen acid was considered to be the appropriate compound for the purposes of the risk assessment for routes that demonstrated rapid conversion of halauxifen-methyl to halauxifen acid.

A detailed review of the toxicological database for halauxifen-methyl and halauxifen acid was conducted. The database is complete, consisting of the full array of toxicity studies currently required for hazard assessment purposes. The studies were carried out in accordance with currently accepted international testing protocols and Good Laboratory Practices. The scientific quality of the data is high and the database is considered adequate to define the majority of the toxic effects that may result from exposure to halauxifen-methyl.

Single or repeated oral metabolism studies with radiolabelled halauxifen-methyl or halauxifen acid in rats demonstrated that both are rapidly and highly absorbed. Similar results were obtained in dogs after single oral dosing with halauxifen acid. Maximum plasma concentrations of total radioactivity were achieved within 30 minutes post-dose in rats and 60 minutes post-dose in dogs. Halauxifen-methyl and halauxifen acid were not widely distributed in the body. Only very low levels were detected in most tissues. At 168 hours post-dosing in rats (single, repeated and IV), levels in the tissues ranged from non-quantifiable to 0.3% of the administered dose (AD) for both forms. Analysis of blood samples from rats administered radiolabelled halauxifen-methyl revealed primarily halauxifen acid, indicating rapid hydrolysis of the ester in vivo. In rats administered the radiolabelled halauxifen acid, elimination from plasma was rapid during the alpha elimination phase ($t_{1/2\alpha}$ = 0.5-4.3 hours) and was followed by slower elimination during a terminal beta phase ($t_{1/2\beta}$ = 5-9 hours). The plasma area-under-the-curve (AUC) was 2.0-2.6 times higher for the high dose of halauxifen acid than would be expected for dose proportionality. The AUC non-linearity is consistent with the longer alpha elimination phase seen in the high dose animals and saturation of elimination. Additional toxicokinetic analyses conducted as part of the short-term toxicity studies confirmed the findings in the metabolism studies, although in some instances very low levels of halauxifen-methyl were detected in the blood and/or urine. The major radiolabelled component present in the urine and fecal extracts from animals administered either form of halauxifen-methyl was halauxifen acid. Minor metabolites of both test materials consisted of an acyl-glucuronide conjugate of the parent acid form and an O-demethylated form of the acid and the corresponding sulfate and glucuronide conjugates.

Toxicokinetic analysis from an oral 90-day rat study with halauxifen-methyl demonstrated the presence of an additional metabolite at high dose levels, an O-demethyl glucuronide conjugated form of halauxifen-methyl. The proposed pathway for this metabolite is the formation of O-demethyl halauxifen-methyl directly from halauxifen-methyl and subsequent conjugation to glucuronide. Only trace levels of O-demethyl halauxifen-methyl and its sulfate conjugate were detected.

In dogs, halauxifen acid was the major component in plasma and urine and was also present in feces at comparable or higher levels to other identified metabolites. Halauxifen acid was poorly

metabolized and readily eliminated in the urine of mice and rats. The orally absorbed dose was excreted in urine (68-92% AD); the majority occurred within the first 24 hours post-dosing. A smaller percentage (11-29% AD) of the oral dose was eliminated in feces. The amount and rates of urinary and fecal elimination after a single oral low dose in rats were comparable between halauxifen-methyl and halauxifen acid. The amount of radioactivity in red blood cells was less than that found in plasma. In dogs, elimination of radioactivity from the blood was also biphasic ($t_{1/2\alpha}$ = 1 hour; $t_{1/2\beta}$ = 9-12 hours) and the AUC data indicated that dogs exhibited slower clearance than rats, which is consistent with saturation of renal elimination. Consistent with the data in rats, the major radiolabelled component in plasma and urine was halauxifen acid. Urinary excretion of the acid accounted for 78% AD and fecal excretion represented 2-5% AD. The primary metabolites identified in dog urine, feces or plasma included O-demethylated halauxifen acid and corresponding sulfate and glucose conjugates, hydroxylated halauxifen acid and a halauxifen acid acyl glucuronide conjugate.

Toxicokinetic data from repeat-dose studies conducted with halauxifen acid in mice indicated a linear relationship with dose; in contrast, sublinear kinetics were demonstrated at higher doses in rats treated with halauxifen-methyl or halauxifen acid, suggesting saturation of elimination after short-term administration. In a 2-year combined chronic/oncogenicity study in rats treated with halauxifen acid, linear kinetics were demonstrated. Sex-specific differences in Phase I and Phase II metabolism were demonstrated in rats after 90 days of halauxifen-methyl treatment, which may suggest a more efficient metabolism observed in females. In dogs treated with halauxifen acid, saturation of elimination was consistently observed at high doses.

Halauxifen-methyl and halauxifen acid were of low acute toxicity by the oral and dermal routes of exposure in rats. A waiver request for an acute inhalation toxicity study was accepted based on the inability to generate a test atmosphere due to large particle size and clogging of the aerosol generator. Both compounds were non- to minimally irritating to the eyes and skin in rabbits, and did not cause dermal sensitization in mice. The associated end-use products, GF-2685 Herbicide, Paradigm Herbicide and Pixxaro A Herbicide were of low acute toxicity via the oral, dermal and inhalation routes of exposure. Paradigm Herbicide was minimally irritating to eyes and skin. Pixxaro A Herbicide was moderately irritating to the eye and mildly irritating to the skin. GF-2685 was minimally irritating to the eye and mildly irritating to the skin. All of the end-use products were dermal sensitizers.

After 28 days of dermal dosing in rats with halauxifen acid, no treatment-related dermal or systemic toxicity was observed at the limit dose of 1000 mg/kg bw/day. A waiver request for a 28-day dermal toxicity study with halauxifen-methyl was accepted, as the expected exposure will be predominantly to halauxifen acid.

A waiver request for a 28-day inhalation toxicity study in rats was submitted and accepted based on the low volatility of halauxifen-methyl and technical difficulties in generating a test atmosphere in the acute inhalation toxicity study due to a large aerosol particle size, clogging of the generation equipment, unsustainable concentrations and/or inefficient delivery of the test material.

Following short-term repeated oral dosing with halauxifen acid in mice, treatment-related effects were observed in males and consisted of kidney, bladder and/or liver histopathological lesions at the limit dose of 1000 mg/kg bw/day. Other than a decrease in serum alanine amino-transferase levels after 28 days, there were no treatment-related observations in female mice. In rats, the primary targets were the liver and thyroid after short-term oral dosing with halauxifen-methyl. The treatment-related liver effects consisted of increased organ weights, hepatocellular hypertrophy, hepatocellular vacuolation and increased mitotic figures in hepatocytes. Treatment-related increases in cholesterol levels were also observed. The primary target organ of halauxifen acid was the kidney. Treatment-related renal toxicity consisted of necrosis, increased mitotic figures, hypertrophy and/or vacuolization of collecting duct epithelium, and tubular dilatation and degeneration.

Following short-term repeated oral dosing in dogs with halauxifen acid, the primary target of toxicity was the kidney and the hematological system. Treatment-related renal effects consisted of epithelial degeneration and regeneration of renal tubules and collecting ducts, and glomerulosclerosis. Decreases in red blood cell, hemoglobin and hematocrit counts were observed at higher doses in the 28-day and 90-day toxicity studies.

In a dietary 78-week mouse oncogenicity study with halauxifen acid, treatment-related effects included inflammation and microscopic calculi in the bladder of males, and decreased body weight gains and increased hypertrophy of the intercalated cells in the kidneys of females. There was no evidence of oncogenicity.

In a dietary 2-year rat oral combined chronic/oncogenicity study with halauxifen acid, treatment-related hyperplasia of the pelvic epithelium of the kidney was observed in females. More marked renal toxicity including hypertrophy, vacuolization, necrosis and increased numbers of mitotic figures in the renal collecting duct epithelium was noted in both sexes at higher doses. Males also exhibited treatment-related calculi in the renal pelvis of the kidney and epithelial degeneration and regeneration of renal tubules, as well as urinary bladder effects including hyperplasia of the transitional epithelium, inflammation of the submucosa and microscopic calculi. There was no evidence of oncogenicity.

There was an increased variety of renal histological lesions observed in mice and rats at lower dose levels and increased mortalities due to renal lesions at the highest dose tested in the long-term toxicity studies. These observations suggest a durational effect of dosing in both species for halauxifen acid.

Halauxifen-methyl and halauxifen acid were not genotoxic in a standard battery of in vitro and in vivo assays. Genotoxicity studies conducted with X11449757 (a desmethyl form of halauxifen acid) a major metabolite in animal matrices and soil transformation product, indicated that it is not genotoxic in bacteria, Chinese hamster ovary cells or human lymphocytes.

In range-finding and 2-generation reproductive toxicity studies in rats with halauxifen acid, treatment-related effects in the parental animals consisted of renal toxicity including collecting duct epithelial cell hypertrophy and hyperplasia, hyperplasia of the pelvic epithelium, increased mitotic figures of the collecting duct epithelium of both sexes, and clinical signs, decreased body

weight gains and food consumption during late gestation/early lactation in females. There were no treatment-related reproductive or offspring effects.

In a rat dietary developmental toxicity study with halauxifen-methyl, treatment-related maternal effects included decreased body weight gain, reduced food consumption and liver effects consisting of increased organ weights, altered cytoplasmic homogeneity of centrilobular and midzonal hepatocytes, and hepatocellular vacuolation consistent with fatty change. There was no evidence of developmental toxicity. Toxicokinetic data in the range-finding study with halauxifen-methyl demonstrated that halauxifen acid is the predominant analyte in dam and fetal blood samples. Fetal blood concentrations of the acid were ~69% of the maternal blood concentrations. In a rat dietary developmental toxicity study with halauxifen acid, treatment-related maternal effects consisted of late-gestation mortalities, clinical signs, decreased body weight, body weight gain, food consumption and gravid uterine weights. Treatment-related developmental effects included decreased fetal weights, a slight increase in resorptions/postimplantation loss and increases in delayed ossification of thoracic centra at a dose producing maternal toxicity.

In a rabbit dietary developmental toxicity study with halauxifen-methyl, treatment-related liver effects in maternal animals included increased organ weights, hypertrophy with altered tinctorial properties (increased cytoplasmic eosinophilia) of periportal hepatocytes, increased number of mitotic figures of hepatocytes and altered cytoplasmic homogeneity of centrilobular/midzonal hepatocytes. The maternal liver effects were not considered adverse but were nonetheless considered to be treatment-related effects and reflective of marginal maternal toxicity. A slightly increased incidence of resorptions/postimplantation loss was observed at the mid and high dose levels, which was considered to be treatment-related, despite the lack of a dose-response relationship and the absence of an impact on mean live fetuses per maternal animal. Toxicokinetic data indicated that halauxifen acid was the only analyte present in maternal animals and fetuses. Proportional blood concentration values were demonstrated to the highest dose in maternal animals and less than dose-proportional blood concentrations were observed between the mid and high dose levels in fetuses. Fetal blood concentrations were on average 27% and 6% of maternal blood concentrations, at the mid and high dose levels respectively, which suggest that the absence of a dose-response is not unexpected. In a rabbit dietary developmental toxicity study with halauxifen acid, treatment-related decreased body weight gains and food consumption were observed in maternal animals, while no treatment-related developmental effects were noted. Systemic exposure to halauxifen acid was demonstrated and fetal plasma concentrations were approximately 3-fold lower than those of maternal animals, consistent with a possibly decreased fetal absorption.

In acute and subchronic neurotoxicity studies in rats with halauxifen acid, treatment-related decreases in body weight, body weight gain and/or food consumption were observed in males. There were no treatment-related effects in female rats. No treatment-related neurotoxic effects were observed in either of the neurotoxicity studies.

In a rat dietary 28-day immunotoxicity study with halauxifen-methyl, there were no treatment-related effects other than a decrease in absolute thymus weight. There was no evidence of immunotoxic effect on T-cell dependent antibody response.

Toxicokinetic investigations in rats demonstrated that post-hepatic systemic exposure following oral administration of halauxifen-methyl is mainly to halauxifen acid, and that the blood/plasma concentrations of halauxifen acid are quantitatively similar following oral administration of equivalent doses of halauxifen-methyl and halauxifen acid. Halauxifen-methyl and halauxifen acid were shown to be toxicologically equivalent with respect to acute toxicity and genotoxicity endpoints. However, 28- and 90-day repeat dose toxicity studies in rats demonstrated different target organs and different no observed adverse effects levels (NOAELs) were established; the NOAELs established for halauxifen-methyl were lower than those established for halauxifen acid. The target organs of halauxifen-methyl were the liver and thyroid, while animals given repeated doses of halauxifen acid showed treatment-related effects in the kidneys and urinary bladder. Mode of action (MOA) studies with halauxifen-methyl demonstrated that the treatment-related liver effects in the rats were mediated through activation of the aryl hydrocarbon receptor (AhR). Several MOA studies were submitted to investigate the AhR-mediated key events including: pre-systemic halauxifen-methyl liver exposure, AhR activation via Cyp1a1 induction and hepatocellular proliferation, and the hydrolysis of halauxifen-methyl to halauxifen acid in vivo and in vitro. The submitted MOA studies demonstrated a threshold for the key events at 52 mg/kg bw/day in the 90-day study and the effects were reversible. In vitro Cyp1a1 and Cyp1a2 gene expression studies in primary cultures of human, mouse and rat hepatocytes suggested that rats may be more sensitive to halauxifen-methyl induced AhR activation than humans. In vitro hydrolysis data demonstrated that the human liver may hydrolyze halauxifen-methyl more quickly than rodents. Physiologically-based pharmacokinetic (PBPK) modelling predicted similar 24 hour AUCs for halauxifen-methyl in the liver and blood, and comparable peak concentrations between rats and humans. Overall, the animal MOA was accepted and the available data indicate that rats may be more sensitive to this AhR-mediated MOA than humans. Taken together, the bridging data demonstrated that halauxifen-methyl and halauxifen acid did not cause adverse effects up to the NOAEL observed for liver effects and that an AhR-mediated MOA is involved in halauxifen-methyl induced liver effects. Therefore, the studies with halauxifen acid were deemed appropriate for assessing halauxifen-methyl by routes that demonstrated rapid conversion to halauxifen acid. For risk assessment purposes, data from halauxifen acid was used for the establishment of endpoints for those scenarios where exposure to halauxifen-methyl was not expected.

Results of the toxicology studies conducted on laboratory animals with halauxifen-methyl, halauxifen acid, desmethyl metabolite and its associated end-use products, are summarized in Appendix I, Tables 2, 3 and 4. The toxicology endpoints for use in the human health risk assessment are summarized in Appendix I, Table 5.

Incident Reports

Since April 26, 2007, registrants have been required by law to report incidents, including adverse effects to health and the environment, to the PMRA within a set time frame. Information on the reporting of incidents can be found in the Pesticides and Pest Management portion of Health Canada's website. Incidents were searched and reviewed for halauxifen-methyl. Any additional information submitted by the applicant during the review process was considered. As of

February 3, 2014, no health-related incidents involving halauxifen-methyl were reported to the PMRA.

3.1.1 *Pest Control Products Act* Hazard Characterization

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

With respect to the completeness of the toxicity database as it pertains to the toxicity to infants and children, extensive data were available for halauxifen-methyl and halauxifen acid. The database contains the full complement of required studies including developmental toxicity studies in rats and rabbits with both halauxifen-methyl and halauxifen acid and a reproductive toxicity study in rats with halauxifen acid. Also, a broad range of toxicokinetic studies indicated that in vivo systemic exposure is to halauxifen acid.

With respect to potential prenatal and postnatal toxicity, no evidence of sensitivity of the young was observed in the 2-generation reproductive toxicity study. There were no treatment-related offspring effects. Decreased fetal weights and increased incidences of resorption/postimplantation loss and skeletal variations were observed in the rat developmental toxicity study with halauxifen acid; however, these effects occurred in the presence of maternal toxicity. A slight increase in the incidence of a serious effect, fetal resorptions/postimplantation loss, was observed in the presence of maternal liver effects in the rabbit developmental toxicity study with halauxifen-methyl. Conventionally, increased liver weight, increased hepatocellular hypertrophy of periportal hepatocytes, increased mitotic figures in hepatocytes and altered cytoplasmic homogeneity are not considered to be adverse liver effects in the adult animal. These effects were nevertheless present in pregnant animals and insufficient information was available to determine whether the treatment-related maternal liver effects had a potential impact upon the developing young, based on the AhR MOA. Therefore, these histological effects were considered to be reflective of marginal maternal toxicity. However, the concern for this serious effect is reduced by the fact that it was not dose-responsive, nor was it observed in a range-finding study at much higher doses (38 times) and it did not have an impact on the mean live fetuses per maternal animal.

Based on the presence of maternal toxicity at the developmental LOAEL, the *Pest Control Products Act* factor was reduced to 3-fold when the rat or rabbit developmental toxicity study with halauxifen acid or halauxifen-methyl was used for risk assessment. For all other scenarios, the *Pest Control Products Act* factor was reduced to 1-fold since there were no residual uncertainties with respect to the completeness of the data, or with respect to potential toxicity to infants and children.

3.2 Determination of Acute Reference Dose

No acute endpoints of concern were identified in the toxicology database; therefore, an ARfD was not established.

3.3 Determination of Acceptable Daily Intake

To estimate dietary risk of repeat dietary exposure, the 1-year dog toxicity study with a NOAEL of 17 mg/kg bw/day and 2-year rat combined chronic/oncogenicity studies with a NOAEL of 20 mg/kg bw/day with halauxifen acid were co-critical endpoints selected for risk assessment. At the LOAEL of 90 mg/kg bw/day in dogs and 102 mg/kg bw/day in rats, treatment-related renal histological effects were observed in females. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability have been applied. As discussed in the *Pest Control Products Act* Hazard Characterization section, the *Pest Control Products Act* factor was reduced to 1-fold. The composite assessment factor (CAF) is thus 100-fold.

The acceptable daily intake (ADI) is calculated according to the following formula:

$$\text{ADI} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{20 \text{ mg/kg bw/day}}{100} = 0.2 \text{ mg/kg bw/day of halauxifen-methyl (acid)}$$

Cancer Assessment

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

3.4 Occupational and Residential Risk Assessment

Occupational exposure to halauxifen-methyl is characterized as short-term and is predominantly by the dermal and inhalation route.

3.4.1 Toxicological Endpoints

Short- and Intermediate-term Dermal

The available information indicates that the expected human dermal exposure would be to halauxifen acid. Therefore, the data supporting halauxifen acid were considered for occupational (dermal) risk assessment.

For short- and intermediate-term dermal risk assessment for adults, the existing short-term dermal toxicity study did not address the endpoint of concern, thus necessitating the use of an oral study for risk assessment. The NOAEL of 140 mg/kg bw/day from the developmental toxicity study in rats with halauxifen acid was selected. At 526 mg/kg bw/day, decreased fetal weights, a slight increase in resorptions/postimplantation loss and delayed ossification of thoracic centra were observed in the presence of maternal toxicity.

The target margin of exposure (MOE) for this endpoint is 300. Ten-fold factors were applied each for interspecies extrapolation and intraspecies variability. The concerns outlined in the *Pest Control Products Act* Hazard Characterization section regarding this endpoint are also relevant to the worker population. For these reasons, an additional factor of 3-fold was applied to the risk assessment to protect for sensitive subpopulations such as unborn children.

The selection of this endpoint and MOE is considered to be protective of all populations, including nursing infants and the unborn children of exposed female workers.

Short- and Intermediate-term Inhalation

There was no information available on whether the expected human inhalation exposure will be to halauxifen-methyl or halauxifen acid. Therefore, halauxifen-methyl was used for occupational (inhalation) risk assessment.

For short- and intermediate-term inhalation risk assessment for adults, a short-term inhalation study was not available and therefore an oral study was used for the risk assessment. The rabbit developmental toxicity study with halauxifen-methyl was selected. At 19 mg/kg bw/day, increased resorptions/postimplantation loss was observed. The NOAEL was 6 mg/kg bw/day.

The target MOE for this endpoint is 300. Ten-fold factors were applied each for interspecies extrapolation and intraspecies variability. The concerns outlined in the *Pest Control Products Act* Hazard Characterization section regarding this endpoint are also relevant to the worker population. For these reasons, an additional factor of 3-fold was applied to the risk assessment to protect for sensitive subpopulations such as unborn children.

The selection of this endpoint and MOE is considered to be protective of all populations, including nursing infants and the unborn children of exposed female workers.

3.4.1.1 Dermal Absorption

In support of the registration of GF-2685 Herbicide, Paradigm Herbicide and Pixxaro A Herbicide, the applicant submitted an in vivo dermal absorption study in rats and an in vitro dermal absorption study in rat and human skin. Together, these studies are referred to as a "triple pack". The submitted dermal penetration studies for halauxifen-methyl were of good quality and the "triple pack" approach was considered for setting a dermal absorption value.

In the in vivo dermal absorption study, four male Wistar rats/dose group were dermally exposed for 10 hours to [^{14}C]-halauxifen-methyl formulated as an emulsifiable concentrate, at three concentrations: 7.5 g a.e./ha (concentrate), *ca* 0.15 g a.e./ha (field dilution 1) and *ca* 0.025 g a.e. /ha (field dilution 2). Test material in 100 µL was applied to an area of shaved skin of 10 cm^2 to give nominal dermal doses of 75, 1.5 and 0.25 µg/cm^2, respectively. Following exposure, the test material was rinsed off and skin was tape-stripped 20 times to remove the stratum corneum. At each concentration, groups were designated for termination at 24, 48, 72, 144 (concentrate only) and 192 (field dilutions) hours post-dosing.

In the in vitro dermal absorption study, human and rat skin membranes were also dermally exposed for the same duration, with the same formulation and nominal concentrations as the in vivo study. After the 10-hour exposure, skin samples were rinsed and then absorption was continued for an additional 14 hours. Over the duration of the study, receptor fluid samples were collected during the following intervals after the dose application: 0-1 hour, 1-2 hours, followed by 2-hour intervals until 24 hours after application. After 24 hours, the application site was washed again. The diffusion cell was dismantled, receptor and donor compartments were washed twice, and each skin membrane was tape stripped maximally 15-20 times.

For both studies, the radioactivity in the matrices was analyzed by liquid scintillation counting (LSC). Dermal absorption values from the in vivo study included the % dose absorbed and found in skin bound residues, since absorption was not complete at the end of the study duration. Dermal absorption values from the in vitro study were calculated by summing the absorbable dose and the potentially absorbable dose.

With an exposure time of 10 hours, the mean percent dermal absorption values from the in vivo study are:

Actual dose	**75 µg/cm^2**	**1.5 µg/cm^2**	**0.25 µg/cm^2**
% dermal absorption at 24-hour sacrifice	9.85 ± 2.60	15.65 ± 6.67	23.25 ± 3.86
% dermal absorption at 48-hour sacrifice	9.87 ± 3.86	17.19 ± 2.81	29.13 ± 10.71
% dermal absorption at 96-hour sacrifice	9.26 ± 2.87	24.22 ± 0.94	21.95 ± 4.29
% dermal absorption at 144/192 hour sacrifice	14.51 ± 4.95	18.39 ± 2.06	30.45 ± 3.21

% dermal absorption = radioactivity recovered from urine, faeces, cage wash, blood, control skin, GI tract, carcass, skin strips and stripped skin.

With an exposure time of 10 hours and post exposure time of 14 hours, the mean percent dermal absorption values from the in vitro study are:

Actual dose (µg/cm^2)	**77.6 (rat) 77.3 (human)**	**1.50 (rat) 1.51 (human)**	**0.26 (rat) 0.25 (human)**
% Absorption* - human skin	0.9	15.5	27.9
% Absorption* - rat skin	5.0	42.5	45.9

* % absorption is % radioactivity in the receptor fluid + the receptor compartment wash + skin membrane + all tape strips

The use of the triple pack approach was considered. To use the triple pack approach, the ratio of the animal in vitro to in vivo dermal absorption factor must be close to 1, which indicates that a human in vitro study conducted under the same conditions as the animal test is likely to be a good predictor of human dermal absorption. In addition, the usefulness of the dermal absorption data would necessarily be dependent on the validity and applicability of the experimental design as well as consideration of the 'minimal standards' discussed in the "NAFTA Dermal Absorption Position Paper on Use of in vitro Dermal Absorption Data in Risk Assessment".

Most of the minimal standards listed in the 2008 draft position paper were met for using the triple pack approach. However, a major limitation with the in vitro study is that all the rat membranes were from the same rat. As such, the intraspecies variability of the rat membrane is not captured in the in vitro rat dermal absorption values, which decreases the confidence in the validity and reliability of the in vitro study results. In addition, the actual doses in the in vitro study were 9% to 24% higher than the target dose, resulting in actual doses that are slightly higher than those in the in vivo study.

The following table compares the ratios of dermal absorption from in vitro rat to in vivo rat (10 hour exposure, 24 hour sacrifice):

Actual dose (µg/cm^2)	Rat in vitro	Rat in vivo	Ratio: in vitro rat / in vivo rat
77 (in vitro) / 75 (in vivo)	5.0	9.9	0.5
1.5 (both)	42.5	15.7	2.7
0.26 (in vitro) / 0.25 (in vivo)	45.9	23.3	2.0

As presented in the above table, the dermal absorption ratios from in vitro rat to in vivo are 0.5 to 2.7 for different concentrations tested. The ratios are not close to 1, especially for field dilutions. In addition, the ratios are inconsistent with the different doses. At the high dose, the in vivo dermal absorption exceeds the in vitro dermal absorption; however, at the mid and low dose, the in vitro dermal absorption exceeds the in vivo dermal absorption.

Due to the results and the study limitations of the in vitro study, the dermal absorption values derived from the in vitro human dermal absorption data cannot be used for human health risk assessments. As such, the in vivo rat dermal absorption data is used to derive the dermal absorption value used for risk assessment purposes. As per the OECD guidance notes, the dermal absorption value from the final time point in the study was chosen to be the most appropriate regulatory value, as the fate of residues can be more adequately characterized. In addition, given the variability in actual deposition under field conditions, it is considered appropriate to derive an estimate of dermal absorption based on the results from the low dose, as percent dermal absorption was greatest at this dose level. Therefore, the dermal absorption is 30%, based on the in vivo rat study from the 0.25 µg/cm^2 dose group sacrificed at 192 hours.

3.4.2 Occupational Exposure and Risk

3.4.2.1 Mixer/Loader/Applicator Exposure and Risk Assessment

Individuals have potential for exposure to halauxifen-methyl during mixing, loading and application. Exposure to workers mixing, loading and applying GF-2685 Herbicide, Paradigm Herbicide or Pixxaro A Herbicide is expected to be short-term in duration and to occur primarily by the dermal and inhalation routes. Exposure estimates were derived for mixers/loaders/applicators applying GF-2685 Herbicide, Paradigm Herbicide and Pixxaro A Herbicide using groundboom and aerial equipment. The exposure estimates are based on mixers/loaders/applicators wearing a single layer (and chemical-resistant gloves when mixing/loading).

As chemical-specific data for assessing human exposures were not submitted, dermal and inhalation exposures for workers involved with groundboom and aerial application were estimated using the Pesticide Handlers Exposure Database (PHED), version 1.1. 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 using the unit exposure values with the amount of product handled per day and the dermal absorption value of 30%. 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.

Exposure estimates were compared to the toxicological endpoints (NOAELs) to obtain the margin of exposure (MOE); the target MOE is 300 for both dermal and inhalation risk. Appendix I, Table 6 presents the PHED unit exposure values used in the risk assessment. Appendix I, Table 7 present the estimates of exposure and risk for GF-2685 Herbicide, Paradigm Herbicide and Pixxaro A Herbicide. The combined MOEs were all above 300, therefore, risks are not of concern provided that workers wear the personal protective equipment stated on the product labels.

3.4.2.2 Exposure and Risk Assessment for Workers Entering Treated Areas

There is potential for exposure to workers re-entering areas treated with GF-2685 Herbicide, Paradigm Herbicide or Pixxaro A Herbicide when scouting. The duration of exposure is considered to be short-term. The primary route of exposure for workers re-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 the active ingredient is relatively non-volatile according to NAFTA criteria for outdoor use and, as such, a risk assessment was not required.

Dermal exposure to workers entering treated areas is estimated by coupling dislodgeable foliar residue values with activity-specific transfer coefficients (TCs). Activity transfer coefficients are based on Agricultural Re-entry Task Force (ARTF) data.

Chemical-specific dislodgeable foliar residue data were not submitted. As such, a default dislodgeable foliar residue value of 25% of the application rate was used in the exposure assessment. Exposure estimates were compared to the toxicological endpoint to obtain the MOE; the target MOE is 300 (Appendix I, Table 8).

3.4.3 Residential Exposure and Risk Assessment

There are no residential uses for GF-2685 Herbicide, Paradigm Herbicide, or Pixxaro A Herbicide and, as such, a residential risk assessment was not required.

3.4.3.1 Bystander Exposure and Risk

Bystander exposure should be negligible since the potential for drift is expected to be minimal. Application is limited to only when there is low risk of drift to areas of human habitation or activity such as houses, cottages, schools and recreational areas, taking into consideration wind speed, wind direction, temperature inversions, application equipment and sprayer settings.

3.5 Food Residues Exposure Assessment

3.5.1 Exposure from Drinking Water

3.5.1.1 Concentrations in Drinking Water

Estimated environmental concentrations (EECs) of combined residues of halauxifen-methyl [halauxifen-methyl and transformation products XDE-729 acid (X11393729) and X11449757] in potential drinking water sources (groundwater and surface water) were generated using computer simulation models. An overview of how the EECs are estimated is provided in the PMRA's Science Policy Notice SPN2004-01, *Estimating the Water Component of a Dietary Exposure Assessment*. EECs of halauxifen-methyl combined residues in groundwater were calculated using the PRZM-GW model to simulate leaching through a layered soil profile over a 50-year period. The concentrations calculated using PRZM-GW are based on the flux, or movement, of pesticide into shallow groundwater with time. EECs of combined residues of halauxifen-methyl in surface water were calculated using the PRZM/EXAMS models, which simulate 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.

A Level 1 drinking water assessment was conducted using conservative assumptions with respect to environmental fate, application rate and timing, and geographic scenario. The Level 1 EECs are expected to allow for future use expansion into other crops at this application rate. Appendix I, Table 9 lists the application information and main environmental fate characteristics used in the simulations. Several (eight for surface water, four for groundwater) initial application dates between early April and mid-July were modelled. The model was run for 50 years for all scenarios. The largest EECs of all selected runs are reported in Appendix I, Table 10.

3.5.2 Residues in Plant and Animal Foodstuffs

The residue definition for risk assessment and enforcement in plant products is halauxifen-methyl. The residue definition for risk assessment and enforcement in edible livestock commodities is halauxifen-methyl and the metabolite X11449757. The data gathering/enforcement analytical method for the quantitation of halauxifen-methyl residues in plant matrices is valid for the determination of this analyte. There is currently no acceptable enforcement method available for the determination of X11449757 in edible livestock commodities. However, the LC-MS/MS data collection method used in the cattle feeding study was demonstrated to be adequate for data collection through the analysis of control samples spiked with X11449757. Residues of halauxifen-methyl are stable in representative high water

(lettuce), high oil (rapeseed), high acid (whole oranges) and high starch (wheat grain) commodities for up to 16 months (489 days) when stored in a freezer at ≤-18°C. The raw agricultural commodity, wheat grain was processed. Quantifiable residues were not observed in the unprocessed wheat grain or in the processed commodities, aspirated grain fractions, bran, total bran, flour (dry mill), whole meal flour, flour-550, bread (white), whole grain bread, middlings, shorts, germ, gluten, gluten feed meal and starch. As a result, processing factors were not determined for any of the processed commodities. An adequate feeding study was carried out in cattle to assess the anticipated residues in edible matrices resulting from the current uses. A hen feeding study is not available and is not currently required given that results from the poultry metabolism study demonstrated that residues would not be expected in edible poultry matrices in birds fed grain from treated crops. Crop field trials conducted throughout the United States and Canada using end-use products containing halauxifen-methyl at approved rates in or on the proposed crops are sufficient to support the proposed maximum residue limits.

3.5.3 Dietary Risk Assessment

Chronic non-cancer dietary risk assessments were conducted using the Dietary Exposure Evaluation Model (DEEM–FCID™, Version 2.14), which uses updated food consumption data from the United States Department of Agriculture's Continuing Surveys of Food Intakes by Individuals, 1994–1996 and 1998.

3.5.3.1 Chronic Dietary Exposure Results and Characterization

The following criteria were applied to the basic chronic non-cancer analysis for halauxifen-methyl: 100% crop treated and residues based on the proposed MRLs for domestic crops. The basic chronic dietary exposure from all supported halauxifen-methyl food uses (alone) for the total population, including infants and children, and all representative population subgroups is <1% of the ADI. Aggregate exposure from food and drinking water is considered acceptable. The PMRA estimates that chronic dietary exposure to halauxifen-methyl from food and drinking water is <1% (≤0.000043 mg/kg bw/day) of the ADI for the total population and all population subgroups.

3.5.3.2 Acute Dietary Exposure Results and Characterization

No appropriate endpoint attributable to a single dose for the general population (including children and infants) was identified. Therefore, an acute dietary exposure assessment was not conducted for halauxifen-methyl.

3.5.4 Aggregate Exposure and Risk

The aggregate risk for halauxifen-methyl consists of exposure from food and drinking water sources only; there are no residential uses.

3.5.5 Maximum Residue Limits

A maximum residue limit (MRL) of 0.01 ppm is being proposed for the commodities: barley and wheat.

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

The nature of the residues in animal and plant matrices, analytical methodologies, field trial data, and acute and chronic dietary risk estimates are summarized in Appendix I, Table 1b, 11a - 11f and 12.

4.0 Impact on the Environment

4.1 Fate and Behaviour in the Environment

Halauxifen-methyl is non-persistent to slightly persistent in terrestrial and aquatic systems based on laboratory and field dissipation studies. Hydrolysis can contribute to the dissipation of halauxifen-methyl in the environment, especially under alkaline conditions. Biotransformation can also contribute to the dissipation of halauxifen-methyl in the environment. Phototransformation on soil is not an important route of dissipation for halauxifen-methyl, while phototransformation in water can be important near the surface of water bodies. Halauxifen-methyl is not expected to volatilize from water or moist soils. Based on field dissipation studies, halauxifen-methyl and transformation products XDE-729 acid (X11393729) and X11449757 are not expected to carry over in appreciable amounts into the next growing season. Halauxifen-methyl and its transformation products can be mobile in soil, but levels detected below 30 cm in field studies were low (less than or equal to 2.4% of maximum measured halauxifen-methyl concentrations). Conservative water modelling of combined residues indicates that levels of halauxifen-methyl and its transformation products that may reach groundwater are very low. Halauxifen-methyl does not appreciably bioaccumulate in fish. A summary of the environmental fate and behaviour of halauxifen-methyl and its transformation products is presented in Appendix I, Table 13.

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. Estimated environmental concentrations 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 RQ is then compared to the level of concern [LOC = 1 for most species, 0.4 for pollinators and 2 for beneficial arthropods (predatory mite and parasitoid wasp)]. If the screening level RQ is below the LOC, the risk is considered negligible and no further risk characterization is necessary. If the screening level RQ is equal to or greater than the LOC, 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 may include further characterization of risk based on exposure modelling, monitoring data, results from field or mesocosm studies, and probabilistic risk assessment methods. Refinements to the risk assessment may continue until the risk is adequately characterized or no further refinements are possible.

As multiple ER_{50} values were available for terrestrial vascular plants, the program ETX 2.0 was used to generate a species sensitivity distribution (SSD) based on normally distributed toxicity data. The hazardous rate to 5% of the species (HR_5) was then calculated for vegetative vigour from the SSD. The HR_5 is the rate which is theoretically protective for 95% of species. At the HR_5 exposure level, 5% of all species will be exposed to a rate which exceeds their LR_{50} toxicity value. The variability around the fraction of species affected value is indicated by the lower and upper confidence limits, which indicates the minimum and maximum percent of species that may be affected at the HR_5 value. The HR_5 values were used to calculate the RQ for terrestrial vascular plants instead of the most sensitive species tested. This provides a more scientifically robust endpoint, which uses all of the data.

4.2.1 Risks to Terrestrial Organisms

A risk assessment for halauxifen-methyl was conducted for terrestrial organisms. For acute toxicity studies, uncertainty factors of 1/2 and 1/10 the EC_{50} (LC_{50}) are typically used in modifying the toxicity values for terrestrial invertebrates, birds and mammals when calculating RQs. No uncertainty factors are applied to chronic no observed effect concentration (NOEC) endpoints. A summary of terrestrial toxicity data for halauxifen-methyl and its transformation products is presented in Appendix I, Table 14. The screening level risk assessment for halauxifen-methyl is presented in Appendix I, Table 15 for terrestrial organisms other than birds and mammals, and Appendix I, Table 16 for birds and mammals. The screening level risk assessment for transformation products of halauxifen-methyl is presented in Appendix I, Table 17 for terrestrial organisms.

Earthworms: Halauxifen-methyl and its transformation products XDE-729 acid (X11393729) and X11449757 were not acutely toxic to earthworms. The RQs for earthworms resulting from

acute exposure to halauxifen-methyl or its soil transformation products XDE-729 acid (X11393729) and X11449757 do not exceed the level of concern at the screening level. The use of halauxifen-methyl is expected to pose a negligible acute risk to earthworms.

Bees: Acute oral and contact exposure to halauxifen-methyl did not result in treatment-related mortality in honey bees. The resulting RQs for both acute contact and oral exposure routes were all below the LOC, indicating halauxifen-methyl is expected to pose a negligible risk to pollinators. Although studies on bee larval toxicity are not available at this time, none are required as larval bee toxicity is not expected from exposure to halauxifen-methyl based on the mode of action, a lack of effects observed for adult bees, and a lack of effects for beneficial arthropods.

Beneficial arthropods: Acute exposure of the predatory mite, *Typhlodromus pyri*, and the parasitoid wasp, *Aphidius rhopalosiphi*, to a formulation of halauxifen-methyl resulted in no statistically significant differences in reproduction or mortality. The RQs for predatory and parasitoid arthropods resulting from exposure to halauxifen-methyl did not exceed the level of concern at the screening level. The use of halauxifen-methyl is expected to pose a negligible risk to predatory and parasitoid arthropods.

Other terrestrial invertebrates: Chronic exposure of the predatory mite, *Hypoaspis aculeifer*, or the springtail, *Folsomia candida*, to halauxifen-methyl or the transformation product X11449757 did not result in treatment-related effects on mortality or reproduction. Chronic exposure of the predatory mite, *H. aculeifer*, to the transformation XDE-729 acid (X11393729) affected reproduction at a soil concentration of 25 mg/kg dry substrate. The RQs for *H. aculeifer* and *F. candida* resulting from chronic exposure to halauxifen-methyl or its transformation products XDE-729 acid (X11393729) and X11449757 did not exceed the level of concern at the screening level. The use of halauxifen-methyl is expected to pose a negligible risk to soil-dwelling invertebrates.

Birds: Halauxifen-methyl was not toxic to birds on an acute or dietary basis, with no treatment-related mortality or sublethal effects. Following reproductive exposure of Northern bobwhite quail, *Colinus virginianus*, to halauxifen-methyl, reproduction was affected at a concentration of 1040 mg a.i./kg diet, equivalent to a daily dietary dose of 93.7 mg a.i./kg bw/day. The RQs for birds resulting from acute or reproductive exposure to halauxifen-methyl did not exceed the level of concern at the screening level. The use of halauxifen-methyl is expected to pose a negligible risk to birds.

Mammals: Halauxifen-methyl was not toxic to mammals on an acute or reproductive basis. Dietary exposure of pregnant female rabbits to halauxifen-methyl resulted in increased resorptions and postimplantation loss at a dose of 19 mg/kg bw/day. The RQs for mammals resulting from acute, reproductive and developmental exposure to halauxifen-methyl did not exceed the level of concern at the screening level. The results of acute, reproduction and developmental toxicity studies with the transformation product XDE-729 acid (X11393729) indicate that the transformation product is less toxic than the parent halauxifen-methyl. As the RQs for acute and reproductive/developmental exposure to halauxifen-methyl were below the level of concern, the transformation product XDE-729 acid (X11393729) is expected to pose a

negligible risk to mammals. The use of halauxifen-methyl is expected to pose a negligible risk to mammals.

Vascular plants: Halauxifen-methyl was toxic to non-target plants in seedling emergence and vegetative vigour studies using standard crop species. The transformation product X11393729 (XDE-729 acid) was toxic to non-target plants in seedling emergence tests, while the transformation product X11449757 was not. The formulation GF-2687, containing the active ingredients halauxifen-methyl and florasulam (as in Paradigm Herbicide), was toxic to non-target plants in seedling emergence and vegetative vigour studies using standard crop species.

Using the seedling emergence ER_{25} for the most sensitive species, the calculated RQs exceeded the level of concern for halauxifen-methyl, the transformation product X11393729 (XDE-729 acid) and the formulation GF-2687. Using the HR_5 values for halauxifen-methyl and for the formulation GF-2687 from the SSD of ER_{50} values for vegetative vigour, the calculated RQs also exceeded the level of concern at the screening level. The risk to terrestrial vascular plants was further characterized by looking at off-field exposure from drift.

Based on the RQs calculated using the off-field EECs from drift, the level of concern for terrestrial vascular plants exposed to halauxifen-methyl and the formulation GF-2687 was still exceeded for vegetative vigour, while the level of concern for plants exposed to transformation product X11393729 (XDE-729 acid) was still exceeded for seedling emergence. Spray buffer zones will be required on product labels to protect non-target terrestrial vascular plants. The spray buffer zones will be rate-specific for the product labels and will range from 1 to 100 metres.

For the end-use product Pixxaro A Herbicide which contains halauxifen-methyl and fluroxypyr, present as methylheptyl ester, the spray buffer zones on the label for the protection of terrestrial habitats will be the largest ones required out of the two active ingredients in the product.

4.2.2 Risks to Aquatic Organisms

A risk assessment for halauxifen-methyl, three of its transformation products, XDE-729 acid (X11393729), X11449757 and X11406790, and for the formulation GF-2687 containing halauxifen-methyl and florasulam was conducted for freshwater and marine aquatic organisms based on available toxicity data. A summary of aquatic toxicity data is presented in Appendix I, Table 18.

For acute toxicity studies, uncertainty factors of 1/2 and 1/10 the EC_{50} (LC_{50}) are typically used for aquatic plants and invertebrates, and fish species, respectively, when calculating RQs. No uncertainty factors are applied to chronic NOEC endpoints. For groups where the LOC is exceeded (in other words, RQ $\geq$1), a refined Tier 1 assessment is conducted to determine risk resulting from spray drift and runoff separately. Risk quotients for halauxifen-methyl and its transformation products were calculated based on the highest maximum seasonal application rate for all uses. The screening level RQs for halauxifen-methyl and its transformation products are summarized in Appendix I, Tables 19 and 20, respectively. The calculated screening level RQs for the GF-2687 formulation are summarized in Appendix I, Table 21. The RQs for the Tier 1

assessment of halauxifen-methyl, its transformation products and the GF-2687 formulation are presented in Appendix I, Table 22 (spray drift only) and Table 23 (runoff only).

Invertebrates: Halauxifen-methyl affected the survival of daphnids but was not acutely toxic up to the limit of solubility in tests with marine crustaceans and mollusks. Acute exposure to halauxifen-methyl in whole sediment tests had no effect on the survival or growth of sediment-dwelling freshwater or marine invertebrates. Chronic exposure to halauxifen-methyl affected reproduction and growth of daphnids at 0.92 mg a.i./L, and affected growth in mysid shrimp at 0.325 mg a.i./L. No effects of halauxifen-methyl on survival, development or emergence were observed up to the limit of water solubility in a long-term emergence test with the freshwater midge *Chironomus riparius*. The major transformation products XDE-729 acid (X11393729), X11449757 and X11406790 were not toxic to freshwater invertebrates on an acute basis. The RQs for freshwater and marine invertebrates resulting from exposure to halauxifen-methyl or its transformation products do not exceed the level of concern at the screening level. The use of halauxifen-methyl is expected to pose a negligible risk to freshwater and marine invertebrates.

Fish: Halauxifen-methyl affected the survival of rainbow trout, *Oncorhynchus mykiss*, on an acute exposure basis. Effects on survival and growth and reproduction of fathead minnow, *Pimephales promelas*, were observed following early life-stage and short-term reproduction exposures to halauxifen-methyl. The major transformation products XDE-729 acid (X11393729), X11449757 and X11406790 were not toxic to freshwater fish on an acute, early-live stage or short-term reproduction basis. The RQs for freshwater and marine fish resulting from exposure to halauxifen-methyl and its transformation products did not exceed the level of concern at the screening level. The use of halauxifen-methyl is expected to pose a negligible risk to fish.

Amphibians: The risk for amphibians was characterized at the screening level by comparing EECs in 15 cm water depth with amphibian toxicity endpoints for halauxifen-methyl. Fish toxicity endpoints were used as surrogates for aquatic life-stages of amphibians for the transformation products XDE-729 acid (X11393729), X11449757 and X11406790. Acute exposure of tadpoles of the African clawed frog, *Xenopus laevis*, to halauxifen-methyl at the maximum achievable test concentration resulted in 45% mortality. Based on results of a metamorphosis study, halauxifen-methyl was not likely thyroid active at up to the solubility limit of the test, 0.38 mg a.i./L. The RQs for amphibians resulting from acute, stage-specific exposures or chronic exposures to halauxifen-methyl and its transformation products do not exceed the level of concern at the screening level. The use of halauxifen-methyl is expected to pose a negligible risk to amphibians.

Algae: Halauxifen-methyl was toxic to freshwater and marine diatoms, while it was not toxic to green algae and blue-green algae at concentrations up to the limit of solubility. The transformation products XDE-729 acid (X11393729), X11449757 and X11406790 were less toxic to algae than halauxifen-methyl. The formulation GF-2687 was toxic to green algae. The RQs for freshwater and marine algae resulting from acute exposure to halauxifen-methyl, its transformation products, or the formulation GF-2687 do not exceed the level of concern at the screening level. The use of halauxifen-methyl is expected to pose a negligible risk to freshwater or marine algae.

Aquatic vascular plants: Halauxifen-methyl, transformation product XDE-729 acid (X11393729), and the formulation GF-2687 were toxic to aquatic vascular plants, rooted aquatic macrophytes in particular, at low concentrations. The halauxifen-methyl transformation products, X11449757 and X11406790, were not toxic to aquatic vascular plants. The RQs resulting from exposure to halauxifen-methyl and XDE-729 acid (X11393729) via direct application to water exceeded the level of concern at the screening level for rooted aquatic macrophytes. For the formulation GF-2687, the RQs exceeded the level of concern at the screening level for duckweed and rooted aquatic macrophytes. The RQs for aquatic vascular plants exposed to transformation products X11449757 and X11406790 did not exceed the level of concern at the screening level. The risk to aquatic vascular plants from exposure to halauxifen-methyl, XDE-729 acid (X11393729) and the formulation GF-2687 was further characterized by looking at exposure from spray drift and runoff.

The refined RQs for rooted aquatic macrophytes exposed to halauxifen-methyl and to XDE-729 acid (X11393729) from spray drift exceeded the level of concern for aerial application but not ground application. Spray buffer zones will be required on halauxifen-methyl product labels to protect rooted aquatic macrophytes from the potential effects of spray drift. The spray buffer zones for halauxifen-methyl will be rate-specific for the product labels and will range from 1 to 10 metres.

The refined RQs for aquatic vascular plants exposed to the formulation GF-2687 from spray drift did not exceed the level of concern. A default spray buffer zone of 1 metre will be required on the label for the end-use product Paradigm Herbicide, which contains halauxifen-methyl and florasulam, to protect aquatic vascular plants from the potential effects of spray drift.

For the end-use product Pixxaro A Herbicide which contains a second active ingredient, fluroxypyr, present as methylheptyl ester, in addition to halauxifen-methyl, the spray buffer zones on the labels for the protection of aquatic habitats will be the largest ones required out of the two active ingredients in the products.

RQs for rooted aquatic macrophytes from exposure of halauxifen-methyl and XDE-729 acid (X11393729) through runoff did not exceed the level of concern. Risk from runoff of the formulation GF-2687 is not expected based on the absence of risk from runoff for halauxifen-methyl or florasulam separately. Standard label statements to mitigate excessive runoff into aquatic habitats will also be required on the label for all halauxifen-methyl end-use products.

5.0 Value

5.1 Effectiveness Against Pests

5.1.1 Acceptable Efficacy Claims

5.1.1.1 GF-2685 Herbicide

Efficacy data were submitted from a total of sixty-nine (69) small plot field trials that were established in western Canada (Alberta, Saskatchewan and Manitoba), eastern Canada (Ontario), and the US (Montana, North Dakota, South Dakota and Minnesota), between 2010 and 2011. GF-2685 Herbicide, applied with 0.5% v/v Turbocharge, was visually assessed as percent weed control on chickweed, cleavers, hemp-nettle, kochia, lamb's quarters, redroot pigweed, wild buckwheat and volunteer flax and compared to an untreated weedy check.

The data support the control of cleavers (1-9 whorl stage), volunteer flax (up to 15 cm in height) and lamb's quarters and the suppression of hemp-nettle and redroot pigweed with a rate of 2.5 g a.e./ha of halauxifen-methyl; the control of chickweed, hemp-nettle and redroot pigweed and the suppression of wild buckwheat and kochia with a rate of 5.0 g a.e./ha of halauxifen-methyl plus the weeds listed with the rate of 2.5 g a.e./ha; and control of wild buckwheat with a rate of 10.0 g a.e./ha of halauxifen-methyl plus the weeds listed with the rate of 5.0 g a.e./ha.

The use claims that are supported for GF-2685 Herbicide are listed in Appendix I, Table 24a.

5.1.1.2 Paradigm Herbicide

Efficacy data were submitted from a total of thirty (30) small plot field trials that were established in western Canada (Alberta, Saskatchewan and Manitoba) between 2010 and 2011. Paradigm Herbicide, applied with 0.5% v/v Turbocharge, was visually assessed as percent weed control on chickweed, cleavers, hemp-nettle, lamb's quarters, redroot pigweed, lady's thumb, volunteer canola, volunteer flax and wild buckwheat and compared to an untreated weedy check.

The data support the control of wild buckwheat, volunteer canola, chickweed, cleavers (1-9 whorl stage), volunteer flax (up to 15 cm in height), lamb's quarters, wild mustard, redroot pigweed, shepherd's purse, green smartweed (lady's thumb), and stinkweed and the suppression of hemp-nettle, kochia, annual sow-thistle and perennial sow-thistle with a rate of 10 g a.e./ha (5.0 g a.e./ha of halauxifen-methyl + 5.0 g a.i./ha of florasulam).

The use claims that are supported for Paradigm Herbicide are listed in Appendix I, Table 24b.

5.1.1.3 Pixxaro A Herbicide

Efficacy data were submitted from a total of forty-four (44) small plot field trials that were established across various ecozones in western Canada (Alberta, Saskatchewan and Manitoba), eastern Canada (Ontario), and the US (Montana, North Dakota, South Dakota and Minnesota),

between 2010 and 2011. Pixxaro A Herbicide, applied with 0.5% v/v Turbocharge, was visually assessed as percent weed control on chickweed, cleavers, hemp-nettle, kochia, lamb's quarters, redroot pigweed, wild mustard, wild buckwheat and volunteer flax and compared to an untreated weedy check.

The data support the control of wild buckwheat, chickweed, cleavers (1-9 whorl stage), volunteer flax (up to 15 cm in height), hemp-nettle, kochia (up to 15 cm in height), lamb's quarters and redroot pigweed and the suppression of wild mustard with a rate of 87.0 g a.e./ha (5.0 g a.e./ha of halauxifen-methyl + 77.0 g a.e./ha of fluroxypyr).

The use claims that are supported for Pixxaro A Herbicide are listed in Appendix I, Table 24c.

5.1.2 Herbicide Tank Mix Combinations

5.1.2.1 GF-2685 Herbicide

Data from replicated field trials (number of trials varies depending on the tank-mix partner) conducted in 2010 and 2011 at several locations throughout the Prairie Provinces were submitted in support of the proposed tank-mixes.

The efficacy of GF-2685 Herbicide plus various tank-mix partners was visually assessed as percent weed control and compared to an untreated weedy check. Observations were made up to three times throughout the growing season. The data support the tank mixtures of GF-2685 Herbicide with Refine SG, Refine SG plus MCPA ester, Axial 100 EC, Horizon 240EC, Horizon NG, Puma[120] Super, Puma Advance, Liquid Achieve SC, Everest 2.0, Traxos Herbicide, Refine SG plus Axial 100 EC, Refine SG plus Horizon 240EC, Refine SG plus Horizon NG, Refine SG plus Everest 2.0, Refine SG plus MCPA ester plus Axial 100 EC, and Refine SG plus MCPA ester plus Everest 2.0 for the control of a broader weed spectrum.

5.1.2.2 Paradigm Herbicide

Data from replicated field trials (number of trials varies depending on the tank-mix partner) conducted in 2010 and 2011 at several locations throughout the Prairie Provinces were submitted in support of the proposed tank-mixes.

The efficacy of Paradigm Herbicide plus various tank-mix partners was visually assessed as percent weed control and compared to an untreated weedy check. Observations were made up to three times throughout the growing season. The data support the tank mixtures of Paradigm Herbicide with MCPA ester, Curtail M Herbicide, Axial 100 EC, Everest 2.0, Simplicity Herbicide, MCPA ester plus Axial 100 EC, MCPA ester plus Everest 2.0, MCPA ester plus Simplicity, Curtail M Herbicide plus Everest 2.0, and Curtail M Herbicide plus Simplicity for the control of a broader weed spectrum.

5.1.2.3 Pixxaro A Herbicide

Data from replicated field trials (number of trials varies depending on the tank-mix partner) conducted in 2010 and 2011 at several locations throughout the Prairie Provinces were submitted in support of the proposed tank-mixes.

The efficacy of Pixxaro A Herbicide plus various tank-mix partners was visually assessed as percent weed control and compared to an untreated weedy check. Observations were made up to three times throughout the growing season. The data support the tank mixtures of Pixxaro A Herbicide with MCPA ester, Curtail M Herbicide, Axial 100 EC, Horizon 240EC, Horizon NG, Puma[120] Super, Puma Advance, Liquid Achieve SC, Everest 2.0, Traxos Herbicide, MCPA ester or Curtail M Herbicide plus Axial 100 EC. MCPA ester or Curtail M Herbicide plus Horizon 240EC, MCPA ester or Curtail M Herbicide plus Horizon NG, MCPA ester or Curtail M Herbicide plus Puma [120] Super, MCPA ester or Curtail M Herbicide plus Puma Advance, MCPA ester or Curtail M Herbicide plus Liquid Achieve SC, MCPA ester or Curtail M Herbicide plus Everest 2.0, and MCPA ester or Curtail M Herbicide plus Traxos Herbicide for the control of a broader weed spectrum.

5.1.3 Rainfastness

Data from a greenhouse experiment conducted in Indianapolis, Indiana were submitted in support of a rainfastness interval of one hour following an application of GF-2685 Herbicide, Paradigm Herbicide and Pixxaro A Herbicide. GF-2685 Herbicide at rates of 2.5 g a.e./ha (min 1x rate) and 5 g a.e./ha (mid 1x rate) plus Turbocharge at 1% v/v (2x rate), Paradigm Herbicide at rates of 5 g a.e./ha (½x rate) and 10 g a.e./ha (1x rate) plus Turbocharge at 1% v/v (2x rate) and Pixxaro A Herbicide at rates of 41 g a.e./ha (1/2x rate) and 82 g a.e./ha (1x rate) plus Turbocharge at 1% v/v (2x rate) were applied to pots seeded with lamb's quarters, cleavers and redroot pigweed. Simulated rainfall treatments were applied to separate groups of plants at 1, 2, 4 and 8 hours after treatment and compared to the treatments that received no rain. Treatments were replicated 3 times and randomized. Percent visual weed control assessments were once every week and up to three weeks after the initial application.

The data support the 1-hour rainfastness interval for GF-2685 Herbicide, Paradigm Herbicide and Pixxaro Herbicide.

5.2 Non-Safety Adverse Effects

5.2.1 GF-2685 Herbicide

Data from a total of sixteen (16) dedicated weed-free crop tolerance trials along with crop tolerance data from seventy-five (75) efficacy trials conducted in 2010 and 2011 in western Canada (Alberta, Saskatchewan and Manitoba) and in the US (Montana, North Dakota, South Dakota and Minnesota). Percent crop injury was visually assessed up to four times during the growing season, and crop yield was reported in thirteen (13) of the dedicated crop tolerance trials.

Crop injury to spring wheat was evaluated in forty-eight (48) efficacy trials and twelve (12) dedicated crop tolerance trials and yield was reported in eleven (11) dedicated weed-free trials. Crop injury was acceptable at the maximum application rate of 10 g a.e./ha.

Crop injury to durum wheat was evaluated in eleven (11) efficacy trials and fourteen (14) dedicated crop tolerance trials and yield was reported in ten (10) dedicated weed-free trials. Crop injury was acceptable at the maximum application rate of 10 g a.e./ha.

Crop injury to winter wheat was evaluated in three (3) efficacy trials and yield was reported in three (3) efficacy trials. Crop injury was acceptable at the maximum application rate of 10 g a.e./ha.

Crop injury to spring barley was evaluated in thirteen (13) efficacy trials and twelve (12) dedicated crop tolerance trials and yield was reported in twelve (12) dedicated weed-free trials. Crop injury was acceptable at the maximum application rate of 10 g a.e./ha.

5.2.2 Paradigm Herbicide

Data from a total of twelve (12) dedicated weed-free crop tolerance trials along with crop tolerance data from thirty (30) efficacy trials conducted in 2010 and 2011 in western Canada (Alberta, Saskatchewan and Manitoba). Percent crop injury was visually assessed up to four times during the growing season, and crop yield was reported in twelve (12) of the dedicated crop tolerance trials.

Crop injury to spring wheat was evaluated in twenty-one (21) efficacy trials and eleven (11) dedicated crop tolerance trials and yield was reported in eleven (11) dedicated weed-free trials. Crop injury was acceptable at the maximum application rate of 10 g a.e./ha.

Crop injury to durum wheat was evaluated in three (3) efficacy trials and eleven (11) dedicated crop tolerance trials and yield was reported in nine (9) dedicated weed-free trials. Crop injury was acceptable at the maximum application rate of 10 g a.e./ha.

Crop injury to winter wheat was not evaluated in any trial; however the crop tolerance of winter wheat to both components of Paradigm Herbicide has been demonstrated with GF-2685 Herbicide and with various herbicides containing florasulam.

Crop injury to spring barley was evaluated in six (6) efficacy trials and twelve (12) dedicated crop tolerance trials and yield was reported in twelve (12) dedicated weed-free trials. Crop injury was acceptable at the maximum application rate of 10 g a.e./ha.

5.2.3 Pixxaro A Herbicide

Data from a total of twelve (12) dedicated weed-free crop tolerance trials along with crop tolerance data from forty-five (45) efficacy trials conducted in 2010 and 2011 in western Canada (Alberta, Saskatchewan and Manitoba) and in the US (Montana, North Dakota, South Dakota

and Minnesota). Percent crop injury was visually assessed up to four times during the growing season, and crop yield was reported in twelve (12) of the dedicated crop tolerance trials.

Crop injury to spring wheat was evaluated in thirty (30) efficacy trials and twelve (12) dedicated crop tolerance trials and yield was reported in eleven (11) dedicated weed-free trials. Crop injury was acceptable at the maximum application rate of 82 g a.e./ha.

Crop injury to durum wheat was evaluated in seven (7) efficacy trials and eleven (11) dedicated crop tolerance trials and yield was reported in nine (9) dedicated weed-free trials. Crop injury was acceptable at the maximum application rate of 82 g a.e./ha.

Crop injury to winter wheat was evaluated in two (2) efficacy trials. Crop injury was acceptable at the maximum application rate of 82 g a.e./ha.

Crop injury to spring barley was evaluated in seven (7) efficacy trials and twelve (12) dedicated crop tolerance trials and yield was reported in twelve (12) dedicated weed-free trials. Crop injury was acceptable at the maximum application rate of 82 g a.e./ha.

5.2.4 Impact on succeeding Crops

Rotational crop tolerance data were submitted from 27 trials that were initiated between 9 and 11 months, and 22 months, following an application of halauxifen-methyl. The number of trials wherein tolerance was evaluated varied by rotational crop. Some trials included multiple varieties/hybrids of one crop. Trials were conducted at various locations in the Prairie Provinces, Montana and North Dakota.

5.2.4.1 Acceptable Claims for Rotational Crops for Halauxifen-methyl

The crop injury and yield data support a rotational crop tolerance claim for the following crops planted after a minimum of 10 months following an application of halauxifen-methyl: spring wheat, spring barley, oats, field corn, canola, flax, Juncea canola, Abyssinian, oriental, brown and yellow mustard, field peas, soybeans, sunflower or fields can be summer fallowed. The crop injury and yield data for lentils support a rotational interval of 22 months for this crop.

5.3 Consideration of Benefits

5.3.1 Social and Economic Impact

Registration of halauxifen-methyl provides growers with a herbicide from a new class of synthetic auxin which is similar to other synthetic auxin herbicides in that it provides broadleaf weed control with a high level of crop safety for spring wheat, winter wheat, durum wheat and barley, and when tank-mixed with other broadleaf and grass herbicides will provide a broad spectrum weed control in a single pass.

Registration of halauxifen-methyl in Canada is part of a global joint review that also includes the United States and Australia. An application for registration has also been submitted to the

European Union in a separate submission. This will allow Canadian growers access to a new herbicide at the same time as their American counterparts, and will enable them to be competitive in the world market.

5.3.2 Survey of Alternatives

Herbicides are the most common tools to control broadleaf and grass weeds in fields in which cereal crops such as spring wheat, durum wheat, winter wheat and barley, are grown. Herbicides that can be applied on wheat and barley include active ingredients from the following modes of action:

- Group 1 such as tralkoxydim (Achieve, Bison, Challenger, etc.), clodinafop-propargyl (Horizon, Bullwhip, etc.), pinoxaden (Axial), fenoxaprop-p-ethyl (Puma, Cougar, Bengal, etc.) which provide mostly grasses control;
- Group 2 such as metsulfuron-methyl, thifensulfuron-methyl + tribenuron-methyl, thiencarbazone-methyl (various end-use products with various combinations of sulfonylureas), flucarbazone (Everest), florasulam (Florasulam Suspension, Frontline HTM, etc.), pyroxsulam (Simplicity) which provide mainly broadleaf control with some grass control;
- Group 3 such as trifluralin (Advance, Rival) for control of grasses and broadleaf weeds;
- Group 4 such as 2,4-D, MCPA, dicamba, fluroxypyr , clopyralid, etc. (various products) for control of broadleaf weeds;
- Group 5 such as metribuzin (Lexone, Sencor, etc.) for control of broadleaf weeds;
- Group 6 such as bromoxynil (various products) for the control of broadleaf weeds;
- Group 11 such as amitrole (Amitrol 240 Liquid) for control of broadleaf weeds;
- Group 14 such as saflufenacil (Heat, Eragon) for control of broadleaf weeds;
- Group 26 such as difenzoquat (Avenge) for the control of wild oats;
- Group 27 such as pyrasulfotole (Infinity) for the control of broadleaf weeds.

There are numerous end-use products registered for use on wheat (spring, winter and durum) and barley that combine 2 or more active ingredients from different modes of action.

5.3.3 Compatibility with Current Management Practices Including Integrated Pest Management

Halauxifen-methyl is a postemergence herbicide that can be used at different rates of application to target specific weeds. It provides control of important broadleaf weeds and may enable growers to control both broadleaf and grass weeds with a single pass in spring wheat, winter wheat, durum wheat, and barley when tank-mixed with various herbicides listed on all three end-use products. Halauxifen-methyl has flexible re-cropping intervals with numerous crops that can be seeded after an interval of 10 months following an application of halauxifen-methyl.

5.3.4 Information on the Occurrence or Possible Occurrence of the Development of Resistance

Halauxifen-methyl is the first member of a new class of synthetic auxin herbicides, the arylpicolinates. The arylpicolinates are a class of herbicides that act through a synthetic auxin mechanism (HRAC Group O, WSSA Group 4). Few cases of resistance to Group 4 herbicides have been reported in Canada (common hempnettle in Alberta and wild mustard in Manitoba); halauxifen-methyl may provide an effective management tool that could control ALS-enzyme inhibitor (HRAC Group B, WSSA Group 2), glyphosate (HRAC Group G, WSSA Group 9), and triazine (HRAC Group C1, WSSA Group 5) resistant weed biotypes.

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 [those that meet all four criteria outlined in the policy: in other words, 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*].

During the review process, halauxifen-methyl 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 following conclusions:

- Halauxifen-methyl does not meet all Track 1 criteria, and is not considered a Track 1 substance. See Appendix I, Table 25 for comparison with Track 1 criteria.

- Halauxifen-methyl does not form any transformation products that meet all Track 1 criteria. Major transformation products X11393729, X11449757 and X11406790 do not meet the criterion for bioaccumulation, based on log K_{OW} values of -1.01 to 0.42, <0.3 and <0.3 to 0.96 for X11393729, X11449757 and X11406790, respectively. Degradates 1, 2, 4, 10, 11 and 14 are major products formed only by aqueous phototransformation (maximum concentrations of 41.2% AR for Degradate 1, and 11.5-15.7% AR for Degradates 2, 4, 10, 11 and 14). They are not expected to be formed in important quantities in the environment as aqueous phototransformation is restricted to the upper layer of clear water bodies. In addition, as they are polar compounds and the bioconcentration factor (BCF) of the parent is low (183-214), they are not expected to meet the criterion for bioaccumulation.

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

6.2 Formulants and Contaminants of Health or Environmental Concern

During the review process, contaminants in the technical and formulants and contaminants in the end-use products are compared against the *List of Pest control Product Formulants and Contaminants of Health or Environmental Concern* maintained in the *Canada Gazette*[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: DIR99-03; and DIR2006-02[8], and taking into consideration the Ozone-depleting Substance Regulations, 1998, of the *Canadian Environmental Protection Act* (substances designated under the Montreal Protocol). The PMRA has reached the following conclusions:

- Technical grade halauxifen-methyl and the end-use products GF-2685 Herbicide, Paradigm Herbicide and Pixxaro A Herbicide do not contain any formulants or contaminants of health or environmental concern identified in the *Canada Gazette.* However, the end-use product Pixxaro A Herbicide does contain an aromatic petroleum distillate. Therefore, the label for the end-use product Pixxaro A Herbicide will include the statement: "This product contains aromatic petroleum distillates that are toxic to aquatic organisms."

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

7.0 Summary

7.1 Human Health and Safety

The toxicology database submitted for halauxifen-methyl and halauxifen acid is adequate to define the majority of toxic effects that may result from exposure. There was no evidence of carcinogenicity in rats or mice after longer-term dosing with halauxifen acid. There were no treatment related effects and no evidence of susceptibility of the young in the rat reproductive toxicity study with halauxifen acid. Halauxifen acid is not neurotoxic and there was no evidence of immunotoxicity after treatment with halauxifen-methyl. In short-term and chronic studies on laboratory animals, the primary target of halauxifen-methyl was the liver and the primary targets of halauxifen acid were the kidney and urinary bladder. Increased incidences of fetal loss were observed after treatment during gestation with halauxifen acid (rats) and halauxifen-methyl (rabbits). The risk assessment protects against the toxic effects noted above by ensuring that the

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6 *Canada Gazette*, Part II, Volume 139, Number 24, SI/2005-114 (2005-11-30) pages 2641–2643: *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern* and in the order amending this list in the *Canada Gazette*, Part II, Volume 142, Number 13, SI/2008-67 (2008-06-25) pages 1611-1613. *Part 1 Formulants of Health or Environmental Concern, Part 2 Formulants of Health or Environmental Concern that are Allergens Known to Cause Anaphylactic-Type Reactions and Part 3 Contaminants of Health or Environmental Concern.*

7 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*.

level of human exposure is well below the lowest dose at which these effects occurred in animal tests.

Mixer/loaders and applicators handling GF-2685 Herbicide, Paradigm Herbicide or Pixxaro A Herbicide, and workers re-entering treated fields are not expected to be exposed to levels of halauxifen-methyl that will result in risks of concern when GF-2685 Herbicide, Paradigm Herbicide and Pixxaro A Herbicide are used according to label directions. The personal protective equipment on the product label is adequate to protect workers.

The nature of the residues in plants and animals is adequately understood. The residue definition for enforcement and dietary exposure assessment is halauxifen-methyl in plant products and is halauxifen-methyl and the metabolite X11449757 in animal matrices. The proposed use of halauxifen-methyl on wheat and barley does not constitute a risk of health concern for chronic or acute dietary exposure (food and drinking water) to any segment of the population, including infants, children, adults and seniors. Sufficient crop residue data have been reviewed to recommend MRLs. The PMRA recommends that the following MRLs be specified for residues of halauxifen-methyl.

Commodity	Recommended MRL (ppm)
Barley, Wheat	0.01

7.2 Environmental Risk

The use of GF-2685 Herbicide containing the active ingredient halauxifen-methyl may pose a risk to non-target terrestrial plants and rooted aquatic macrophytes. As a result, spray buffer zones to protect sensitive terrestrial and aquatic habitats from spray drift and label statements to inform users of potential risks to the environment are required.

The use of the end-use product Paradigm Herbicide, containing the active ingredients halauxifen-methyl and florasulam, may pose a risk to non-target terrestrial plants and aquatic vascular plants. Risks to non-target terrestrial and aquatic vascular plants can be mitigated with label statements and spray buffer zones to protect sensitive terrestrial and aquatic habitats. Florasulam and its major soil transformation product, 5-hydroxy-XDE-570, have the potential to leach. Also, 5-hydroxy-XDE-570 has the potential to carry over into the next growing season. Statements are required on label for Paradigm Herbicide to inform users of the potential risks of leaching and carry-over.

The use of the end-use product Pixxaro A Herbicide, containing the active ingredients halauxifen-methyl and fluroxypyr (present as methylheptyl ester), may pose a risk to non-target terrestrial plants and aquatic vascular plants. Risks to non-target terrestrial and aquatic vascular plants can be mitigated with label statements and spray buffer zones to protect sensitive terrestrial and aquatic habitats. Pixxaro A Herbicide contains aromatic petroleum distillates which are toxic to aquatic organisms. Label statements are required on the label for Pixxaro A Herbicide to inform users of the potential risks.

7.3 Value

In summary, the weight of evidence provided through trial data support the proposed uses from a value standpoint. The registration of halauxifen-methyl provides growers with an herbicide from a new class of synthetic auxin which provides broadleaf weed control with a high level of crop safety for spring wheat, winter wheat, durum wheat and barley and which can be tank-mixed with other broadleaf and grass herbicides to provide a broad spectrum weed control in a single pass.

8.0 Proposed Regulatory Decision

Health Canada's PMRA, under the authority of the *Pest Control Products Act* and Regulations, is proposing full registration for the sale and use of XDE-729 Methyl Technical Herbicide and its end-use products, GF-2685 Herbicide, Paradigm Herbicide and Pixxaro A Herbicide, containing the technical grade active ingredient halauxifen-methyl, to control annual broadleaf weeds in cereal crops (spring wheat, winter wheat, durum wheat and spring barley).

An evaluation of available scientific information found that, under the approved conditions of use, the product has value and does not present an unacceptable risk to human health or the environment.

List of Abbreviations

1/n	exponent for the Freundlich isotherm
°C	degree Celsius
µg	micrograms)
µL	microliter(s)
µm	micrometre(s)
♂ and ♀	male and female symbols
3-MC	3-methylcholanthrene
a.e.	acid equivalent
a.i.	active ingredient
abs	absolute
AD	administered dose
ADI	acceptable daily intake
ADME	Absorption, Distribution, Metabolism and Elimination
AhR	aryl hydrocarbon receptor
ALS	acetolactate synthase
ALT	alanine aminotransferase
AME	Absorption, Metabolism and Elimination
ARfD	acute reference dose
ARTF	Agricultural Re-entry Task Force
AST	aspartate aminotransferase
atm	atmosphere
ATPD	area treated per day
AUC	area-under-the-curve
BBCH	Biologishe Bundesanstalt, Bundessortenamt and Chemical industry
BCF	bioconcentration factor
BrdU	bromodeoxyuridine
bw	body weight
bwg	bodyweight gain
CAF	composite assessment factor
CAS	Chemical Abstracts Service
CEPA	Canadian Environmental Protection Ac
cm	centimetres
cm^2	centimetre(s) squared
cm^3	cubic centimetre(s)
C_{max}	maximum plasma concentration
C_{min}	minimum plasma concentration
CQM	cloquintocet-mexyl
Cyp	cytochrome P450; proceeding identifier refers to the sub-type
d	day(s)
DAT	days after treatment
DFR	dislodgeable foliar residue
DT_{50}	dissipation time 50% (the dose required to observe a 50% decline in concentration)
DT_{90}	dissipation time 90% (the dose required to observe a 90% decline in concentration)
dw	dry weight

EC	Emulsifiable concentrate
EC3	concentration required to induce a threshold positive sensitization response (SI=3)
EC_{50}	effective concentration on 50% of the population
EDE	estimated daily exposure
EEC	estimated environmental concentration
ELISA	enzyme-linked immunosorbent assay
EPA	Environmental Protection Agency
ER_{25}	effective rate on 25% of the population
ER_{50}	effective rate on 50% of the population
fc	food consumption
FIR	food ingestion rate
g	gram(s)
GD	gestation day
GI	Gastrointestinal
h	hour(s)
ha	hectare(s)
HAFT	highest average field trial
HCT	hematocrit
HDL	high-density lipoprotein
HDPE	high-density polyethylene
Hg	mercury
HGB	hemoglobin
HPLC	high performance liquid chromatography
HR_5	hazardous rate to 5% of the species
HRAC	Herbicide Resistance Action Committee
ILV	independent laboratory validation
ITE	2-(1'H-indole-3'-carbonyl)-thiazole-4-carboxylic acid methyl ester
IUPAC	International Union of Pure and Applied Chemistry
IV	intravenous
Kd	soil-water partition coefficient
K_F	Freundlich adsorption coefficient
K_{FOC}	Freundlich adsorption coefficient normalized to organic carbon
kg	kilogram(s)
K_{oc}	organic-carbon partition coefficient
K_{ow}	n–octanol-water partition coefficient
L	litre(s)
LC_{50}	lethal concentration to 50%
LC-MS/MS	liquid chromatography with tandem mass spectrometry
LD	lactation day
LD_{50}	lethal dose to 50%
LDL	low-density lipoprotein
LLQ	lower limit of quantitation
LLNA	local lymph node assay
LOAEL	lowest observed adverse effect level
LOC	level of concern
LOQ	limit of quantitation
LR_{50}	lethal rate 50%
LSC	liquid scintillation counting

m^2	metre(s) squared
m^3	cubic metre(s)
m/z	mass-to-charge ratio of an ion
MAS	maximum average score
MCV	mean corpuscular volume
mg	milligram(s)
MIS	maximum irritation score
mL	millilitre(s)
mm	millimetre(s)
mm Hg	millimeter of mercury
mmol	millimole(s)
MMAD	mass median aerodynamic diameter
MOA	mode of action
MOE	margin of exposure
mol	mole(s)
MRL	maximum residue limit
mRNA	messenger ribonucleic acid
MS	mass spectrometry
MS/MS	tandem mass spectrometry
N/A	not applicable
NA	not analyzed
NAFTA	North American Free Trade Agreement
nm	nanometre
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
NOEL	no observed effect level
NR	not reported
NZW	New Zealand White
OECD	Organisation for Economic Co-operation and Development
Pa	Pascal
PB	phenobarbital
PBI	plantback interval
PBPK	physiologically-based pharmacokinetic
PH	phenyl
PHED	Pesticide Handlers Exposure Database
PHI	preharvest interval
p*Ka*	dissociation constant
PMRA	Pest Management Regulatory Agency
PND	postnatal day
PPE	personal protective equipment
ppm	parts per million
PY	pyridine
RBC	red blood cells
rel	relative
RQ	risk quotient
SC	soluble concentrate
SI	stimulation index
SRBC	sheep red blood cell

SSD	species sensitivity distribution
$t_{1/2}$	half-life
$t_{1/2\alpha}$	elimination half-life alpha
$t_{1/2\beta}$ or $t_{1/2}$	elimination half-life beta or terminal elimination half-life
TC	transfer coefficient
TG	triglyceride
TGAI	technical grade active ingredient
TK	toxicokinetics
TRR	total radioactive residue
TSMP	Toxic Substances Management Policy
US	United States
UV	ultraviolet
v/v	volume per volume dilution
w	weight
WDG	water dispersible granule
wk	week(s)
WSSA	Weed Science Society of America

Appendix I Tables and Figures

Table 1a Residue Analysis – Environmental Matrices

Matrix	Analyte	Transition	Method Type	LOQ	Reference (PMRA#)
Soil	parent	m/z 345→250	HPLC-MS/MS	0.05 µg/kg in sand, clay loam, silt loam and clay	2226437, 2226438
	XDE-729 acid	m/z 331→250			
	X11449757	m/z 317→236			
Sediment	extended from soil				
Water	parent	m/z 345→285	HPLC-MS/MS	0.05 µg/L in drinking, ground and surface water	2226439, 2226440
	XDE-729 acid	m/z 331→250			
	X11449757	m/z 317→236			
	X11406790	m/z 331→236			

Table 1b Residue Analysis – Plant and Animal Matrices

Matrix	Method ID	Analyte	Method Type	LOQ		Reference (PMRA#)
Plant	110005	Halauxifen-methyl ester and halauxifen acid	LC-MS/MS	0.01 ppm	Turnip root; wheat forage; barley and wheat grain, hay and straw; canola seed; soybean seed; apples; oranges; aspirated grain fractions of wheat; wheat processed commodities (total bran, whole grain bread, flour, germ gluten shorts, and starch	2226432
	110004 (Enforcement method)	Halauxifen-methyl ester and halauxifen acid	LC-MS/MS	0.01 ppm for each analyte	Wheat forage, wheat flour, canola oil	2226433, 2226435
Livestock	110505	Halauxifen-methyl, halauxifen acid and X11449757	LC-MS/MS	0.01 ppm for each analyte	Whole milk, skim milk, cream, muscle, liver, kidney, subcutaneous fat, mesenteric fat, and perirenal fat.	2226442, 2226441.

Table 2 Toxicity Profile of End-Use Product(s) Containing Halauxifen-Methyl
(Effects are known or assumed to occur in both sexes unless otherwise noted; in such cases, sex-specific effects are separated by semi-colons)

Study Type/Animal	Study Results	Reference (PMRA#)
GF-2685 Herbicide		
Acute oral toxicity Fischer 344 rats	$LD_{50♀}$ >5000 mg/kg bw Low toxicity	2226179
Acute dermal toxicity Fischer 344 rats	LD_{50} >5000 mg/kg bw Low toxicity	2226180
Acute inhalation toxicity (nose-only) Fischer 344 rats	LC_{50} >5.16 mg/L Low toxicity	2226183
Dermal irritation NZW rabbits	MAS (24, 48, 72 h) = 2.4/8 Mildly irritating	2226185
Eye irritation NZW rabbits	MAS (24, 48, 72 h) = 0.4/110 Minimally irritating	2226187
Dermal sensitization (LLNA) CBA/J mice	High variability of data; decreased confidence in results. SI = 1.0, 1.0, 2.2 (1♀ = 5.5), 1.9 (1♀ = 3.0) (positive control SI = 6.0) Potential dermal sensitizer	2226189
Paradigm Herbicide		
Acute oral toxicity Wistar rats	$LD_{50♀}$ >5000 mg/kg bw Low toxicity	2226247
Acute dermal toxicity Wistar rats	LD_{50} >5000 mg/kg bw Low toxicity	2226248
Acute inhalation toxicity (nose-only) Wistar rats	LC_{50} >2.27 mg/L Low toxicity	2226249
Dermal irritation NZW rabbits	MAS (24, 48, 72 h) = 0.1/8 Minimally irritating	2226250
Eye irritation NZW rabbits	MAS (24, 48, 72 h) = 0.9/110 Minimally irritating	2226251

Study Type/Animal	Study Results	Reference (PMRA#)
Dermal sensitization (LLNA) CBA/J mice	Positive: SI = 1.0, 1.6, 2.3, 3.8 (EC_{50} = 37.5%) (positive control SI = 11.6) Dermal sensitizer	2226252
Pixxaro A Herbicide		
Acute oral toxicity Fischer 344 rats	LD_{50} >5000 mg/kg bw Low toxicity	2226305
Acute dermal toxicity Fischer 344 rats	LD_{50} >5000 mg/kg bw Low toxicity	2226306
Acute inhalation toxicity (nose-only) Fischer 344 rats	LC_{50} >5.57 mg/L Low toxicity	2226307
Dermal irritation NZW rabbits	MAS (24, 48, 72 h) = 1.7/8 Mildly irritating	2226308
Eye irritation NZW rabbits	MAS (24, 48, 72 h) = 28.2/110 Moderately irritating	2226309
Dermal sensitization (LLNA) CBA/J mice	Positive: SI = 1.0, 0.9, 2.4, 5.2 (EC_{50} = 41%) (positive control SI = 2.4) Dermal sensitizer	2226310

Table 3 Toxicity Profile of Halauxifen-Methyl Technical and Halauxifen Acid

(Effects are known or assumed to occur in both sexes unless otherwise noted; in such cases, sex-specific effects are separated by semi-colons). Organ weight effects reflect both absolute organ weights and relative organ to bodyweights unless otherwise noted.

Study Type/Animal/ PMRA #	Study Results
Metabolism and Toxicokinetics Halauxifen acid (referred to as XR-729 acid) Absorption, Distribution, Metabolism and Elimination (ADME) Fischer 344 rats and CD-1 mice	A probe study, was conducted to determine ADME of labeled ^{14}C-XR-729 acid rats (2/sex) and mice (4/sex) after administration of a single oral dose at 100 mg/kg bw. Time-course blood (plasma and RBC) and excreta were collected from rats and time-course excreta only were collected from mice for up to 72 hours post-dosing. The urine samples collected during the first 12 hours post-dosing were analyzed for parent compound and metabolite(s). Additionally, two rats (1/sex) and four mice (2/sex) were orally dosed with ^{14}C-XR-729 acid at 100 mg/kg bw and plasma was collected at the peak plasma concentration (t_{max}; 0.5 hour post-dosing estimated from rats) and analyzed for parent and metabolite(s). The orally administered ^{14}C-XR-729 acid was rapidly absorbed

Study Type/Animal/ PMRA #	Study Results
PMRA # 2226444	from the GI tract both by the rats and mice with a t_{max} of approximately 0.5 hours and eliminated mainly in the urine. The rate of absorption of ^{14}C-XR-729-derived radioactivity from the GI tract was the same for both male and female rats. Total urinary elimination accounted for 65-75% of the dose in rats and 65-66% of the dose in mice, most of which occurred within the first 12 hours after dosing. Fecal elimination accounted for 12-21% in rats and 19-20% in mice. Elimination of radioactivity from plasma was bi-exponential in the rat with an initial half-life ($t_{½\alpha}$) of 0.14 hours indicating rapid distribution to tissues and terminal elimination half-life ($t_{½\beta}$) ranging from 3.37 (male) to 3.67 (female) hours. Elimination of ^{14}C-XR-729-derived radioactivity from red blood cells (RBC) was mono-exponential with a half-life ($t_{½}$) of 0.84 (male) and 0.77 (female) hours. In the 12-hour urine samples, eight peaks were detected, but only one peak was found representing >5% of the dose and was identified as XR-729 acid (parent). Four metabolites were tentatively identified: the glucuronide conjugate of O-demethyl XR-729, the sulfate conjugate of O-demethyl XR-729, O-demethyl XR-729, and acyl-glucuronide conjugate of parent XR-729. The metabolic profiles were similar between sexes and species. Unchanged XR-729 acid was found as the major component in all C_{max} plasma extracts and the acyl glucuronide conjugate of XR-729 acid was also found in the male mouse plasma extract, representing approximately 7.5% of the recovered radioactivity.
Metabolism and toxicokinetics Halauxifen acid (as the sodium salt) (referred to as XDE-729 acid or XDE-729 Na Salt) Absorption, Metabolism and Elimination (AME) Beagle dogs PMRA # 2226445	In a non-guideline study, 3 male and 3 female beagle dogs were administered 50 mg/kg bw ^{14}C-XDE-729, formulated as the sodium salt, via oral gavage. Time-course plasma and excreta were collected up to 168 hours post-dosing to determine AME. Urine and fecal samples collected at 168 hours post-dosing and plasma samples collected at C_{max} and ½C_{max} were analyzed to characterize and quantify XDE-729 acid (parent) and metabolites. Plasma C_{max} was achieved slightly earlier in females than male dogs (mean t_{max}: 0.7 vs. 1.3 h) and was also slightly higher in female dogs (143 vs. 118 µg-Na eq./g). The majority of the ^{14}C-radioactivity cleared from dog plasma by 6 hours post-dosing. Elimination of radioactivity from the plasma was biphasic, with initial half-life ($t_{½\alpha}$) of 1 h indicating rapid distribution to tissues and terminal elimination half-life ($t_{½\beta}$) of 9-12 h. XDE-729 acid represented the major radiolabeled component in plasma. AUC_{24} in dogs was 2 to 4-fold higher than rats administered 10 and 100 mg/kg bw of ^{14}C-XDE-729 sodium salt indicating higher systemic exposure to ^{14}C-XDE-729 acid in dogs following a single oral

Study Type/Animal/ PMRA #	Study Results
	dose. Analysis of excreta showed that approximately 80% of the dose was excreted in the urine in 168 h, with the largest fraction excreted within 12 h. Fecal elimination accounted for ~10% (males) or ~14% (females) of the dose, most of which were excreted within 48 hours post-dosing. In total, 95-98% of the dose was recovered from excreta and cage wash within 168 hours post-dosing demonstrating adequate mass balance. XDE-729 acid was the major radio-labeled component in urine/rinse (77-79% of the dose) and was present in feces at levels higher than or similar to those of other identified metabolites. The primary metabolites identified in urine, feces, or plasma included O-demethyl XDE-729 and the sulfate and glucose conjugates of O-demethyl XDE-729, hydroxy XDE-729, and an acyl glucuronide conjugate of XDE-729.
Metabolism and toxicokinetics Halauxifen acid (as the sodium salt) (referred to as XDE-729 acid or XDE-729 Na Salt) or Halauxifen-methyl (referred to as XDE-729 methyl) Absorption, Distribution, Metabolism and Elimination (ADME), Bioequivalence Fischer 344 rats PMRA # 2226446	This study was conducted for 168 hours post-dosing to determine ADME of ^{14}C-XDE-729 (^{14}C-(UL-phenyl)-XDE-729 or ^{14}C-(2,6-pyridine)-XDE-729), as the sodium salt, following oral (single or multiple dose of 10 mg/kg bw; single dose of 750 mg/kg bw) and intravenous (IV) exposure (single 10 mg/kg bw) to groups (n = 4) of male and female F344/DuCrl rats. In addition, ADME of ^{14}C-XDE-729 methyl (the methyl ester form of XDE-729; 10 mg/kg bw) was also determined in male and female F344/DuCrl rats (n=4/sex) to determine the bioequivalence between the acid as the sodium salt (further identified as XDE-729 acid to avoid confusion) and methyl ester forms of XDE-729. Orally administered XDE-729 acid, was rapidly absorbed (t_{max} 0.1-0.2 hours and 0.3-1.8 hours following low oral single doses and a high oral single dose, respectively). The t_{max} for the low oral XDE-729 methyl group was slightly longer (0.44-0.50 hours) compared to the low oral XDE-729 acid. The percent absorption of the orally administered acid form in all low oral groups was at least 77-93%, based on recovery in urine and non-GI tissues and was comparable for low oral XDE-729 methyl dose group (82%). The percent absorption estimated from urine and non-GI tissue was slightly lower following the high single oral dose of ^{14}C-XDE-729 acid (69-73%). Total recovery of radioactivity from all the animals averaged 102 ± 3 and 99 ± 3% in the oral and IV dose groups, respectively. Absolute oral bioavailability, calculated from comparison of the plasma AUC data for the low oral and IV dose groups (^{14}C-(UL-phenyl)-XDE-729 acid) was ~100% for both female and male rats. The orally absorbed dose was rapidly excreted mainly in urine (68-92% of the administered dose (AD) for the oral dose groups) with a higher percentage excreted in the

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	urine of female rats. The majority of the urinary elimination (90-99%) occurred within the first 24 hours post-dosing. A smaller percent (11-29% for the oral dose groups) of the administered oral dose was eliminated in feces. The amount and rates of urinary and fecal elimination were comparable between XDE-729 acid (both labels) and XDE-729 methyl as a low oral dose. Rats orally administered 750 mg ^{14}C-XDE-729 acid/kg bw demonstrated decreased urinary elimination compared to rats administered 10 mg ^{14}C-XDE-729 acid/kg bw. The IV-administered XDE-729 acid was also rapidly and extensively excreted in urine (85-88% of AD). The majority of the urinary elimination (98-99%) occurred in the first 24 hours post-dosing. A smaller percent (11-15%) of the IV dose was eliminated in feces. At 168 hours post-dosing, levels in the tissues ranged from non-quantifiable to 0.3% of the orally AD from either XDE-729 acid (low single, high single, multiple dose, and low single pyridine-ring label) or ^{14}C-XDE-729 methyl (low single). Less than 0.03% of the IV administered ^{14}C-XDE-729 remained in the tissues at 168 hours post-dosing. In the rats orally administered as a single dose at 10 mg ^{14}C-XDE-729 acid/kg bw (both labels) or 10 mg ^{14}C-XDE-729 methyl/kg bw, the C_{max} was 1.6 to 3.6 fold lower for the methyl group. Elimination of the radioactivity from plasma was rapid during the initial distribution phase ($t_{½\alpha}$ = 0.5-0.9 hours) followed by a slower elimination during the terminal phase ($t_{½\beta}$ = 5-16 hours). Rats orally administered 750 mg ^{14}C-XDE-729 acid/kg bw displayed a slower initial distribution phase ($t_{½\alpha}$ = 2.7-4.3 hours), while the terminal β phase ($t_{½\beta}$ = 5.6-8.7 hours) was within the range of the 10 mg/kg bw group. Clearance of the IV-administered XDE-729 acid was ~ 0.5 mL/h/kg. The plasma AUC was 2.0-2.6 times higher at the high dose than would be expected for dose proportionality demonstrating a supraproportional increase in systemic exposure at the high dose. The AUC non-linearity is consistent with the longer initial distribution phase of the 750 mg/kg bw group and decreased urinary elimination at 168 h post-dose, likely due to a slower redistribution at the high dose and saturation of elimination. The time-course of radioactivity in RBC was less than the plasma time-course concentration profiles with lower concentrations. At 10 mg/kg bw oral dose (both labels, acid and methyl forms) when compared to the concentrations in plasma, the maximum concentrations in RBC were 8- to 33-fold less. At the high dose of 750 mg/kg bw, the C_{max} was 2- to 3-fold less than in plasma. The time to peak, maximum concentration and absorption half-lives in RBC were comparable to plasma numbers. The time for distribution, as reflected by $t_{½\alpha}$, and elimination ($t_{½\beta}$) was less than those in plasma for all five treatment groups, with the

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	exception of the high dose group with demonstrated a longer elimination ($t_{½\beta}$) in RBC compared to plasma. The AUC numbers were substantially less than those in plasma for all five treatment groups . Overall, similar kinetics were observed across sexes for the acid and methyl test materials. The IV-administered XDE-729 acid demonstrated higher clearance values for RBC (5- to 8-fold) when compared to plasma. As seen in plasma in RBC's there was a supraproportional increase in AUC from the low to the high dose, however, in contrast to plasma the AUC non-linearity is consistent with the longer terminal elimination phase of the 750 mg/kg bw group. Analysis of blood samples from the methyl dose group afforded primarily XDE-729 acid and no parent ester, indicating rapid hydrolysis of the ester in vivo. Although XDE-729 methyl showed increased t_{max} and decreased C_{max} when compared to the same dose of XDE-729 acid/kg bw, the administration of both test compounds resulted in similar AUC values. The major radiolabeled component present in the urine and fecal extracts from animals administered ^{14}C-XDE-729 acid as the sodium salt, was XDE-729 acid. The major radiolabeled component present in urine and fecal extracts of animals dosed with XDE-729 methyl was the hydrolysis product, XDE-729 acid. Minor metabolites of both test materials consisted of the acyl-glucuronide conjugate of parent XDE-729 (present in selected samples at greater than 5% of the AD) and O-demethylated XDE-729 and the corresponding sulfate and glucuronide conjugates.
Acute oral toxicity Halauxifen acid Fischer 344 rats PMRA # 2226447	$LD_{50♀}$ >5000 mg/kg bw Low toxicity
Acute oral toxicity Halauxifen-methyl Fischer 344 rats PMRA # 2226448	$LD_{50♀}$ >5000 mg/kg bw Low toxicity
Acute dermal toxicity Halauxifen acid Fischer 344 rats PMRA # 2226449	LD_{50} >5000 mg/kg bw Low toxicity

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Acute dermal toxicity Halauxifen-methyl Fischer 344 rats PMRA # 2226450	LD_{50} >5000 mg/kg bw Low toxicity
Acute inhalation toxicity Waiver Halauxifen acid and halauxifen-methyl PMRA # 2226453	Waiver was accepted based on the inability to generate a test atmosphere due to clogging of the aerosol generator, large particle size (MMAD >4 μm), and high variability in chamber aerosol concentration.
Dermal irritation Halauxifen acid NZW rabbits PMRA # 2226454	MAS (24, 48, 72 h) = 0.11/8 Minimally irritating
Dermal irritation Halauxifen-methyl NZW rabbits PMRA # 2226455	MAS (24, 48, 72 h) = 0/8 Non-irritating
Eye irritation Halauxifen acid NZW rabbits PMRA # 2226456	MAS (24, 48, 72 h) = 1.1/110 Minimally irritating
Eye irritation Halauxifen-methyl NZW rabbits PMRA # 2226457	MAS (24, 48, 72 h) = 0/110 Non-irritating
Dermal sensitization (LLNA) Halauxifen acid CBA/J mice PMRA # 2226458	Negative; SI = 1.0, 0.7, 0.7, 1.1 (positive control = 5.4) Not a dermal sensitizer
Dermal sensitization (LLNA)	Negative; SI = 1.0, 0.8, 0.9, 1.3 (positive control = 3.5) Not a dermal sensitizer

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Halauxifen-methyl CBA/J mice PMRA # 2226459	
28-day dietary toxicity Halauxifen acid CD-1 mice PMRA # 2226464	**1025/958 mg/kg bw/day (♂/♀):** ↓ serum ALT; ↓ kidney weight, ↑ kidney tubule degeneration, ↑ liver multifocal karyomegaly and focal necrosis (♂) No overt evidence of saturation of either systemic bioavailability or apparent steady-state urinary elimination of the parent chemical. Slight disproportional decrease of parent chemical concentration in urine at the highest dose non-adverse; potentially reflecting altered kidney function (♂)
28-day dietary toxicity Halauxifen acid Fischer 344 rats PMRA # 2226460	**734/982 mg/kg bw/day** (♂/♀)**:** ↓ bw, bwg, fc, ↑ urinary volume, ↓ urine specific gravity, ↑ rel. brain weight (secondary to ↓ bw), epithelial degeneration and hypertrophy of renal tubules and vacuolization of collecting duct epithelium, splenic extramedullary hematopoiesis; 1♂ was thin, thrombocytosis, ↓ TG, ↑ rel. kidney weight (♂); ↑cloudy urine, phosphate crystals in urine sediment (♀) Absorption was slightly saturated at the top 3 levels. Halauxifen acid was quickly eliminated, primarily via the urine as parent. Urinary metabolites included glucuronide, sulfate and acyl-glucuronide conjugates.
28-day dietary toxicity Halauxifen-methyl Fischer 344 rats PMRA # 2226461	NOAEL = 11/56 mg/kg bw/day (♂/♀) LOAEL = 56/277 mg/kg bw/day (♂/♀) **≥56/56 mg/kg bw/day** (♂/♀)**:** ↑ liver weight; hepatocellular hypertrophy (↑ cytoplasmic eosinophilia), ↑ mitotic figures in hepatocytes, hepatocellular vacuolization (consistent with fatty change), hypertrophy of thyroid gland follicular cells (♂)
28-day dietary toxicity Halauxifen acid Beagle dogs PMRA # 2226465	**≥80 mg/kg bw/day:** epithelial degeneration and regeneration of renal tubules (♂) **635/323 mg/kg bw/day** (♂/♀)**:** bw loss (♂>♀), ↓ fc, thymic atrophy (attributed to stress); ↑ cholesterol (total, HDL), 1♂ had atypical muscle tone, ↓ RBC, HGB, HCT, reticulocytes, ↑ LDL-cholesterol, ↑ bilirubin, ↓ abs. epididymides, heart, kidneys, spleen, thyroid/parathyroid weights (may be secondary to bw effect). The other ♂ had atypical palpebral closure, ↑ AST; epithelial degeneration and regeneration of renal tubules (♀) Saturation of elimination in high-dose ♂ (may also occur in ♀ but

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	confounded by high variability between the 2 samples); ♀ were more efficient in eliminating the acid than ♂
90-day dietary toxicity Halauxifen acid CD-1 mice PMRA # 2226468	NOAEL = 495/1008 mg/kg bw/day (♂/♀) LOAEL = 989 mg/kg bw/day/not established (♂/♀) **989/1008 mg/kg bw/day (♂/♀):** ↑ neutrophils in blood, urinary bladder toxicity (2/10; acute inflammation, submucosal edema, hyperplasia of transitional epithelium, multiple foci of ulceration, crystals), 1♂ seminal vesicle acute unilateral inflammation (secondary to bladder toxicity) (♂) Linear kinetics in plasma and urine (high variability noted in the 495/512 mg/kg bw/day urine group); ~32-47% dose in 24 h urine; no apparent sex differences
90-day dietary toxicity Halauxifen acid Fischer 344 rats PMRA # 2226467	NOAEL = 262/252 mg/kg bw/day (♂/♀) LOAEL = 782/758 mg/kg bw/day (♂/♀) **782/758 mg/kg bw/day (♂/♀):** ↑ urinary volume, ↓ urine specific gravity, renal toxicity (necrosis, ↑ mitotic figures, hypertrophy of collecting duct epithelial cells, vacuolization of collecting duct epithelium in the papilla of the kidney (♂>♀); ↓ bw, bwg, ↑ rel. thyroid, kidney, brain weight (secondary to ↓ bw), ↑ tubular dilatation & epithelial degeneration (♂); amorphous crystals in urine sediment (♀) Dose proportionality with dose in plasma TK; non-linearity of urinary excretion in ♀ between 252 and 758 mg/kg bw/day
90-day dietary toxicity Halauxifen-methyl Fischer 344 rats PMRA # 2226466	NOAEL = 10/10 mg/kg bw/day (♂/♀) LOAEL = 53/52 mg/kg bw/day (♂/♀) **≥53/52 mg/kg bw/day (♂/♀):** ↑ hepatocellular vacuolation (consistent with fatty change; graded very slight with ↑ severity with dose) (♂); ↑ liver weight, ↑ cholesterol (♀)
90-day dietary toxicity Halauxifen acid Beagle dogs PMRA # 2226469	NOAEL = 81/80 mg/kg bw/day (♂/♀) LOAEL = 424/415 mg/kg bw/day (♂/♀) **424/415 mg/kg bw/day (♂/♀):** ↓ bw, bwg, ↓ RBC, HGB, HCT, ↓ thymus weight, epithelial degeneration and regeneration of renal tubules, epithelial degeneration of collecting ducts, focal granuloma in cortex or medulla, thymic lymphoid atrophy, hyperplasia of bone marrow, ↑ myelopoiesis; ↓ fc, 1♀ had ↑ band neutrophils & reactive lymphocytes, while another lacked mature neutrophils, ↓ band neutrophils, ↑ reactive lymphocytes, monocytes (ineffective myelopoiesis, maturation arrest at band neutrophil stage), ↑ liver weight, extramedullary hematopoiesis of

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	liver & spleen (♀) Saturation of elimination at the high dose. However, kinetic nonlinearity in the daily systemic doses (AUC_{24h}); statistically significant only in ♀, and kinetic non-linearity in the total dose excreted in 24 h urine; statistically significant only in ♂.
1-year dietary toxicity Halauxifen acid Beagle dogs PMRA # 2226470	NOAEL = 82/17 mg/kg bw/day (♂/♀) LOAEL = 355/90 mg/kg bw/day (♂/♀) **90 mg/kg bw/day:** epithelial degeneration with regeneration of renal proximal and distal tubules, epithelial degeneration of collecting ducts, multifocal glomerulosclerosis (♀) **355 mg/kg bw/day:** epithelial degeneration with regeneration of renal proximal and distal tubules, epithelial degeneration of collecting ducts , multifocal glomerulosclerosis, granulomas in the renal cortex; multifocal fibrosis of renal cortex (♂) Supralinear kinetics in ♂ (13 wk), in both sexes (26 wk). 52 wk time-point could not be assessed due to too few plasma samples, terminal plasma levels (after a 16 h fast) were below LOQ. Amount excreted in urine over 24 h was linear for all 3 doses in ♀ and between 500-2500 ppm in ♂. Urine levels were sublinear in high-dose ♂ at all time-points.
28-day dermal toxicity Halauxifen acid Fischer 344 rats PMRA # 2226471	NOAEL = 1000 mg/kg bw/day LOAEL not established No treatment-related effects up to a limit dose.
21/28-day dermal toxicity Waiver Halauxifen-methyl PMRA # 2279917	Waiver accepted as the expected exposure is predominantly to the acid form of halauxifen-methyl (see PMRA 2226471).
28-day inhalation Waiver PMRA # 2279916	Waiver request was accepted based on the following: • Low volatility: vapour pressure 5.9×10^{-9} Pa (4.4×10^{-11} mmHg) at 25°C which is $<1\times10^{-4}$ kPa (7.5×10^{-4} mmHg) at 20-30°C (the threshold for non-volatility). • Large aerosol particle size: In an acute inhalation toxicity study with halauxifen-methyl or its acid form, repeated attempts to generate a stable, respirable aerosol failed for one or more of the following reasons: low aerosol concentrations, large particle size (>4 µm MMAD), clogging of the generation equipment, unsustainable concentrations, and/or inefficient delivery of the

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	test material. • Toxicity Category IV/Extrapolated MOE: Low acute toxicity.
78-week oncogenicity Halauxifen acid CD-1 mice PMRA # 2226485	NOAEL = 50 mg/kg bw/day LOAEL = 251 mg/kg bw/day **≥251/251 mg/kg bw/day:** ↑ subacute to chronic inflammation in bladder, presence of microscopic calculi in the lumen of bladder (♂); ↓ bwg, ↑ hypertrophy of the intercalated cells in kidneys (♀)
2-year combined chronic/oncogenicity, dietary Halauxifen acid Fischer 344 rats PMRA # 2226483	NOAEL = 101/20 mg/kg bw/day (♂/♀) LOAEL = 404/102 mg/kg bw/day (♂/♀) **≥102 mg/kg bw/day:** ↑ hyperplasia of pelvic epithelium of kidney (24 months) (♀) **≥404/407 mg/kg bw/day (♂/♀):** ↑ urinary volume, ↓ urine specific gravity, ↑ kidney weight, ↑ renal toxicity (hypertrophy of renal collecting duct epithelium, increased numbers of mitotic figures in collecting duct epithelial cells (♂, 12 months only), chronic interstitial inflammation of medulla, hyperplasia of pelvic epithelium (♀, 12 months), vacuolization of collecting duct epithelium in the papilla, slight necrosis of collecting duct epithelium & individual tubular epithelial cells (24 months); ↓ terminal bw, hypertrophy of the zona glomerulosa of adrenal glands, presence of calculi in the renal pelvis of kidney, epithelial degeneration and regeneration of renal tubules, bladder effects (extensive hyperplasia of the transitional epithelium, subacute to chronic inflammation in the submucosa beneath the hyperplastic epithelium, microscopic calculi in the lumen of the urinary bladder) (♂) The acid was present in plasma and urine and exhibited a linear relationship with dose. The only exception was the male group at 6 months, in which plasma levels (plotted against dose) were sublinear at 633 mg/kg bw/day. Terminal sacrifice plasma levels (after overnight fasting) were very low or <LLQ. **No evidence of oncogenicity.**
Reproductive/developmental (range-finding), dietary Halauxifen acid Sprague-Dawley rats PMRA # 2226495	**754/535 mg/kg bw/day (♂/♀):** ↑ multifocal hypertrophy and hyperplasia of the epithelial cell lining of kidney collecting ducts with nuclear karyomegally, ↑ necrosis of individual collecting duct epithelial cells, ↑ # mitotic figures within collecting ducts, tubular dilatation, ↑ tubular dilatation with inflammation (♀>♂);↓ gestation bw, ↓bwg (♀), 1♀ was prematurely sacrificed on day 20 due to bw loss (renal lesions at necropsy)

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	1000 mg/kg bw/day: bw loss, ↓ fc, fecal output (termination on day 8) PND 4 pup plasma concentrations were less than maternal plasma concentrations.
2-generation reproductive toxicity, dietary Halauxifen acid Sprague-Dawley rats PMRA # 2226496	Parental NOAEL = 104/103 mg/kg bw/day (♂/♀) Parental LOAEL = 465/465 mg/kg bw/day (♂/♀) **465/465 mg/kg bw/day (♂/♀):** ↑ renal toxicity (collecting duct epithelial cell hypertrophy and hyperplasia, hyperplasia of pelvic epithelium, mitotic figures of the collecting duct epithelium) (♂); clinical signs (↓ quantity & abnormal colour of feces, periocular soiling, dehydrated skin, pale mucous membranes, thin) &↓ bwg GD 14-21 & ↓ fc GD 17-21 in 2♀ in late gestation/early lactation, ↑ abs./rel. kidney weights, ↑ mineralization of the aorta, renal arteries, renal tubular basal lamina and mammary gland artery (♀) Reproductive NOAEL = 443 mg/kg/day Reproductive LOAEL not established Offspring NOAEL = 443 mg/kg/day Offspring LOAEL not established **No evidence of sensitivity**
Developmental toxicity, dietary Halauxifen acid Sprague-Dawley rats PMRA # 2226500	Maternal NOAEL = 140 mg/kg bw/day LOAEL = 526 mg/kg bw/day 526 mg/kg bw/day: 2 mortalities (GD 17, 18), ↓ fecal output, perinasal red soiling, ↓ bw (GD 21), ↓ bwg, ↓ fc, slight ↑ total resorptions, ↓ gravid uterine weight, ↑ rel. kidney weight Developmental NOAEL = 140 mg/kg bw/day LOAEL = 526 mg/kg bw/day 526 mg/kg bw/day: ↓ fetal weight, slight ↑ total resorptions, resorptions per dam and postimplantation loss, ↑delayed ossification of thoracic centra (variation) **Evidence of developmental toxicity** **No evidence of sensitivity**
Developmental toxicity, dietary (range-finding) Halauxifen-methyl	Maternal 303 mg/kg bw/day: ↓ bwg, fc 490 mg/kg bw/day: ↓ bwg GD 6-9; animals sacrificed on GD 9

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Sprague-Dawley rats PMRA # 2226497	Developmental Developmental effects were not assessed. Blood concentrations showed linear kinetics across all three doses for both halauxifen-methyl, when present, and the acid metabolite. Halauxifen-methyl was present above LLQ (0.03-0.16 µg/g) during early sampling times on GD 20 and was absent in GD 21 dams. In contrast, the main metabolite, the acid, was present in all dams and fetal blood samples. When present, halauxifen-methyl concentrations were ~ 0.9% that of the acid metabolite. Fetal blood concentrations of the acid were ~69% of the dam blood concentrations.
Developmental toxicity, dietary Halauxifen-methyl Sprague-Dawley rats PMRA # 2226499	Maternal NOAEL = 159 mg/kg bw/day LOAEL = 323 mg/kg bw/day **≥159 mg/kg bw/day:** ↓ bwg GD 6-9, fc GD 6-9, ↑ liver weights, ↑ altered cytoplasmic homogeneity of centrilobular & midzonal hepatocytes (non-adverse at 159 mg/kg bw/day) Developmental NOAEL = 323 mg/kg bw/day LOAEL not established **No evidence of developmental toxicity.** **No evidence of sensitivity.** Halauxifen-methyl was not present in any GD 21 dam and fetal blood samples. In contrast, the acid metabolite was present at quantifiable levels (≥LLQ) in all of the blood samples from exposed animals. The acid was present in fetal blood samples at concentrations ~ 65% of the dam blood levels. Acid blood concentrations were linear at all three doses in dams and fetuses.
Developmental toxicity, dietary (range-finding) Halauxifen acid NZW rabbits PMRA # 2226503	No treatment-related maternal & developmental effects. Plasma concentrations of halauxifen acid were dose proportional in maternal animals and fetuses, with fetal concentrations being ~40% of the maternal concentrations. TK analysis demonstrated similar systemic exposure over a 24-h period between diet and gavage administration; however, due to the relatively short half-life of elimination ($t_{1/2}$ = 1.08 h) dietary administration resulted in far more consistent exposure over a 24-h period relative to gavage with only a six-fold vs. 368-fold fluctuation between C_{min} and C_{max} by the diet vs. gavage,

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	respectively. Furthermore, plasma halauxifen acid concentrations were detectable only up to 12-h by gavage, but up to 24-h by dietary administration, driven by continued dietary test material intake over a 24-h period.
Developmental toxicity, dietary Halauxifen acid NZW rabbits PMRA # 2226504	Maternal NOAEL = 434 mg/kg bw/day LOAEL = 1094 mg/kg bw/day **1094 mg/kg bw/day:** ↓ bwg, fc Developmental NOAEL = 1094 mg/kg bw/day LOAEL not established **No evidence of developmental toxicity.** **No evidence of sensitivity.** Mean terminal plasma concentrations of the acid in both dam and fetal blood demonstrated systemic exposure. Fetal plasma acid concentrations were on average 3-fold lower than those in maternal animals. Analysis of kinetic dose proportionality was not possible due to high variability (attributed to short plasma $t_{1/2}$ & maternal feeding patterns at the end of gestation).
Developmental toxicity, dietary (range-finding) Halauxifen-methyl NZW rabbits PMRA # 2226502	Maternal: ≥22 mg/kg bw/day: ↑ liver weights ≥83 mg/kg bw/day: ↓ bwg, ↓ fc ≥244 mg/kg bw/day: bw loss, ↓ fc Developmental: ≥83.3 mg/kg bw/day: ↓ fetal weight Blood TK analysis demonstrated the presence of only the metabolite, the acid, and not the parent molecule, halauxifen-methyl, in treated animals at concentrations above the analytical LLQ. Diurnal systemic exposure values for the metabolite (acid) exhibited linear kinetics through the highest analyzed dose group (4167 ppm).
Developmental toxicity, dietary Halauxifen-methyl NZW rabbits PMRA # 2226501	Maternal: NOAEL = 6 mg/kg bw/day LOAEL = 19 mg/kg bw/day **≥19 mg/kg bw/day:** ↑ resorptions **≥19 mg/kg bw/day:** ↑ liver weight, ↑ hypertrophy with altered tinctorial properties (increased cytoplasmic eosinophilia) of periportal hepatocytes, ↑ # mitotic figures of hepatocytes, ↑ altered cytoplasmic homogeneity of centrilobular/midzonal hepatocytes (↑

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	cytoplasmic glycogen) (non-adverse at 19 mg/kg bw/day) Developmental: NOAEL = 6 mg/kg bw/day LOAEL = 19 mg/kg bw/day **≥19 mg/kg/day:** ↑ resorptions, postimplantation loss **Evidence of developmental toxicity (variation)** The acid, but not the parent molecule, halauxifen-methyl, was detected in treated maternal animals and their litters at concentrations above LLQ. Blood concentration values for the acid metabolite exhibited linear kinetics through the highest analyzed group (1539 ppm) in maternal animals and sublinear kinetics at 1539 ppm in fetuses. Fetal acid blood concentrations in the 391 and 1539 ppm groups were on average 27 and 6% of maternal blood concentrations, respectively.
Gene mutations in bacteria Halauxifen acid *Salmonella typhimurium. E. Coli WP2uvrA* PMRA # 2226473	Negative
Gene mutations in bacteria Halauxifen-methyl *Salmonella typhimurium. E. Coli WP2uvrA* PMRA # 2226472	Negative
Gene mutations in bacteria Halauxifen-methyl *Salmonella typhimurium. E. Coli WP2uvrA* PMRA # 2226475	Negative
Gene mutations in mammalian cells in vitro Halauxifen acid Chinese hamster ovary cells (HGPRT locus)	Negative

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PMRA # 2226481	
Gene mutations in mammalian cells in vitro Halauxifen-methyl Chinese hamster ovary cells (HGPRT locus) PMRA # 2226480	Negative
Gene mutations in mammalian cells in vitro Halauxifen-methyl Chinese hamster ovary cells (HGPRT locus) PMRA # 2226479	Negative
Chromosome aberrations in vitro Halauxifen acid Rat lymphocytes PMRA # 2226478	Negative
Chromosome aberrations in vitro Halauxifen-methyl Rat lymphocytes PMRA # 2226477	Negative
Chromosome aberrations in vitro Halauxifen-methyl Human peripheral lymphocytes PMRA # 2226476	Negative
In vivo mammalian cytogenetics Halauxifen acid CD-1 mice	Negative One ♂ at 2000 mg/kg bw had clinical signs by 5 h on the 2nd day of dosing and died.

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PMRA # 2226482	
Acute neurotoxicity, gavage Halauxifen acid Fisher 344 rats PMRA # 2226505	NOAEL = 750/2000 mg/kg bw (♂/♀) LOAEL = 2000/not established (♂/♀) **2000 mg/kg bw:** ↓ bw (Days 2 and 8) (♂) **No evidence of neurotoxicity**
13-week neurotoxicity, dietary Halauxifen acid Fischer 344 rats PMRA # 2226506	NOAEL = 250/750 mg/kg bw/day (♂/♀) LOAEL = 750 mg/kg bw/day/not established (♂/♀) **750 mg/kg bw/day:** ↓ bw, bwg, fc (♂) **No evidence of neurotoxicity**
28-day immunotoxicity (SRBC response via ELISA) Halauxifen-methyl Fischer 344 rats PMRA # 2226514	NOAEL = 52 mg/kg bw/day LOAEL = 500 mg/kg bw/day **500 mg/kg bw/day:** ↓ abs. thymus weight **No evidence of immunotoxicity**
7-day hepatic gene expression and biomarker analyses Halauxifen-methyl CD-1 mice PMRA # 2226491	**778/863 mg/kg bw/day (♂/♀):** ↑ Cyp1a1 mRNA expression (AhR activation) Both parent and the primary metabolite, the acid, exhibited linear kinetics up to the high-dose in liver, blood (6 am) and urine; the only exception was the terminal sample in ♂. Halauxifen-methyl was detected at low levels in ~50% of blood samples at all doses but represented ≤1% of the acid levels (0.03-0.07 µg/mL). Halauxifen-methyl was only in urine at the high dose (0.20-0.24 µg/mL). Acid was present in all treated animals at 100 and 9000-fold higher than halauxifen-methyl for blood and urine, respectively. In liver, halauxifen-methyl was 50 to 100-fold higher than blood (1.39-4.95 µg/g). In liver, acid was 2-fold higher than halauxifen-methyl. Levels of both halauxifen-methyl and acid were generally lower in female mice compared to males in blood (6 am), liver and urine, despite having consumed slightly larger doses of halauxifen-methyl; the only exceptions were the terminal blood concentrations, where slightly higher halauxifen-methyl and acid levels were seen in females. Kinetics of halauxifen-methyl are similar in male mice and rats. Kinetic data beyond 7 days are not available for females. The rat is

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	more sensitive than the mouse to halauxifen-methyl-induced hepatic responses (liver weight, hepatocellular hypertrophy and mitoses, Cyp1a1 gene induction).
Comparative 7-day dietary hepatic gene expression and biomarker analyses Halauxifen-methyl & Halauxifen acid Fischer 344 rats PMRA # 2226494	Halauxifen acid: **672 mg/kg/day:** ↓ bwg, ↓ fc Halauxifen-methyl: **766 mg/kg/day:** ↑ liver and thyroid weights, ↑ panlobular hepatocyte hypertrophy (↑ cytoplasmic eosinophilia), ↑ number of mitotic figures in hepatocytes, ↑ hypertrophy of thyroid follicular cells, ↑ number of mitotic figures in thyroid follicular cells, ↑ Cyp1a1 and Ugt1a6 mRNA expression (markers of AhR activation) Concentrations of acid in liver or blood from animals given the acid form were 1.75- or 1.37-fold higher, respectively, than animals given halauxifen-methyl at the corresponding acid equivalent dose. After administration of acid, 47% was excreted in urine as acid over the first 24 h compared to only 24% in rats receiving halauxifen-methyl. Additionally, concentrations of 4 identified metabolites of the acid were lower in blood, liver tissue and urine after administration of the acid versus halauxifen-methyl. ↑ methyl-derived metabolites via O-demethylation pathway (3% of the acid dose in urine vs. 18% from the halauxifen-methyl dose).
28-day dietary (molecular and cellular changes in the liver) Halauxifen-methyl Fischer 344 rats PMRA # 2226489	**≥3 mg/kg bw/day:** No quantifiable methyl in liver at 3 mg/kg bw/day, ≤0.36 µg/g at 10 and 52 mg/kg bw/day, 3.0 µg/g at 261 mg/kg bw/day **≥55 mg/kg bw/day:** ↑ liver weight, ↑ Cyp1a1 mRNA expression, ↑ hepatocellular hypertrophy with ↑ cytoplasmic eosinophilia, hepatocellular vacuolation, mitotic figures **271 mg/kg bw/day:** Marginal ↑ BrdU uptake in liver, ↑ Cyp1a2, Ugt1a6 and Cyp2b1 mRNA expression Recovery: Complete reversal of changes in liver weight, liver histopathology, Cyp gene expression and quantifiable liver concentrations of halauxifen-methyl and acid Low levels of halauxifen-methyl in liver, which became supralinear between 54.8-271 mg/kg/day. Levels of methyl <LLQ in all blood samples; acid was present in all blood samples (minor metabolites not measured). Blood levels of halauxifen-methyl were sub-linear at 271 mg/kg/day. In urine, ~0.05% dose was excreted as halauxifen-methyl and ~50% dose was excreted as acid. Total

Study Type/Animal/ PMRA #	Study Results
	amount of acid in urine was sub-linear at 271 mg/kg/day.
Comparative in vitro AhR transactivation (Luciferase reporter & competition ligand binding assays) Halauxifen-methyl & Halauxifen acid Mouse (Hepa 1.1), human (Hep G2 40/6) liver cell lines PMRA # 2226490	Halauxifen-methyl: **≥10 µM:** Weak ↑AhR transactivation activity in mouse Hepa 1.1 reporter cell line only, compared to positive control ITE Halauxifen-methyl ultrapure (99.7%) is an AhR ligand that weakly competes with the photoaffinity ligand for the rat AhR (EC_{50} = 1.5×10^{-5} (halauxifen-methyl), 8.4×10^{-7} (ITE)). No AhR transactivation was observed with the acid.
In vitro AhR nuclear receptor activation & Cyp1a mRNA expression Halauxifen-methyl Mouse (CD-1), rat (F344) and human hepatocytes PMRA # 2226487	**Halauxifen-methyl:** **≥30 µM:** Limited induction of Cyp1a1 and Cyp1a2 in mouse and human hepatocytes at multiple time-points up to 24 h compared to 3-MC. Human hepatocytes were less responsive than mouse and rat hepatocytes to Cyp1a1 induction but more responsive to Cyp1a2 induction compared to mice. Peak expression occurred from 8-12 h. Sensitivity to Cyp1a induction: Rat>Mouse>Human (Cyp1a1>Cyp1a2) **3-MC:** Dose responsive ↑Cyp1a1 and Cyp1a2 in all species. Cyp1a1 was more responsive compared to Cyp1a2 with the mouse and human, but Cyp1a2 was induced to a greater extent in the rat. For Cyp1a1 induction, mouse was the most sensitive, followed by the human where all but 1 donor had a higher CYP1A1 induction than rat. Rat was most responsive to 3-MC with respect to Cyp1a2 induction, human was the next most responsive and mouse had the least amount of Cyp1a2 induction. **PB:** Induction of Cyp2b10 (mouse; modest response), Cyp2b6 (rat) and CYP2B6 (human) in hepatocytes
Comparative in vitro methyl ester hydrolysis, PBPK modeling Halauxifen-methyl Mouse (CD-1), rat (F344) and human tissues (liver S9 cell fraction, whole blood and synthetic gastric fluid (SGF)) PMRA # 2226488	Rapid hydrolysis to the acid by liver S9 in all species with relative rate of metabolism in order of (fastest to slowest) human>>rat>mouse. In human liver S9, methyl was not present at >LOQ after 8 min of incubation. Halauxifen-methyl was metabolized in whole blood by first order kinetics (fastest to slowest): rat>mouse>>human Rate of metabolism in synthetic gastric fluid was the slowest. Fastest rate of conversion at pH 1.2 (pH of human GIT) = $t_{1/2}$ 100 h (much slower than liver S9 and whole blood)

Study Type/Animal/ PMRA #	Study Results
	Predicted hydrolysis of halauxifen-methyl was most dependent on the rate of metabolism in liver tissue for both species (~60% of total hydrolysis in rat and >95% in human). Halauxifen-methyl and its acid achieve steady-state concentrations soon after exposure is begun, the levels clear rapidly from blood and liver following the cessation of exposure, and neither halauxifen-methyl nor acid would be expected to accumulate in either liver or blood. Model-derived peak concentrations (and 24 h AUCs) of halauxifen-methyl in liver and blood are comparable between rats and human. Peak concentrations from simulated 28 d exposure to methyl at 0.001 mg/kg bw/day (relevant exposure level based on residue data) resulted in levels 10000-15000-times lower than LOQ (LOQs: in blood ~0.01 µg halauxifen-methyl/g; in liver ~0.04 µg halauxifen-methyl/g).

Table 4 Toxicity Profile of a Desmethyl Metabolite, X11449757, of Halauxifen-Methyl Technical

Study Type/Animal/PMRA #	Study Results	Reference (PMRA #)
Gene mutations in bacteria *Salmonella typhimurium*	Negative	2226509
Gene mutations in mammalian cells in vitro Chinese hamster ovary cells (HGPRT locus)	Negative	2226507
Chromosome aberrations in vitro Human peripheral lymphocytes	Negative	2226508

Table 5 Toxicology Endpoints for Use in Health Risk Assessment for Halauxifen-Methyl

Exposure Scenario	Study		Point of Departure and Endpoint	CAF[1] or Target MOE
Acute dietary general population	No acute toxicity endpoint was determined			
	ARfD = N/A			
Repeated dietary		NOAEL = 20 mg/kg bw/day		100
	Co-critical studies	1-year Toxicity in dogs (Halauxifen acid)	Renal toxicity	
		Chronic toxicity/Carcinogenicity in Rats (Halauxifen acid)		

Exposure Scenario	Study	Point of Departure and Endpoint	CAF[1] or Target MOE
	ADI = 0.2 mg/kg bw/day		
Short-term to intermediate-term inhalation[2]	Rabbit oral developmental toxicity (Halauxifen-methyl)	Developmental NOAEL = 6 mg/kg bw/day based on increased resorptions, postimplantation loss	300
Short-term to intermediate-term dermal[3]	Rat oral developmental toxicity (Halauxifen acid) Note: exposure via dermal route is to acid, not methyl	Developmental NOAEL = 140 mg/kg bw/day based on decreased fetal weight, slight increase in total resorptions, resorptions per dam and postimplantation loss, increased delayed ossification of thoracic centra	300
Cancer	Not required		

1 CAF (composite assessment factor) refers to a total of uncertainty and *Pest Control Products Act* factors for dietary assessments; MOE refers to a target MOE for occupational assessments

2 Since an oral NOAEL was selected, an inhalation absorption factor of 100% (default value) was used in route-to-route extrapolation.

3 Since an oral NOAEL was selected, a dermal absorption factor (30%) was used in a route-to-route extrapolation

Table 6 PHED Unit Exposure Estimates for Mixer/Loader and Applicators while Handling GF-2685 Herbicide, Paradigm Herbicide and Pixxaro A Herbicide Wearing a Single Layer (and Chemical-Resistant Gloves when Mixing/Loading)

Exposure scenario		PHED unit exposure (µg/kg a.i. handled)		
		Dermal	Adjusted Dermal*	Inhalation
A	Dry flowable open mixing/loading (with CR gloves)	163.77	49.13	1.02
B	Liquid open mixing/loading (with CR gloves)	51.14	15.34	1.60
C	Groundboom application, open cab (without CR gloves)	32.98	9.89	0.96
D	Aerial application (without CR gloves)	9.66	2.90	0.07
A+C	Open dry flowable ML, open cab groundboom A	196.75	59.03	1.98
B+C	Open liquid ML, open cab groundboom A	84.12	25.24	2.56

CR = chemical-resistant, ML = mixing/loading, A = application

* Adjusted dermal = Dermal × 30% dermal absorption

Table 7 Mixer/Loader/Applicator Risk Assessment for GF-2685 Herbicide, Paradigm Herbicide and Pixxaro A Herbicide for Workers Wearing a Single Layer and Chemical-Resistant Gloves (gloves not required for application)

Exposure scenario		PHED UE[1] (µg/kg a.i. handled)		ATPD[2] (ha/day)	Rate (kg a.e./ ha)	Daily Exposure[3] (mg/kg bw/day)		Calculated MOE[4]		Combined MOE[5]
		Adjusted Dermal	Inhal.			Dermal	Inhalation	Dermal	Inhalation	
WETTABLE GRANULE FORMULATIONS (Halauxifen-methyl in GF-2685 Herbicide and Paradigm Herbicide) assessed at the maximum rate (10 g a.e./ha for GF-2685 Herbicide)										
A+C	Farmer Groundboom MLA	59.03	1.98	107	0.01	7.89E-04	2.65E-05	177,000	227,000	99,500
A+C	Custom Groundboom MLA	59.03	1.98	360	0.01	2.66E-03	8.91E-05	52,700	67,300	29,600
A	Aerial ML*	49.13	1.02	400	0.01	2.46E-03	5.10E-05	57,000	118,000	38,400
D	Aerial A*	2.90	0.07	400	0.01	1.45E-04	3.50E-06	966,000	1,710,000	618,000
EMULSIFIABLE CONCENTRATE FORMULATION (Halauxifen-methyl in Pixxaro A Herbicide) assessed at the maximum proposed rate (5 g a.e./ha)										
B+C	Farmer Groundboom MLA	25.24	2.56	107	0.005	1.69E-04	1.71E-05	830,000	350,000	246,000
B+C	Custom Groundboom MLA	25.24	2.56	360	0.005	5.68E-04	5.76E-05	247,000	104,000	73,200
A	Aerial ML*	15.34	1.60	400	0.005	3.84E-04	4.00E-05	365,000	150,000	106,000
D	Aerial A*	2.90	0.07	400	0.005	7.25E-05	1.75E-06	1,930,000	3,430,000	1,240,000

ML = mixing/loading, A = application,
[1] PHED unit exposures (UE) from Table 6.
[2] Area treated per day (ATPD) values from Default Area Treated per day tables (2010)
[3] Daily exposure = (PHED unit exposure × ATPD × Rate) / (80 kg bw × 1000 µg/mg)
[4] Based on dermal NOAEL = 140 mg/kg bw/day and inhalation NOAEL = 6 mg/kg bw/day (target MOE = 300).
[5] Combined MOE = $\frac{1}{(1/\text{Dermal MOE}) + (1/\text{Inhalation MOE})}$

Table 8 Postapplication Exposure and Risk Estimates for Re-Entry Workers

Crop	Activity	Rate	DFR (µg/cm^2)[1]	TC (cm^2/hr)[2]	Exposure (mg/kg bw/day)[3]	Calculated MOE[4]
Wheat and barley	Scouting in full foliage	One application at 0.01 kg a.e./ha*	0.0250	1100	0.0008	170,000
	Scouting in minimal foliage			100	0.0001	1,870,000

[1] Dislodgeable foliar residue (DFR) calculated based on the default values: 25% of the application rate dislodgeable on the day of application, 10% daily dissipation)
[2] Transfer coefficients (TCs) from ARTF data
[3] Exposure = (Peak DFR × TC × 8 hr/day × 30% dermal absorption) / (80 kg bw × 1000 µg/mg)
[4] Based on NOAEL = 140 mg/kg bw/day, target MOE = 300
* Assessed using the maximum rate of the three end-use products (10 g a.e. /ha for GF-2685 Herbicide)

Table 9 Major Groundwater and Surface Water Model Inputs for Level 1 Assessment of Halauxifen-Methyl Residues (Halauxifen-Methyl and Transformation Products XDE-729 Acid (X11393729) and X11449757) in Drinking Water Sources

Type of Input	Parameter	Value
Application Information	Crop(s) to be treated	Spring wheat, durum wheat, winter wheat, spring barley
	Maximum allowable application rate per year (g a.e./ha)	10
	Maximum rate each application (g a.e./ha)	10
	Maximum number of applications per year	1
	Minimum interval between applications (days)	Not applicable
	Method of application	Field sprayer or aerial application equipment
Environmental Fate Characteristics	Hydrolysis half-life at pH 7 (days)	4319
	Photolysis half-life in water (days)	0.014
	Adsorption K_d (mL/g)	0.9176 (20^{th} percentile of seven K_d values for X11449757)
	Aerobic soil biotransformation half-life (days)	22.6 (90^{th} percentile confidence bound on mean of four combined residue half-life values adjusted to 25ºC)
	Aerobic aquatic biotransformation half-life (days)	81.4 (longest of two combined residue half-lives)
	Anaerobic aquatic biotransformation half-life (days)	Stable (longest of two combined residue half-lives)

Table 10 Level 1 Estimated Environmental Concentrations of Combined Residues of Halauxifen-Methyl in Potential Drinking Water Sources

Compound	Groundwater EEC (µg/L)		Surface Water EEC (µg/L) Reservoir	
	Daily[1]	Yearly[2]	Daily[3]	Yearly[4]
1 × 10 g a.e./ha on spring wheat, durum wheat, winter wheat and spring barley				
Halauxifen-methyl + XDE-729 acid (X11393729) + X11449757	0.032	0.032	0.50	0.0051

[1] 90^{th} percentile of daily average concentrations
[2] 90^{th} percentile of yearly average concentrations
[3] 90^{th} percentile of yearly peak concentrations
[4] 90^{th} percentile of yearly average concentrations

Table 11a Integrated Food Residue Chemistry Summary

NATURE OF THE RESIDUE IN WHEAT				PMRA # 2226516	
Radiolabel Position	[^{14}C]-Halauxifen-methyl labeled separately in the phenyl [PH] and pyridine [PY] rings				
Test Site	Outdoor plots in California.				
Treatment	A single foliar application.				
Total Rate	10 g a.i./ha (9.6 g a.e./ha). Each radiolabeled compound was applied with and without the safener cloquintocet-mexyl (CQM; nominal rate of 10 g/ha).				
Formulation	Emulsifiable concentrate [EC]				
Preharvest interval	Immature forage: 7 days after application Hay: 24 days after application Mature straw and grain: 84 days after application				
Matrices	**PHI (days)**	**TRRs (ppm)**			
		[^{14}C]-PH label		**[^{14}C]-PY label**	
		- CQM	**+ CQM**	**- CQM**	**+ CQM**
Immature Forage	7	0.094	0.202	0.139	0.146
Hay	24	0.279	0.236	0.357	0.411
Straw	84	0.294	0.190	0.353	0.062
Grain	84	0.004	0.004	0.003	0.002
Metabolites Identified	**Major Metabolites (>10% of the TRRs)**		**Minor Metabolites (<10% of the TRRs)**		
Radiolabel Position (with and without safener)	**[^{14}C]-PH label**				
	- CQM	**+ CQM**	**- CQM**	**+ CQM**	
Immature Forage (7-day PHI)	--	X11406790 glucose-malonyl conjugate (X12245409) (10.3% of the TRRs; 0.021 ppm)	Halauxifen-methyl; X11449757; halauxifen acid; X11861662; X11406790 glucose conjugate; X12245409; X11406790	Halauxifen-methyl; X11449757; halauxifen acid; X11861662; X11406790 glucose conjugate; X11406790	
Hay (7-day PHI)	--	--	Halauxifen-methyl; X11449757; halauxifen acid; X11861662; X11406790 glucose conjugate ; X12245409; X11406790	Halauxifen-methyl; X11449757; halauxifen acid; X11861662; X11406790 glucose conjugate; X12245409; X11406790	
Mature Straw (84 day PHI)	--	--	Halauxifen-methyl; X11449757; halauxifen acid; X11861662; X11406790 glucose conjugate; X12245409; X11406790	Halauxifen-methyl; X11449757; halauxifen acid; X11861662; X11406790 glucose conjugate; X12245409; X11406790	
Grain (84-day PHI)	NA	NA	NA	NA	
NA = not analysed: TRRs in grain were too low to warrant further residue characterization/identification					

Metabolites Identified	Major Metabolites (>10% of the TRRs)		Minor Metabolites (<10% of the TRRs)	
Radiolabel Position (with and without safener)	**[^{14}C]-PY label**			
	- CQM	**+ CQM**	**- CQM**	**+ CQM**
Immature Forage (7-day PHI)	--	--	Halauxifen-methyl; X11449757; halauxifen acid; X11861662; X11406790 glucose conjugate; X12245409; X11406790	Halauxifen-methyl; X11449757; halauxifen acid; X11861662; X11406790 glucose conjugate; X12245409; X11406790
Hay (7-day PHI)	--	--	Halauxifen-methyl; X11449757; halauxifen acid; X11861662; X11406790 glucose conjugate; X12245409; X11406790	Halauxifen-methyl; X11449757; halauxifen acid; X11861662; X11406790 glucose conjugate; X12245409; X11406790
Mature Straw (84 day PHI)	--	--	Halauxifen-methyl; X11449757; halauxifen acid; X11861662; X11406790 glucose conjugate; X12245409; X11406790	Halauxifen-methyl; X11449757; halauxifen acid; X11861662; X11406790 glucose conjugate; X12245409; X11406790
Grain (84-day PHI)	NA	NA	NA	NA
NA = not analysed: TRRs in grain were too low to warrant further residue characterization/identification.				

NATURE OF THE RESIDUE IN TURNIP		**PMRA # 2226517**
Radiolabel Position	[^{14}C]-Halauxifen-methyl labeled separately in the phenyl [PH] and pyridine [PY] rings	
Test Site	Outdoor plots	
Treatment	Single postemergent foliar ground application at BBCH17	
Total Rate	10 g a.e./ha	
Formulation	Emulsifiable concentrate [EC]	
Preharvest interval [PHI]	14 days: immature roots and tops; 28 days: mature roots and tops	

Matrices	**PHI (days)**	**TRRs (ppm)**	
		[^{14}C]-PH label	**[^{14}C]-PY label**
Immature tops	14	0.079	0.082
Immature roots		<0.01	<0.01
Mature tops	28	0.091	0.109
Mature roots		<0.01	<0.01

Metabolites Identified	Major Metabolites (>10% of the TRRs)		Minor Metabolites (<10% of the TRRs)	
Radiolabel Position	**[^{14}C]-PH label**	**[^{14}C]-PY label**	**[^{14}C]-PH label**	**[^{14}C]-PY label**
14-day Tops	Halauxifen-methyl N-glucose conjugate* (19.0% of the TRRs; 0.015 ppm); halauxifen-methyl (13.5% of the TRRs; 0.011 ppm); halauxifen acid (12.5% of the TRRs; 0.01 ppm);	Halauxifen-methyl N-glucose conjugate* (21.4-0.018 ppm); halauxifen-methyl (12.2% of the TRRs; 0.01 ppm); halauxifen acid glucose conjugate (12.6% of the TRRs; 0.01 ppm)	Halauxifen-methyl N-glucose conjugate*; halauxifen acid; X11406790 malonyl glucose conjugate; low level metabolite (RT = 13.7 minutes); X11406790	Halauxifen-methyl N-glucose conjugate*; halauxifen acid; X11406790 malonyl glucose conjugate; low level metabolite (RT = 13.7 minutes); X11406790
28-day Tops	Halauxifen-methyl N glucose conjugate* (14.9% of the TRRs; 0.014 ppm); halauxifen acid glucose conjugate (12.9% of the TRRs; 0.012 ppm)	Halauxifen-methyl N glucose conjugate* (17.4% of the TRRs; 0.019 ppm); halauxifen acid glucose conjugate (14.1% of the TRRs; 0.015 ppm)	Halauxifen-methyl; low level metabolite (RT = 13.7 min); halauxifen acid; X11406790 malonyl glucose conjugate ; halauxifen-methyl N-glucose conjugate*; X11406790	Halauxifen-methyl; low level metabolite (RT = 13.7 min); halauxifen acid; X11406790 malonyl glucose conjugate; halauxifen-methyl N-glucose conjugate*; X11406790
14-day Roots	NA			
28-day Roots				

*α and β anomers; the corresponding identity was not indicated in the study.
NA = not analysed: TRRs in roots were too low to warrant further residue characterization/identification.

Proposed Metabolic Scheme in Wheat and Turnip

Metabolism of halauxifen-methyl in wheat and turnip applied as a single foliar application is similar. Little translocation of the active ingredient from the point of application occurs. Halauxifen-methyl undergoes extensive metabolism which may proceed through N-conjugation with glucose, or dissociation producing halauxifen acid, or de-methylation of the methoxy group on the phenyl ring producing the metabolite X11406790. X11406790 is then conjugated with glucose followed by further conjugation with malonic acid. Halauxifen acid is also conjugated with glucose, through either the nitrogen or oxygen. The higher proportions of conjugates to primary metabolites indicate that conjugation is the preferential route of metabolism.

The metabolite X11861662, present at very low levels in all analysed wheat matrices (<0.01 ppm halauxifen-methyl equivalents in the majority of cases), arises from the dechlorination of halauxifen-methyl. As dechlorination is an uncommon plant metabolic route, and as X11861662 was identified as an aqueous photodegradation product, this metabolite likely arises from photolysis of halauxifen-methyl on the leaf surface.

Table 11b Integrated Food Residue Chemistry Summary

CONFINED ACCUMULATION IN ROTATIONAL CROPS – Wheat, lettuce and radish	**PMRA #2226531**
Radiolabel Position	[^{14}C]-Halauxifen-methyl labeled separately in the phenyl [PH] and pyridine [PY] rings
Test site	Bare sandy loam soil contained in above ground boxes maintained initially outdoors. The boxes were moved into a greenhouse 140 days post treatment; the 270-day PBI wheat plots were moved outdoors, 361 days post-treatment.
Formulation	Not reported
Application rate and timing	Bare soil was treated at 10 g a.e./ha, and aged for 14, 90 and 270 days.

Metabolites Identified			Major Metabolites (>10% of the TRRs)		Minor Metabolites (<10% of the TRRs)	
Crop	**Matrix**	**PBI (days)**	**PH-label**	**PY-label**	**PH-label**	**PY-label**
TRRs in all crop matrices harvested at all PBIs were <0.01 ppm halauxifen-methyl equivalents. Therefore further analyses were not conducted. Halauxifen-methyl applied as foliar treatment to cereals according to maximum proposed label rate is not expected to accumulate in rotational crops.						

NATURE OF THE RESIDUE IN LAYING HEN	**PMRA #2226518**

Halauxifen-methyl radiolabeled in either the phenyl [PH] (specific activity: 8.31 mCi/mmol) or pyridine [PY] (specific activity: 8.75 mCi/mmol) ring was orally dosed to laying hens for 7 days at the rate of 11.3 and 11.6 mg a.i./kg dry feed per day in the diet, for the PH- and PY-labeled groups, respectively. Eggs were collected twice daily and pooled, and excreta were collected daily. The birds were sacrificed approximately 6-9 hours after the final dose and liver, muscle (breast and leg), fat, and skin with subcutaneous fat were collected. Cage rinse, blood and gastro-intestinal contents were also collected. TRRs were determined by oxidative combustion and LSC, residue characterization/identification was determined using LC-MS or LC-MS/MS.

Matrices	**[^{14}C]–PH label**		**[^{14}C]–PY label**	
	TRRs (ppm)	**% of Administered Dose**	**TRRs (ppm)**	**% of Administered Dose**
Excreta (days 1-7)	8.509-16.380	94.5 (total over the 7 days)	9.152-16.721	93.8 (total over the 7 days)
Cage rinse (at sacrifice)	1.180	0.063	0.468	0.044
Liver	0.046	0.028	0.043	0.023
Fat - subcutaneous	0.008	0.003	0.005	0.003
Skin with fat	0.016	0.019	0.009	0.012
Muscle (breast)	<0.001	0.001	<0.001	0.001
Muscle (leg)	0.003	0.005	0.002	0.006
Eggs (days 1-7)	<0.001-0.003	0.0002-0.0016	<0.001-0.003	0-0.0022
Unless otherwise indicated, values represent the average of duplicate analyses				

Metabolites identified	**Major Metabolites (>10% of the TRRs)**		**Minor Metabolites (<10% of the TRRs)**	
Radiolabel Position	**[^{14}C]–PH label**	**[^{14}C]–PY label**	**[^{14}C]–PH label**	**[^{14}C]–PY label**
Liver	X11449757 (32.3% of the TRRs; 0.015 ppm); sulphate conjugate of X11406790 (14.5% of the TRRs; 0.007 ppm)	X11449757 (20.9% of the TRRs; 0.009 ppm)	Halauxifen acid; X11406790; sulphate conjugate of X11449757; polar radioactivity	Sulphate conjugate of X11406790; XDE-729 acid; X11406790; sulphate conjugate of X11449757; polar radioactivity
Skin with Fat	Halauxifen acid (26.0% of the TRRs; 0.004 ppm); sulphate conjugate of X11406790 (12.3% of the TRRs; 0.002 ppm)	NA	Halauxifen-methyl; X11406790; X11449757; sulphate conjugate of X11449757; polar radioactivity	NA
Excreta*	Halauxifen acid (54.7% of the TRRs; 8.953 ppm); X11449757 (21.6% of the TRRs; 2.393 ppm)	XDE-729 acid (52.0% of the TRRs; 8.698 ppm); X11449757 (23.6% of the TRRs; 3.953 ppm)	X11406790; halauxifen-methyl; sulphate conjugate of X11406790	Halauxifen-methyl; sulphate conjugate of X11406790; X11406790; sulphate conjugate of X11449757
Unless otherwise indicated, values represent the average of duplicate analyses *Maximum residues observed among day 1, 4 and 7 samples NA = Not Analysed. Residues were too low to warrant further analyses.				

NATURE OF THE RESIDUE IN LACTATING GOAT	PMRA #2226519
Two goats were dosed via capsule administered with a balling gun with halauxifen-methyl radiolabeled in either the phenyl [PH] (specific activity: 9.63 mCi/mmol) or pyridine [PY] (specific activity: 9.50 mCi/mmol) ring for 5 consecutive days at a feeding level of approximately 10.25 and11.17 mg/kg dry feed per day, respectively. Milk was collected twice daily, once in the morning and once in the afternoon and the samples were maintained separate. Urine and feces were collected at 24-hour intervals immediately prior to dose administration. Cage washes were collected after necropsy. The animals were sacrificed approximately 6-8 hours after the final dose and muscle (loin and flank), liver, kidney, fat (subcutaneous, omental and renal) were collected. GI tract and contents were also collected for mass balance purposes only. TRRs were determined by oxidative combustion and LSC, residue characterization/identification was determined using LC with UV detection or LC-MS/MS.	

Table 11c Integrated Food Residue Chemistry Summary

Matrices	[^{14}C]–PH label		[^{14}C]–PY label	
	TRRs (ppm)	% of Administered Dose	TRRs (ppm)	% of Administered Dose
Milk (days 1-5)	0.001-0.004	0.001-0.005	0.001-0.012	0.002-0.012
Urine (days 1-5)	0.331-1.175	2.5-6.6	1.571-3.385	2.7-8.6
Feces (days 1-5)	0.694-2.412	3.5-8.8	0.394-2.639	1.9-14.1
Cage rinse (at sacrifice)	0.361	0.10	1.385	0.39
Muscle (flank)	0.002	0.001	0.001	0.001
Muscle (loin)	<0.001	0.00	<0.001	0.000
Liver	0.077	0.11	0.032	0.034
Fat- omental	0.005	0.001	0.001	0.001
Fat-subcutaneous	(0.003)	0.0001	0.002	0.0001
Fat - renal	0.016	0.002	0.002	0.0001
Kidney	0.121	0.039	0.041	0.008
GI Tract	0.265	1.4	0.219	0.55
GI contents	0.858	11.6	0.876	6.42
Blood	0.010	0.027	0.006	0.013
Unless otherwise indicated, values represent the average of duplicate analyses				

Metabolites identified	Major Metabolites (>10% of the TRRs)		Minor Metabolites (<10% of the TRRs)	
Radiolabel Position	[^{14}C]–PH label	[^{14}C]–PY label	[^{14}C]–PH label	[^{14}C]–PY label
Renal Fat	Halauxifen acid (44.8% of the TRRs; 0.007 ppm); X11449757 (17.4% of the TRRs, 0.003 ppm)	NA	Sulfate conjugate of X11449757; polar radioactivity	NA
Liver	X11449757 (62.0% of the TRRs; 0.048ppm); halauxifen acid (12.1% of the TRRs; 0.009 ppm)	X11449757 (31.9% of the TRRs; 0.01 ppm)	--	Polar radioactivity; halauxifen acid; N-or O-glucuronic acid conjugate of X11406790; X11406790

Kidney	Halauxifen acid (36.7% of the TRRs; 0.044 ppm); sulphate conjugate of X11449757 (18.3% of the TRRs;, 0.022 ppm); X11449757 (14.7% of the TRRs; 0.018 ppm)	Sulphate conjugate of X11449757 (10.4% of the TRRs, 0.004 ppm); X11449757 (14.4% of the TRRs; 0.006 ppm); halauxifen acid (34.4% of the TRRs; 0.014 ppm)	X11406790, sulphate conjugate of X11406790; N- or O-glucuronic acid conjugate of X11406790; polar radioactivity	Halauxifen-methyl; polar radioactivity; N- or O-glucuronic acid conjugate of X11406790; X11406790
Milk (days 3-4)*	NA	X11449757 (21.9% of the TRRs; 0.002 ppm); N- or O-glucuronic acid conjugate of X11406790 (40.7% of the TRRs; 0.005 ppm); sulphate conjugate of X11406790 (21.8% of the TRRs; 0.003 ppm)	NA	Halauxifen-methyl; polar radioactivity; halauxifen acid; N-glucuronic acid conjugate of halauxifen-methyl; X11406790
Feces (days 1, 3 and 5)**	Halauxifen-methyl (105% of the TRRs; 1.493 ppm); X11449757 (21.6% of the TRRs; 0.521 ppm); X11406790 (28.3% of the TRRs; 0.682)	Halauxifen-methyl (110% of the TRRs; 1.291 ppm); X11449757 (28.8% of the TRRs; 0.416 ppm); X11406790 (46.5% of the TRRs; 0.671)	Halauxifen acid; N- or O-glucuronic acid conjugate of X11406790	Polar radioactivity; halauxifen acid
Urine (days 1- 5)***	X11449757 (34.9% of the TRRs; 0.240 ppm); sulphate conjugate of X11449757 (21.5% of the TRRs; 0.173); halauxifen acid (47.1% of the TRRs; 0.380 ppm); X11406790 (11.7%; 0.108 ppm)	Sulphate conjugate of X11449757 (12.8% of the TRRs; 0.220); X11449757 (46.7% of the TRRs; 1.122 ppm); halauxifen acid (56.3% of the TRRs; 0.971 ppm); X11406790 (14.8% of the TRRs; 0.400 ppm)	Polar radioactivity; N-glucuronic acid conjugate of halauxifen-methyl; sulphate conjugate of X11406790	N-glucuronic acid conjugate of halauxifen-methyl; sulphate conjugate of X11406790

Unless otherwise indicated, values represent the average of duplicate analyses
*Maximum residues observed between day 3 and 4 samples
** Maximum residues observed among day 1, 3, and 5 samples
*** Maximum residues observed among day 1 through 5 samples
NA = Not Analysed. Residues were too low to warrant further analyses.

Proposed Metabolic Scheme in Livestock

The metabolic pathway for halauxifen-methyl in livestock was proposed based on the identified components. The majority of the radioactivity was excreted as unchanged halauxifen-methyl (feces) or as the demethylated carboxylic acid, halauxifen acid. Any significant amount of retained radioactivity was observed in liver and kidney and consisted primarily of the metabolite X11449757. Other metabolites observed in the edible tissues were X11406790 (the phenol) and halauxifen acid. Based on these results, metabolism proceeds through demethylation to either halauxifen acid or X11406790, or both (X11449757). Halauxifen-methyl or metabolites can then conjugate with sulfate or glucuronic acid. The metabolic pathway of halauxifen-methyl is similar in goats, hens, and rats.

FREEZER STORAGE STABILITY	PMRA# 2286048 (plant matrices); PMRA #2286049 (livestock matrices)

Plant matrices: **wheat grain, lettuce, rapeseed, and whole oranges**
The freezer storage stability data indicate that residues of halauxifen-methyl and the metabolite halauxifen acid are stable for up to 489 days (16 months) in representative dry (wheat grain), high water content (lettuce), high fat content (rapeseed), and high acid content (oranges) commodities.

Animal matrices: Bovine muscle, poultry liver, milk and eggs
The freezer storage stability data indicate that residues of halauxifen-methyl and the metabolite halauxifen acid are stable in all matrices for up to 371 days, and that residues of the metabolite X11449757 is stable in all matrices for up to 182 days.

Table 11d Integrated Food Residue Chemistry Summary

CROP FIELD TRIALS ON WHEAT	PMRA #s 2226523 & 2226520

Twenty-seven US and Canadian field trials were conducted during the 2010 and 2011 growing seasons on wheat (spring and winter varieties) in Zones 2 (2 trials), 5 (6 trials), 6 (2 trials), 7 (6 trials), 8 (4 trials), 11 (2 trials) and 14 (5 trials). Each trial site consisted of one untreated control and one treated plot. At the treated plot, halauxifen-methyl (formulated as GF-2685, a 10% water dispersible granule [WDG] containing 104-106 g a.e. halauxifen methyl/kg) was applied as a single foliar spray broadcast treatment at approximately the flag leaf stage (BBCH39; actual stages at application: BBCH32-41) at rates of 9.73-11.09 g a.i./ha. In the 2010 and 2011trials, the safener cloquintocet-mexyl was included in the spray applications at rates of 9.94-10.1 g cloquintocet-mexyl/ha. Forage samples were cut and collected, and hay samples were cut 1-day (BBCH33-41; BBCH 43-55 at one 2011 trial site) and 17-31 days (BBCH65-85; late flowering to soft dough stage) after treatment (DAT), respectively; samples of straw and grain were collected at early maturity, at pre-harvest intervals (PHIs) of 42-73 days (BBCH87-97, with the exception of samples from 4 of the 2010 trials for which the exact growth stage was unknown: referred to as "BBCH99"). The applications were made in volumes of 97-192 L/ha and a locally available adjuvant was included in all spray mixtures. At two sites from the 2010 trials, forage was collected and hay samples were cut at PHIs of 1-, 7-, 14-, 21- and 28-days, and grain and straw samples were collected approximately 7-days prior to maturity and subsequently at 7-, 14-, 21- and 28-days after maturity, at PHIs ranging from 45-85 days, in order to evaluate residue decline behaviour. Hay samples from all trials were dried to a moisture content of 10-20% in the field or under a shelter 1-13 days prior to collection. Grain samples were separated from straw using a field or stationary combine and straw samples were collected from the material remaining after combining.

Commodity	Total Application Rate (g a.i./ha)	PHI (days)	n	Residue Levels (ppm)						
				Min.[a]	Max.[a]	LAFT[b]	HAFT[b]	Median[b]	Mean[b]	SD[b]
Halauxifen-methyl*										
Wheat forage	9.73-11.09	1	27	0.036	0.389	0.043	0.384	0.157	0.159	0.08
Wheat hay		17-31	27	<0.01	0.026	<0.01	0.025	<0.01	<0.011	0.004
Wheat grain		42-73	27	<0.01	<0.01	--	--	<0.01	<0.01	--
Wheat straw		42-73	27	<0.01	0.013	<0.01	0.012	<0.01	<0.01	0.0004

PHI = pre-harvest interval; LAFT = Lowest Average Field Trial; HAFT = Highest Average Field Trial; SD = Standard Deviation; n = number of field trials. For computation of the LAFT, HAFT, median, mean and standard deviation, values <LOQ are assumed to be at the LOQ.
[a] Values based on individual residue measurements.
[b] Values based on per trial averages.
* Halauxifen-methyl = the residue definition in plants

CROP FIELD TRIALS ON BARLEY	PMRA #2226525 & 2226528

Eighteen US and Canadian field trials were conducted on barley in the 2010 and 2011 growing seasons in Zones 1 (1 trial), 5/5A/5B (3 trials), 7 (4 trials), 7A (1 trial), 9 (1 trial), 10 (1 trial), 11 (1 trial) and 14 (6 trials). At each test location, consisting of one untreated and one treated plot, halauxifen-methyl (formulated as GF-2685, a 10% water dispersible granule [WDG] containing 104-106 g a.e. halauxifen methyl/kg) was applied as a single foliar spray broadcast treatment targeting the flag leaf stage (BBCH39; actual crop stages at application were BBCH22-49) at rates of 9.98-10.98 g halauxifen methyl/ha. In the 2010 and 2011 trials, the safener cloquintocet-mexyl was included in the spray applications at rates of 9.53-10.42 g cloquintocet-mexyl/ha. Hay samples were cut 17-33 days after treatment (DAT) (BBCH73-85; between milk and soft dough stages) and samples of straw and grain were collected at early maturity, at pre-harvest intervals (PHIs) of 43-83 days (BBCH85-92). The applications were made in volumes of 97-191 L/ha and a locally available adjuvant was included in all spray mixtures. At two sites from the 2010 trials, hay samples were cut at PHIs of 1-, 7-, 14-, 21- and 28-days (approximately spanning the interval between application and hay cutting at milk to dough stage), and grain and straw samples were collected approximately 7 days prior to earliest maturity, and at 7-, 14-17, 21- and 28-31 days after earliest maturity, at PHIs ranging from 38-78 days, in order to evaluate residue decline behaviour. The majority of hay samples from all trials were dried to a moisture content of 8-20% in the field or under a shelter 1-18 days prior to collection, with the exception of two and three of the 2010 trials in which moisture content was >20% due to incomplete sample drying and <8%, respectively. Grain was separated from straw using a field or stationary combine and straw samples were collected from the material remaining after combining.

Commodity	Total Application Rate (g a.i./ha)	PHI (days)	n	Residue Levels (ppm)						
				Min.[a]	Max.[a]	LAFT[b]	HAFT[b]	Median[b]	Mean[b]	SD[b]
Halauxifen-methyl*										
Barley hay	9.98-10.98	17-33	18	<0.01	<0.01	--	--	<0.01	<0.01	--
Barley grain		43-83	18	<0.01	<0.01	--	--	<0.01	<0.01	--
Barley straw		43-83	18	<0.01	<0.01	--	--	<0.01	<0.01	--

PHI = pre-harvest interval; LAFT = Lowest Average Field Trial; HAFT = Highest Average Field Trial; SD = Standard Deviation; n = number of field trials. For computation of the LAFT, HAFT, median, mean and standard deviation, values <LOQ are assumed to be at the LOQ.

[a] Values based on individual residue measurements.

[b] Values based on per trial averages.

* Halauxifen-methyl = the residue definition in plants

Table 11e Integrated Food Residue Chemistry Summary

RESIDUE DATA IN ROTATIONAL CROPS	--

Data are not required given that, in the submitted confined rotational crop study, TRRs in all crop matrices harvested at all PBIs were <0.01 ppm halauxifen-methyl equivalents.

PROCESSED FOOD AND FEED – WHEAT	PMRA# 2226530
Test Site	One trial in the US (Zone 5)
Treatment	A single foliar application at the flag leaf stage (~BBCH39)
Rate	Side-by-side plots; 10.4 and 52.1 g a.i./ha; including an adjuvant (LASER, a paraffinic mineral oil and surfactant blend; 0.5%, v/v)
End-use product/formulation	GF-2685; water-dispersible granule (WDG) formulation of 100 g a.e. halauxifen-methyl/kg and 100 g a.i. cloquintocet- mexyl/kg
Preharvest interval	60 days
Processed Commodity	**Average Processing Factor**
Aspirated grain fraction	Residues of halauxifen-methyl and halauxifen acid were below the limit of quantitation in unprocessed wheat grain samples (from both plots) and all processed commodities. As a result, processing factors could not be determined for any of the processed commodities.
Bran	
Total bran	
Flour (dry mill)	
Whole meal flour	
Flour-550	
Bread (white)	

Whole grain bread
Middlings
Shorts
Germ
Gluten
Gluten feed meal
Starch

LIVESTOCK FEEDING – Dairy cattle	**PMRA #2226529**

Lactating dairy cows were orally administered halauxifen-methyl at dose levels of 1.0, 3.1 and 15.6 ppm via a compound feed containing the test items added as a solution in acetone for 28-29 consecutive days. The dose levels of 1.0, 3.1 and 15.6 ppm represent 100x, 310x, and 1560x, respectively, the estimated dietary burden for beef cattle, and 3.1, 9.7, and 48.8x, respectively, the estimated dietary burden for dairy cattle.

Commodity	**Feeding Level (ppm)**	**Highest Residues* (ppm)**	**MBD (ppm)**	**Anticipated Residues at MBD (ppm)**
			Dairy	
Whole milk	15.6	<0.02	0.32	$<2.1\times10^{-4}$
Skim Milk		<0.02		
Cream		<0.02		
Liver		0.184		3.8×10^{-3}
Kidney		0.063		1.3×10^{-3}
Muscle		<0.02		$<2.1\times10^{-4}$
Fat (subcutaneous, mesenteric and perirenal)		<0.02		$<2.1\times10^{-4}$

*Combined residues of halauxifen-methyl plus the metabolite X11449757 (which was converted to and reported as halauxifen-methyl equivalents), reported as total halauxifen-methyl equivalents.

Table 11f Integrated Food Residue Chemistry Summary

LIVESTOCK FEEDING – Laying hens

A laying hen feeding study was not provided for review. The dietary burden determined from the more balanced diet was calculated using data from the hen metabolism study (PMRA #2226518).

Commodity	**Feeding Level (ppm)**	**Highest Residues (ppm)**	**MBD (ppm)**	**Anticipated Residue at MBD (ppm)**
Muscle	11.3-11.6	--	0.01	--
Skin + Fat		<0.002		1.7×10^{-6}
Liver		<0.016		1.4×10^{-5}
Eggs		--		--

Table 12 Food Residue Chemistry Overview of Metabolism Studies and Risk Assessment

PLANT STUDIES	
RESIDUE DEFINITION FOR ENFORCEMENT Primary and rotational crops	Halauxifen-methyl
RESIDUE DEFINITION FOR RISK ASSESSMENT Primary crops and rotational crops	Halauxifen-methyl
METABOLIC PROFILE IN DIVERSE CROPS	Similar in wheat and turnip
ANIMAL STUDIES	
ANIMALS	**Ruminant and Poultry**
RESIDUE DEFINITION FOR ENFORCEMENT	Halauxifen-methyl and the metabolite X11449757
RESIDUE DEFINITION FOR RISK ASSESSMENT	Halauxifen-methyl and the metabolite X11449757
METABOLIC PROFILE IN ANIMALS	Similar in goat, hen and rat.
FAT SOLUBLE RESIDUE	No

DIETARY RISK FROM FOOD AND WATER			
	POPULATION	**ESTIMATED RISK % of ACCEPTABLE DAILY INTAKE (ADI)**	
		Food Alone	**Food and Water**
Basic chronic non-cancer dietary exposure analysis	**All infants <1 year**	<1	<1
	Children 1–2 years	<1	<1
ADI = 0.2 mg/kg bw/day	**Children 3 to 5 years**	<1	<1
	Children 6–12 years	<1	<1
Estimated chronic drinking water concentration = 0.07 □g a.i./L (Level 1)	**Youth 13–19 years**	<1	<1
	Adults 20–49 years	<1	<1
	Adults 50+ years	<1	<1
	Females 13-49 years	<1	<1
	Total population	<1	<1

Table 13 Fate and Behaviour of Halauxifen-methyl and Transformation Products in the Environment

Property	Test substance	Value[1]	Transformation products	Comments	Reference (PMRA #)
Abiotic transformation					
Hydrolysis	Halauxifen-methyl	10ºC pH 4, DT_{50}: 245 d; pH 7, DT_{50}: 660 d; pH 9, DT_{50}: 18 d (SFO – combined labels) 25ºC pH 4, DT_{50}: 81 d; pH 7, DT_{50}: 155 d; pH 9, DT_{50}: 3 d (SFO – combined labels) 50ºC pH 4, DT_{50}: 12 d; pH 7, DT_{50}: 17 d; pH 9, DT_{50}: 0.2 d (SFO – combined labels)	Major: X11393729	Hydrolysis can contribute to the overall dissipation of halauxifen-methyl, especially at alkaline pH.	2226413
Phototransfor-mation on soil	Halauxifen-methyl	DT_{50} (irradiated): 8.66 d; DT_{50} (dark): 3.48 d (SFO – combined labels) A phototransformation half-life could not be calculated as dissipation was faster in the dark controls.	Major, Irradiated: X11393729 Major, Dark: X11393729 X11449757 Minor, Irradiated: X11449757 CO_2 Minor, Dark: CO_2	Not expected to be an important route of dissipation	2226535

Property	Test substance	Value[1]	Transformation products	Comments	Reference (PMRA #)
Phototransformation in water	Halauxifen-methyl	Sterile pH 7 buffer DT_{50} (irradiated): 0.003 d; DT_{50} (dark): 158 d (SFO – combined labels) Sterile natural water DT_{50} (irradiated): 0.005 d; DT_{50} (dark): 7.43 d (SFO – combined labels) Predicted environmental DT_{50} for halauxifen-methyl in sterile pH 7 buffer and natural water is less than 10 minutes for summer sunlight at 40ºN latitude Quantum yield, φ = 5.63	Major, Irradiated: X11393729 Deg 1 Deg 2 Deg 4 Deg 10 Deg 11 Deg 14 CO_2 Major, Dark: X11393729 Minor, Irradiated: X11861662 Deg 3 Deg 5 Deg 9 Deg 13 Deg 16 Volatile organics Minor, Dark: None	Can be an important route of dissipation for halauxifen-methyl and its transformation products near the surface in water bodies	2226414
Phototransformation in air	Halauxifen-methyl	Halauxifen-methyl is not expected to be volatile under field conditions based on vapour pressure and Henry's law constant. Supplemental information submitted indicates a DT_{50} of 2.155 d (estimated using the Atkinson method)			2226416
Biotransformation					
Biotransformation in aerobic soil	Halauxifen-methyl	20ºC clay loam : DT_{50}: 2.13 d; DT_{90}: 17.5 d (IORE – combined labels; representative half-life for modelling purposes: 5.27 d) loam: DT_{50}: 1.43 d; DT_{90}: 5.35 d (IORE – combined labels; representative half-life for modelling purposes: 1.61 d) silt loam: DT_{50}: 1.27 d; DT_{90}: 6.52 d (IORE – combined labels; representative half-life for modelling purposes: 1.96 d) sandy loam: DT_{50}: 1.08 d; DT_{90}: 3.59 d (SFO – combined labels)	Major: X11393729: DT_{50}: 0.972-19.5 d; DT_{90}: 6.62-138 d (IORE – combined labels) X11449757: DT_{50}: 9.85-85.7 d; DT_{90}: 83.7-327 d (IORE – combined labels) CO_2 Minor: X11406790	Halauxifen-methyl is non-persistent. X11393729 is non-persistent to slightly persistent. X11449757 is non-persistent to moderately persistent. Biotransformation in aerobic soil is a route of dissipation for halauxifen-methyl.	2226534
		10ºC silt loam:	Major: X11393729:	Halauxifen-methyl is non-persistent.	2226533

Property	Test substance	Value[1]	Transformation products	Comments	Reference (PMRA #)
		DT_{50}: 2.62 d; DT_{90}: 13 d (IORE – combined labels)	DT_{50}: 14.9 d; DT_{90}: 74.2 d (IORE – combined labels) X11449757: DT_{50}: 73.2 d; DT_{90}: 243 d (SFO – combined labels) CO_2 <u>Minor:</u> X11406790	X11393729 is slightly persistent. X11449757 is moderately persistent. Biotransformation in aerobic soil is a route of dissipation for halauxifen-methyl.	
Biotransformation in anaerobic soil	Halauxifen-methyl	<u>clay loam:</u> DT_{50}: 2.75 d; DT_{90}: 23.6 d (IORE – combined labels; representative half-life for modelling purposes: 7.1 d) <u>loam:</u> DT_{50}: 1.23 d; DT_{90}: 10.3 d (IORE – combined labels; representative half-life for modelling purposes: 3.09 d) <u>silt loam:</u> DT_{50}:0.935 d; DT_{90}: 3.11 d (SFO – combined labels) <u>sandy loam:</u> DT_{50}: 1.43 d; DT_{90}: 13.5 d (IORE– combined labels; representative half-life for modelling purposes: 4.07 d)	<u>Major:</u> X11393729: DT_{50}: 16.6-108 d; DT_{90}: 47-340 d (SFO or IORE – combined labels) X11449757: DT_{50} could not be calculated as concentrations increased until study termination <u>Minor:</u> X11406790 CO_2	Halauxifen-methyl is non-persistent. X11393729 is slightly to moderately persistent. X11449757 accumulated throughout the study period. Biotransformation in anaerobic soil is a route of dissipation for halauxifen-methyl.	2226533
Biotransformation in aerobic water-sediment systems	Halauxifen-methyl	<u>lake water: loamy sand sediment</u> Total system DT_{50}: 5.01 d; DT_{90}:16.6 d (SFO – combined labels) <u>lake water:silt loam sediment</u> Total system DT_{50}: 0.85 d; DT_{90}: 3.03 d (IORE– combined labels; representative half-life for modelling purposes: 0.911 d)	<u>Major:</u> X11393729: Total system DT_{50}: 2.96-11.6 d; DT_{90}: 9.85-38.6 d (SFO – combined labels) X11449757: Total system DT_{50}: 37.7-81.6 d; DT_{90}: 125-734 d (SFO or IORE – combined labels) X11406790: Total system DT_{50}:	Halauxifen-methyl, X11393729 and X11406790 are non-persistent. X11449757 is slightly to moderately persistent. Biotransformation in aerobic water-sediment systems is a route of dissipation for halauxifen-methyl.	2226540

Property	Test substance	Value[1]	Transformation products	Comments	Reference (PMRA #)
			2.19-6.69 d; DT_{90}: 7.28-22.2 d (SFO – combined labels) CO_2 <u>Minor:</u> None		
Biotransformation in anaerobic water-sediment systems	Halauxifen-methyl	<u>river water: clay loam sediment</u> Total system DT_{50}: 0.538 d; DT_{90}: 1.79 d (SFO – combined labels) <u>natural water: sandy clay loam sediment</u> Total system DT_{50}: 1.01 d; DT_{90}: 9.22 d (IORE– combined labels; representative half-life for modelling purposes: 2.78 d)	<u>Major:</u> X11393729: Total system DT_{50}: 3.72-4.4 d; DT_{90}: 12.4-14.6 d (SFO – combined labels) X11449757: DT_{50} could not be calculated as concentrations increased until study termination in both systems tested. X11406790: Total system DT_{50}: 3.69-6.06 d; DT_{90}: 12.2-20.1 d (SFO – combined labels) <u>Minor:</u> CO_2	Halauxifen-methyl, X11393729 and X11406790 are non-persistent. X11449757 accumulated throughout the study period. Biotransformation in anaerobic water-sediment systems is a route of dissipation for halauxifen-methyl.	2226539
Mobility					
Adsorption / desorption in soil	Halauxifen-methyl and major soil transformation products	<u>Seven soils:</u> K_F: 6.2-670.6 $\mu g^{1-1/n} mL^{1/n} g^{-1}$; K_{FOC}: 141-2197 $\mu g^{1-1/n} mL^{1/n} g^{-1}$; 1/n: 0.74-0.93; K_d: 12.9-880.3 mL/g; K_{OC}: 378-2660 mL/g	<u>X11393729</u> K_F: 0.4-113 $\mu g^{1-1/n} mL^{1/n} g^{-1}$; K_{FOC}: 26-341 $\mu g^{1-1/n} mL^{1/n} g^{-1}$; 1/n: 0.83-0.95; K_d: 0.4-140.2 mL/g; K_{OC}: 28-423 mL/g <u>X11449757</u> K_F: 0.3-134.2 $\mu g^{1-1/n} mL^{1/n} g^{-1}$; K_{FOC}: 15-405 $\mu g^{1-1/n} mL^{1/n} g^{-1}$; 1/n: 0.83-0.95; K_d: 0.3-162.3 mL/g; K_{OC}: 15-490 mL/g	Halauxifen is classified as having slight to moderate potential for mobility in soil. X11393729 and X11449757 are classified as having moderate to very high potential for mobility in soil.	2226537

Property	Test substance	Value[1]	Transformation products	Comments	Reference (PMRA #)
Soil leaching	Not required as an acceptable adsorption/desorption study was submitted.				
Volatilization	Not required based on the low vapour pressure (5.9×10^{-9} Pa at 20°C) and Henry's law constant (1.2×10^{-11} atm·m^3/mol at 20°C).				
Field studies					
Field dissipation in Canada and the United States	GF-2685 (water dispersible formulation; 10.42% halauxifen-methyl)	Six bare ground sites and two cropped sites DT_{50}: 1.54-14.8 d DT_{90}: 19.3-908 d (IORE and DFOP kinetics) Deepest layer with detections: 30-45 cm to 60-75 cm[2]	<u>Major:</u> X11393729: DT_{50}: 11.5-409 d DT_{90}: 38.1-1359 d; Deepest layer with detections: 0-15 cm to 60-75 cm X11449757: DT_{50}: 6.52-428 d DT_{90}: 72.4-1791 d; Deepest layer with detections: 0-15 cm to 60-75 cm <u>Minor:</u> None	Halauxifen-methyl is non-persistent to slightly persistent under a variety of terrestrial field conditions. X11393729 and X11449757 are non-persistent to persistent. The majority of halauxifen-methyl and transformation products was measured in the top 30 cm. Levels below 30 cm were low (≤ 2.4% of maximum measured parent concentrations). No significant carryover of residues into the next growing season.	2266231
Aquatic field dissipation	No aquatic field dissipation study with halauxifen-methyl was submitted, and data on the aquatic field dissipation of halauxifen-methyl are not required.				
Bioconcentration/bioaccumulation					
Bioconcentration in fish	Halauxifen-methyl	Whole body steady state BCF: 183-214 Whole body kinetic BCF: 214-233 Time to 95% depuration of ^{14}C-residues: 0.5-1.6 d for whole fish	X11393729 X11406790 X11449757 Glucuronide conjugates of halauxifen-methyl Sulfate conjugate for X11406790	Did not bioconcentrate in large amounts in fish under the test conditions of the study. Clearance time to 95% depuration of ^{14}C-residues was 0.5-1.6 days.	2226556

[1] Kinetics models: SFO = single first-order; IORE = indeterminate order rate equation; DFOP = double first order in parallel.

[2] Halauxifen-methyl was detected at 0.7% of initial measured concentrations at one site on day 1. The rapid downward movement in the soil could have been due to a process other than leaching, such as preferential flow.

Table 14 Toxicity of Halauxifen-methyl and Major Transformation Products to Non-Target Terrestrial Species

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[1]	Reference (PMRA #)
Invertebrates					
Earthworm, *Eisenia foetida*	14-d Acute	Halauxifen-methyl	LC_{50}: >1000 mg a.i./kg soil	No classification	2226588
	14-d Acute	XDE-729 acid (X11393729)	LC_{50}: >1000 mg/kg soil	No classification	2226589
	14-d Acute	X11449757	LC_{50}: >1000 mg/kg soil	No classification	2226590
Honeybee, *Apis mellifera*	48-h Oral	Halauxifen-methyl	LD_{50}: >108 µg a.i./bee	Relatively non-toxic	2226584
	48-h Contact	Halauxifen-methyl	LD_{50}: >98.1 µg a.i./bee	Relatively non-toxic	2226584
Predatory mite, *Typhlodromus pyri*	7-d Contact, Glass plates (screening level)	GF-2685 (formulation; 10.6% w/w halauxifen-methyl)	LR_{50}: >1000 g GF-2685/ha (>106 g a.i./ha)	No classification	2279879
Parasitoid wasp, *Aphidius rhopalosiphi*	48h-Contact, Glass plates (screening level)	GF-2685 (formulation; 10.6% w/w halauxifen-methyl)	LR_{50}: >1000 g GF-2685/ha (>106 g a.i./ha)	No classification	2279878
Predatory soil mite, *Hypoaspis aculeifer*	14-d Chronic (artificial soil)	Halauxifen-methyl	NOEC: 25 mg a.i./kg soil (highest concentration tested)	No classification	2226586
	14-d Chronic (artificial soil)	XDE-729 acid (X11393729)	NOEC: 12.5 mg/kg soil (mean number of juveniles)	No classification	2279932
	14-d Chronic (artificial soil)	X11449757	NOEC: 25 mg/kg soil (highest concentration tested)	No classification	2279933
Collembola, *Folsomia candida*	28-d Chronic (artificial soil)	Halauxifen-methyl	NOEC: 1000 mg a.i./kg soil (highest concentration tested)	No classification	2226585
	28-d Chronic (artificial soil)	XDE-729 acid (X11393729)	NOEC: 25 mg/kg soil (highest concentration tested)	No classification	2279934
	28-d Chronic (artificial soil)	X11449757	NOEC: 10 mg/kg soil (highest concentration tested)	No classification	2279935

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[1]	Reference (PMRA #)
Birds					
Northern bobwhite quail, *Colinus virginianus*	Acute	Halauxifen-methyl	LD_{50}: >2250 mg a.i./kg bw	Practically non-toxic	2226541
	5-d Dietary	Halauxifen-methyl	LC_{50}: >6000 mg a.i./kg diet; (LD_{50}: >1500 mg a.i./kg bw/d)	Practically non-toxic	2226543
	21-wk Reproduction	Halauxifen-methyl	NOEC: 403 mg a.i./kg diet (reduced hatchlings/3-week embryos) (NOEL: 36.9 mg a.i./kg bw/d)	No classification	2226545
Mallard duck, *Anas platyrhynchos*	5-d Dietary	Halauxifen-methyl	LC_{50}: >6000 mg a.i./kg diet (LD_{50}: >2234 mg a.i./kg bw/d)	Practically non-toxic	2226544
	20-wk Reproduction	Halauxifen-methyl	NOEC: 1040 mg a.i./kg diet (highest concentration tested) (NOEL: 160.5 mg a.i./kg bw/d)	No classification	2226546
Zebra finch, *Poephila guttata*	Acute	Halauxifen-methyl	LD_{50}: >2250 mg a.i./kg bw	Practically non-toxic	2226542
Mammals					
Rat	Acute	Halauxifen-methyl	LD_{50}: >5000 mg/kg bw	Practically non-toxic	2226448
		GF-2685 (formulation; 10.5% halauxifen-methyl)	LD_{50}: >5000 mg/kg bw	Formulation is practically non-toxic	2226179
		GF-2687 (formulation; 21% halauxifen-methyl and 20.6% florasulam)	LD_{50}: >5000 mg/kg bw	Formulation is practically non-toxic	2226247
		GF-2688 (formulation; 1.56% halauxifen-methyl and 35% fluroxypyr)	LD_{50}: >5000 mg/kg bw	Formulation is practically non-toxic	2226305
		XDE-729 acid (X11393729)	LD_{50}: >5000 mg/kg bw/d	Practically non-toxic	2226447
	2-generation Reproduction	XDE-729 acid (X11393729)	<u>Parental</u> NOAEL: 104/103 mg /kg bw/d for males/females (body weight gain, feed consumption, gross pathology, histology) <u>Reproduction</u> NOAEL: 443 mg/kg bw/d (highest dose	No classification	2226496

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[1]	Reference (PMRA #)
			tested)		
	Developmental, dietary exposure to pregnant females	Halauxifen-methyl	Maternal NOAEL: 159 mg/kg bw/d (body weight gain, food consumption, liver weights, cytoplasmic homogeneity of hepatocytes) Developmental NOAEL: 323 mg/kg bw/d (highest dose tested)	No classification	2226499
		XDE-729 acid (X11393729)	Maternal NOAEL: 140 mg/kg bw/day (mortality, body weight, body weight gain, food consumption, gravid uterine weight) Developmental NOAEL: 140 mg/kg bw/d (fetal weight, total resorptions, resorptions/dam, postimplantation loss, delayed ossification of thoracic centra)	No classification	2226500
Rabbit	Developmental, dietary exposure to pregnant females	Halauxifen-methyl	Maternal NOAEL: 391 mg/kg bw/d (gravid uterine weight) Developmental NOAEL: 6 mg/kg bw/d (resorptions, postimplantation loss)	No classification	2226501
		XDE-729 acid (X11393729)	Maternal NOAEL: 434 mg/kg bw/d (body weight gain, food consumption) Developmental NOAEL: 1094 mg/kg bw/d (highest dose tested)	No classification	2226504

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[1]	Reference (PMRA #)
Vascular plants					
Monocot and dicot crop species (onion, ryegrass, oat, sugarbeet, cucumber, carrot, oilseed rape, soybean, tomato, and/or corn, and/or field bean and /or sunflower)	21-d Seedling emergence	GF-2685 (formulation; 10.6% halauxifen-methyl)	Most sensitive of 10 species: ER_{25}: 2.05 g a.e./ha ER_{50}: 7.47 g a.e./ha (shoot weight in carrot, *Daucus carota*)	No classification	2363994
		GF-2687 (formulation; 200 g halauxifen-methyl/kg and 200 g florasulam/ kg)	Most sensitive of 11 species: ER_{25}: 0.82 g GF-2687/ha ER_{50}: 3.83 g GF-2687/ha (shoot length in sunflower, *Helianthus annus*)	No classification	2279898
		XDE-729 acid (X11393729)	Most sensitive of 11 species: ER_{25}: not reported ER_{50}: 0.38 g/ha (fresh weight in carrot, *Daucus carota*)	No classification	2226598
		X11449757	All 11 species tested: ER_{25}: >15 g/ha ER_{50}: >15 g/ha (highest rate tested)	No classification	2226602
	21-d Vegetative vigour	GF-2685 (formulation; 10.6% halauxifen-methyl)	Most sensitive of 10 species: ER_{25}: 0.0114 g a.e./ha ER_{50}: 0.0745 g a.e./ha (shoot weight in soybean, *Glycine max*) HR_5 of SSD of the ER_{50}: 0.039 g a.e./ha	No classification	2226597
		GF-2687 (formulation; 200 g halauxifen-methyl/kg and 200 g florasulam/ kg)	Most sensitive of 11 species: ER_{25}: 0.14 g GF-2687/ha ER_{50}: 1.40 g GF-2687/ha (shoot length in sunflower, *Helianthus annus*) HR_5 of SSD of the ER_{50}: 0.45 g GF-2687/ha	No classification	2279897

[1] US EPA classification, where applicable

Table 15 Screening Level and Refined Risk Assessment of Halauxifen-methyl for Non-Target Species, Other than Birds and Mammals

Organism	Exposure	Endpoint Value	EEC	RQ	Level of Concern
Invertebrates					
Earthworm	Acute	LC_{50}/2: >500 mg a.i./kg soil	0.00446 mg a.i./kg soil	<0.0001	Not exceeded
Bee	Contact	LD_{50}: >98.1 µg a.i./bee	0.0105 kg a.i./ha × 2.4 µg a.i./bee per kg/ha = 0.0245 µg a.i./bee	<0.0002	Not exceeded
	Oral	LD_{50}: >108 µg a.i./bee	0.0105 kg a.i./ha × 29 µg a.i./bee per kg/ha = 0.30 µg a.i./bee	<0.003	Not exceeded
	Brood / hive	Risk is not expected from exposure to halauxifen-methyl based on the mode of action, a lack of effects observed for adult bees, and a lack of significant effects to other immature insects (chironomid and beneficial arthropods).			
Predatory arthropod, *Typhlodromus pyri*	Contact, glass plate	LR_{50}: >106 g a.i./ha	In-field: 10.5 g a.i./ha	In-field: <0.1	Not exceeded
			Off-field (aerial appl., 17% drift): 1.8 g a.i./ha	Off-field (aerial): <0.02	Not exceeded
			Off-field (ground appl., 3% drift): 0.3 g a.i./ha	Off-field (ground): <0.003	Not exceeded
Parasitoid arthropod, *Aphidius rhopalosiphi*	Contact, glass plate	LR_{50}: >106 g a.i./ha	In-field: 10.5 g a.i./ha	In-field: <0.09	Not exceeded
			Off-field (aerial appl., 17% drift): 1.8 g a.i./ha	Off-field (aerial): <0.02	Not exceeded
			Off-field (ground appl., 3% drift): 0.3 g a.i./ha	Off-field (ground): <0.003	Not exceeded
Terrestrial invertebrate, *Hypoaspis aculeifer*	Chronic, artificial soil	NOEC: 25 mg a.i./kg soil	0.00464 mg a.i./kg soil	0.0002	Not exceeded
Vascular plants					
Vascular plant	Seedling emergence	ER_{25}: 2.05 g a.e./ha	In-field: 10 g a.e./ha	In-field: 4.9	Exceeded
			Off-field (aerial appl., 17% drift): 1.7 g a.e./ha	Off-field (aerial): 0.83	Not exceeded
			Off-field (ground appl., 3% drift): 0.3 g a.e./ha	Off-field (ground): 0.15	Not exceeded
	Vegetative vigour	HR_5 of SSD for ER_{50} values: 0.039 g a.e./ha	In-field: 10 g a.e./ha	In-field: 256	Exceeded
			Off-field (aerial appl., 17% drift): 1.7 g a.e./ha	Off-field (aerial): 43.6	Exceeded
			Off-field (ground appl., 3% drift): 0.3 g a.e./ha	Off-field (ground): 7.7	Exceeded
	Seedling emergence – GF-2687	ER_{25}: 0.82 g GF-2687/ha	In field: 25 g GF-2687/ha	In-field: 30	Exceeded
			Off-field (ground appl., 3% drift): 0.75 g GF-2687/ha	Off-field (ground): 0.9	Not exceeded
	Vegetative vigour – GF-2687	HR_5 of SSD for ER_{50} values: 0.45 g GF-2687/ha	In field: 25 g GF-2687/ha	In-field: 56	Exceeded
			Off-field (ground appl., 3% drift): 0.75 g GF-2687/ha	Off-field (ground): 1.7	Exceeded

Table 16 Screening Level Risk Assessment of Halauxifen-Methyl for Birds and Mammals

	Toxicity (mg a.i./kg bw/d)	Feeding Guild (food item)	EDE (mg a.i./kg bw)[1]	RQ	Level of Concern
Small Bird (0.02 kg)					
Acute	>225	Insectivore (small insects)	0.53	<0.002	Not exceeded
Reproduction	36.9	Insectivore (small insects)	0.53	0.01	Not exceeded
Medium Sized Bird (0.1 kg)					
Acute	>225	Insectivore (small insects)	0.41	<0.002	Not exceeded
Reproduction	36.9	Insectivore (small insects)	0.41	0.01	Not exceeded
Large Sized Bird (1 kg)					
Acute	>225	Herbivore (short grass)	0.43	<0.002	Not exceeded
Reproduction	36.9	Herbivore (short grass)	0.43	0.01	Not exceeded
Small Mammal (0.015 kg)					
Acute	>500	Insectivore (small insects)	0.30	<0.001	Not exceeded
Reproduction	6	Insectivore (small insects)	0.30	0.05	Not exceeded
Medium Sized Mammal (0.035 kg)					
Acute	>500	Herbivore (short grass)	0.95	<0.002	Not exceeded
Reproduction	6	Herbivore (short grass)	0.95	0.16	Not exceeded
Large Sized Mammal (1 kg)					
Acute	>500	Herbivore (short grass)	0.51	<0.001	Not exceeded
Reproduction	6	Herbivore (short grass)	0.51	0.08	Not exceeded

[1] EDE = Estimated dietary exposure; is calculated using the following formula: (FIR/bw) × EEC, where:
FIR: Food Ingestion Rate. For generic birds with body weight less than or equal to 200 g, the "passerine" equation was used; for generic birds with body weight greater than 200 g, the "all birds" equation was used:
Passerine Equation (body weight <or = 200 g): FIR (g dry weight/day) = $0.398(\text{bw in g})^{0.850}$
All birds Equation (body weight >200 g): FIR (g dry weight/day) = $0.648\ (\text{bw in g})^{0.651}$
For mammals, the "all mammals" equation was used: FIR (g dry weight/day) = $0.235(\text{bw in g})^{0.822}$
bw: Generic Body Weight
EEC: Concentration of pesticide on food item. At the screening level, relevant food items representing the most conservative EEC for each feeding guild are used.

Table 17 Screening Level and Refined Risk Assessment of Halauxifen-Methyl Transformation Products for Terrestrial Species

Organism	Exposure	Endpoint Value	EEC	RQ	Level of Concern
XDE-729 acid (X11393729)					
Earthworms	Acute	LC_{50}/2: >500 mg/kg soil	0.0044 mg/kg soil	<0.0001	Not exceeded
Terrestrial invertebrates	Chronic, artificial soil	NOEC: 12.5 mg/kg soil	0.0044 mg/kg soil	0.0004	Not exceeded
Vascular plants	Seedling emergence	ER_{50}/2 (to estimate an ER_{25}): 0.19 g/ha	In-field: 10 g/ha	In-field: 52.2	Exceeded
			Off-field (aerial appl., 17% drift): 1.7 g/ha	Off-field (aerial): 8.9	Exceeded
			Off-field (ground appl., 3% drift): 0.3g/ha	Off-field (ground): 1.6	Exceeded
X11449757					
Earthworms	Acute	LC_{50}/2: >500 mg/kg soil	0.0042 mg/kg soil	<0.0001	Not exceeded

Organism	Exposure	Endpoint Value	EEC	RQ	Level of Concern
Terrestrial invertebrates	Chronic, artificial soil	NOEC: 10 mg/kg soil	0.0042 mg/kg soil	0.0004	Not exceeded
Vascular plants	Seedling emergence	ER_{25}: >15 g/ha	In-field: 9.6 g/ha	In-field: 0.6	Not exceeded

Table 18 Toxicity of Halauxifen-Methyl, Major Transformation Products and Halauxifen-Methyl formulations to Non-Target Aquatic Species

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[1]	Reference (PMRA#)
Freshwater species					
Daphnia magna	48-h Acute	Halauxifen-methyl	EC_{50}: 2.12 mg a.i./L	Moderately toxic	2226558
	48-h Acute	XDE-729 acid (X11393729)	EC_{50}: >106 mg/L	Practically non-toxic	2226559
	48-h Acute	X11449757	EC_{50}: >115 mg/L	Practically non-toxic	2226560
	48-h Acute	X11406790	EC_{50}: >25 mg/L	Not toxic up to the limit of solubility of the test	2226557
	21-d Chronic	Halauxifen-methyl	NOEC: 0.484 mg a.i./L (adult length and reproduction)	No classification	2226562
	21-d Chronic	XDE-729 acid (X11393729)	NOEC: 98.3 mg/L (highest concentration tested)	No classification	2226561
Sediment dwelling invertebrate, *Chironomus dilutus*	10-d Acute; spiked sediment	Radiolabelled and unlabelled halauxifen-methyl	LC_{50}: >89.3 mg TRR/kg dw sediment (>1.0 mg TRR/L in overlying water; >5.63 mg TRR/L in pore water) (geometric mean-measured concentrations)	Not toxic up to the highest test concentration	2226575
Sediment dwelling invertebrate, *Chironomus riparius*	28-d Chronic, spiked water	Radiolabelled and unlabelled halauxifen-methyl	NOEC: 1.20 mg TRR/L in overlying water (0.12 mg TRR/L in pore water and 1.81 mg TRR/kg dw sediment) (highest concentration tested; geometric mean-measured concentrations)	Not toxic up to the solubility limit of the test	2226563
Rainbow trout, *Oncorhynchus mykiss*	96-h Acute	Halauxifen-methyl	LC_{50}: 2.01 mg a.i./L	Moderately toxic	2226547
	96-h Acute	XDE-729 acid (X11393729)	LC_{50}: >107 mg/L	Practically non-toxic	2226550
	96-h Acute	X11449757	LC_{50}: >124 mg/L	Practically non-toxic	2226551
	96-h Acute	X11406790	LC_{50}: >29 mg/L	Not toxic up to the	2226549

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[1]	Reference (PMRA#)
				limit of solubility of the test	
Fathead minnow, *Pimephales promelas*	96-h Acute	Halauxifen-methyl	LC_{50}: >3.22 mg a.i./L (limit of solubility) (30% mortality observed at highest test concentration)	Not toxic up to the limit of solubility of the test	2226548
	35-d Early-life stage	Halauxifen-methyl	NOEC: 0.259 mg a.i./L (post-hatch survival and fry length)	No classification	2226554
	33-d Early-life stage	XDE-729 acid (X11393729)	NOEC: 11.8 mg/L (highest concentration tested)	No classification	2226555
	34-d Early-life stage	X11449757	NOEC: 8.9 mg/L (highest concentration tested)	No classification	2226552
	21-d Short term reproduction	Halauxifen-methyl	NOEC: 0.077 mg a.i./L (fecundity and fertility) No treatment-related effects on male and female secondary sex characteristics, male VTG, or male and female gonad histopathology	No classification The reductions in fecundity and fertility were not considered to be due to (anti)estrogenic activity, (anti)androgenic activity or aromatase inhibition	2226605
			NOEC: 0.078 mg a.i./L (highest concentration tested)	No classification	2279931
	21-d Short term reproduction	XDE-729 acid (X11393729)	NOEC: 12 mg/L (highest concentration tested)	No classification	2226603
Amphibian, African clawed frog, *Xenopus laevis*	96-h Acute, tadpoles	Halauxifen-methyl	EC_{50}: >2.0 mg a.i./L (maximum achieved concentration) (45% mortality at highest test concentration)	No classification	2226606
	21-d Amphibian metamorphosis	Halauxifen-methyl	NOEC: 0.38 mg a.i./L (highest concentration tested) Negative thyroid activity and no adverse effect caused by the solvent carrier alone	No classification Not likely thyroid active at up to 0.38 mg a.i./L.	2226604
Green algae, *Pseudokirchneriella subcapitata*	96-h Acute	Halauxifen-methyl	EC_{50}: >0.245 mg a.i./L (limit of solubility) (all endpoints)	No classification Not toxic up to the solubility limit of the test	2226570
	72-h Acute	GF-2685	EC_{50}: 10.6 mg GF-	No classification	2279883

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[1]	Reference (PMRA#)
		(formulation; 10.6% halauxifen-methyl)	2685/L (1.12 mg a.i./L) (yield)		
	72-h Acute	GF-2687 (formulation; 20.9% halauxifen-methyl and 20.4% florasulam)	Most sensitive endpoint: EC_{50}: 0.00975 mg GF-2687/L (growth rate)	No classification	2279894
	72-h Acute	XDE-729 acid (X11393729)	Most sensitive endpoint: EC_{50}: 23.2 mg/L (yield)	No classification	2226569
	72-h Acute	X11449757	Most sensitive endpoint: EC_{50}: 4.13 mg/L (yield)	No classification	2226574
	72-h Acute	X11406790	Most sensitive endpoint: EC_{50}: 1.8 mg/L (yield)	No classification	2226564
Blue-green algae, *Anabaena flos-aquae*	96-h Acute	Halauxifen-methyl	EC_{50}: >0.775 mg a.i./L (limit of solubility) (all endpoints)	No classification Not toxic up to the solubility limit of the test	2226572
	72-h Acute	XDE-729 acid (X11393729)	Most sensitive endpoint: EC_{50}: 51.7 mg/L (yield)	No classification	2226567
Diatom, *Navicula pelliculosa*	96-h Acute	Halauxifen-methyl	Most sensitive endpoint: EC_{50}: 0.5608 mg a.i./L (biomass)	No classification	2226571
	72-h Acute	XDE-729 acid (X11393729)	Most sensitive endpoint: EC_{50}: 49.6 mg/L (biomass)	No classification	2226568
Monocot vascular plant, duckweed, *Lemna gibba*	7-d Dissolved	Halauxifen-methyl	Most sensitive endpoint: EC_{50}: 2.13 mg a.i./L (frond yield)	No classification	2226582
	7-d Dissolved	GF-2685 (formulation; 10.6% halauxifen-methyl)	Most sensitive endpoint: EC_{50}: 35.6 mg GF-2685/L (3.8 mg a.e./L) (frond yield)	No classification	2279884
	7-d Dissolved	GF-2687 (formulation; 20.9% halauxifen-methyl and 20.4%	Most sensitive endpoint: EC_{50}: 0.0017 mg GF-2687/L (frond yield)	No classification	2279895

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[1]	Reference (PMRA#)
		florasulam)			
	7-d Dissolved	XDE-729 acid (X11393729)	Most sensitive endpoint: EC_{50}/IC_{50}: 13.4 mg/L (frond number yield)	No classification	2226583
	7-d Dissolved	X11449757	EC_{50}: >92.9 mg/L (all endpoints)	No classification	2226581
	7-d Dissolved	X11406790	EC_{50}: >12 mg/L (all endpoints)	No classification	2226580
Dicot rooted aquatic macrophyte, Eurasian water milfoil, *Myriophyllum spicatum*	14-d Water-sediment system	Halauxifen-methyl	Most sensitive endpoint: EC_{50}: 0.000149 mg a.i./L (yield based on shoot length)	No classification	2226579
	14-d Water-sediment system	GF-2573 (formulation; 7.8 g halauxifen-methyl/L)	EC_{50}: 0.0402 mg GF-2573/L (approximately 0.00035 mg a.i./L) (yield based fresh weight)	No classification	2279885
	14-d Water-sediment system	GF-2687 (formulation; 20.9% halauxifen-methyl and 20.4% florasulam)	Most sensitive endpoint: EC_{50}: 0.00133 mg GF-2687/L (yield based on fresh weight)	No classification	2279896
	14-d Water-sediment system	XDE-729 acid (X11393729)	EC_{50}: 0.0008 mg/L (yield based on shoot length)	No classification	2226578
	14-d Water-sediment system	X11449757	EC_{50}: >0.1 mg/L (all endpoints)	No classification	2226577
	14-d Water-sediment system	X11406790	EC_{50}: >0.1 mg/L (all endpoints)	No classification	2226576
Marine/estuarine species					
Crustacean, mysid shrimp, *Americamysis bahia*	48-h Acute	Halauxifen-methyl	LC_{50}: >1.3 mg a.i./L (limit of solubility) (40% mortality observed at highest concentration)	Not toxic up to the limit of solubility of the test	2226593
	28-d Chronic	Halauxifen-methyl	NOEC: 0.152 mg a.i./L (growth of P-generation of males and females)	No classification	2226591
Sediment-dwelling amphipod, *Leptocheirus plumulosus*	10-d Acute; spiked sediment	Radiolabelled and unlabelled halauxifen-methyl	LC_{50}: >58.1 mg TRR/kg sediment (>0.97 mg TRR/L in overlying water; >5.08 mg TRR/L in pore water)	Not toxic up to the highest test concentration	2226596
Mollusk, Eastern oyster, *Crassostrea*	96-h Acute	Halauxifen-methyl	Shell deposition: EC_{50}: >1.21 mg a.i./L	Not toxic up to the limit of solubility of	2226594

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[1]	Reference (PMRA#)
virginica			(limit of solubility under the test conditions)	the test	
Sheepshead minnow, *Cyprinodon variegatus*	96-h Acute	Halauxifen-methyl	LC_{50}: >1.33 mg a.i./L (limit of solubility under the test conditions)	Not toxic up to the limit of solubility of the test	2226592
	36-d Early-life stage	Halauxifen-methyl	NOEC: 0.00272 mg a.i./L (length)	No classification	2226595
Marine diatom, *Skeletonema costatum*	96-h Acute	Halauxifen-methyl	Most sensitive endpoint: EC_{50}: 0.8374 mg a.i./L (biomass)	No classification	2226573
	96-h Acute	XDE-729 acid (X11393729)	Most sensitive endpoint: EC_{50}: 64.6 mg/L (biomass)	No classification	2226566
[1] US EPA classification, where applicable					

Table 19 Screening Level Risk Assessment of Halauxifen-Methyl for Aquatic Species

Organism	Exposure	Endpoint Value (mg a.i./L)	EEC (mg a.i./L)	RQ	Level of Concern
Freshwater species					
Invertebrates	Acute	EC_{50}/2 1.06	0.00131	0.001	Not exceeded
	Chronic	NOEC: 0.484	0.00131	0.003	Not exceeded
Fish	Acute	LC_{50}/10: 0.201	0.00131	0.007	Not exceeded
	Early-life stage	NOEC: 0.259	0.00131	0.005	Not exceeded
	Short-term reproduction	NOEC: 0.077	0.00131	0.02	Not exceeded
Amphibians	Acute, tadpoles	LC_{50}/10: >0.2	0.0070	<0.04	Not exceeded
	Metamorphosis	NOEC: 0.38	0.0070	0.02	Not exceeded
Algae	Acute	EC_{50}/2: 0.2804	0.00125	0.0054	Not exceeded
Vascular plants (monocot, *Lemna gibba*)	Dissolved	EC_{50}/2: 1.065	0.00131	0.001	Not exceeded
Rooted vascular plants (dicot, *Myriophyllum spicatum*)	Water-sediment system	EC_{50}/2: 0.0000745	Direct application: 0.00131	17.6	Exceeded
Marine species					
Crustacean	Acute	LC_{50}/2: >0.65	0.00131	<0.002	Not exceeded
	Chronic	NOEC: 0.152	0.00131	0.009	Not exceeded
Mollusk	Acute	EC_{50}/2: >0.605	0.00131	<0.002	Not exceeded
Fish	Acute	LC_{50}/10: >0.133	0.00131	<0.01	Not exceeded
	Early-life stage	NOEC: 0.00272	0.00131	0.5	Not exceeded
Algae	Acute	EC_{50}/2: 0.4187	0.00131	0.003	Not exceeded

Table 20 Screening Level Risk Assessment of Halauxifen-Methyl Transformation Products for Aquatic Species

Organism	Exposure	Endpoint Value (mg/L)	EEC (mg/L)	RQ	Level of Concern
XDE-729 acid (X11393729)					
Freshwater species					
Invertebrates	Acute	EC_{50}/2: >53	0.00125	<0.001	Not exceeded
	Chronic	NOEC: 98.3	0.00125	<0.001	Not exceeded
Fish	Acute	LC_{50}/10: >10.7	0.00125	<0.001	Not exceeded
	Early-life stage	NOEC: 11.8	0.00125	<0.001	Not exceeded
	Short-term reproduction	NOEC: 12	0.00125	<0.001	Not exceeded
Amphibians	Acute	LC_{50}/10: >10.7	0.0067	<0.001	Not exceeded
	Early-life stage	NOEC: 11.8	0.0067	<0.001	Not exceeded
	Short-term reproduction	NOEC: 12	0.0067	<0.001	Not exceeded
Algae	Acute	EC_{50}/2: 11.6	0.00125	<0.001	Not exceeded
Vascular plants (monocot, *Lemna gibba*)	Dissolved	EC_{50}/2: 6.7	0.00125	<0.001	Not exceeded
Rooted vascular plants (dicot, *Myriophyllum spicatum*)	Water-sediment system	EC_{50}/2: 0.0004	Direct application: 0.00125	3.1	Exceeded
Marine species					
Algae	Acute	EC_{50}/2: 32.3	0.00125	<0.001	Not exceeded
X11449757					
Freshwater species					
Invertebrates	Acute	EC_{50}/2: >57.5	0.0012	<0.001	Not exceeded
Fish	Acute	LC_{50}/10: >12.4	0.0012	<0.001	Not exceeded
	Early-life stage	NOEC: 8.9	0.0012	<0.001	Not exceeded
Amphibians	Acute	LC_{50}/10: >12.4	0.00642	<0.001	Not exceeded
	Early-life stage	NOEC: 8.9	0.00642	<0.001	Not exceeded
Algae	Acute	EC_{50}/2: 2.065	0.0012	<0.001	Not exceeded
Vascular plants (monocot, *Lemna gibba*)	Dissolved	EC_{50}/2: >46.45	0.0012	<0.001	Not exceeded
Rooted vascular plants (dicot, *Myriophyllum spicatum*)	Water-sediment system	EC_{50}/2: >0.05	0.0012	<0.02	Not exceeded
X11406790					
Freshwater species					
Invertebrates	Acute	EC_{50}/2: >12.5	0.00125	<0.001	Not exceeded
Fish	Acute	LC_{50}/10: >2.9	0.00125	<0.001	Not exceeded
Amphibians	Acute	LC_{50}/10: >2.9	0.0067	<0.002	Not exceeded
Algae	Acute	EC_{50}/2: 0.9	0.00125	0.001	Not exceeded
Vascular plants (monocot, *Lemna gibba*)	Dissolved	EC_{50}/2: >6	0.00125	<0.001	Not exceeded
Rooted vascular plants (dicot, *Myriophyllum spicatum*)	Water-sediment system	EC_{50}/2: >0.05	0.00125	<0.03	Not exceeded

Table 21 Screening Level Risk Assessment of GF-2687, a Formulation Containing Halauxifen-Methyl and Florasulam, for Aquatic Species

Organism	Exposure	Endpoint Value (mg GF-2687/L)	EEC (mg GF-2687/L)	RQ	Level of Concern
Freshwater species					
Algae	Acute	EC_{50}/2: 0.0049	0.0031	0.6	Not exceeded
Vascular plants (monocot, *Lemna gibba*)	Dissolved	EC_{50}/2: 0.00085	Direct application: 0.0031	3.6	Exceeded
Rooted vascular plants (dicot, *Myriophyllum spicatum*)	Water-sediment system	EC_{50}/2: 0.00067	Direct application: 0.0031	4.7	Exceeded

Table 22 Risk Quotients for Aquatic Organisms Determined for Drift of Halauxifen-Methyl, its Transformation Products and the Halauxifen-Methyl and Florasulam Formulation, GF-2687

Organism	Exposure	Endpoint value	Refined EEC	RQ	Level of Concern
Halauxifen-Methyl					
Rooted vascular plants (*Myriophyllum spicatum*)	Water-sediment system	EC_{50}/2: 0.0000745 mg a.i./L	Aerial appl. (17% drift): 0.00022 mg a.i./L	3.0	Exceeded
			Ground appl. (3% drift): 0.00004 mg a.i./L	0.5	Not exceeded
XDE-729 acid (X11393729)					
Rooted vascular plants (*Myriophyllum spicatum*)	Water-sediment system	EC_{50}/2: 0.0004 mg/L	Aerial appl. (17% drift): 0.00021 mg/L	1.2	Exceeded
			Ground appl. (3% drift): 0.00004 mg/L	0.2	Not exceeded
Halauxifen-Methyl and florasulam formulation, GF-2687					
Vascular plants (monocot, *Lemna gibba*)	Dissolved	EC_{50}/2: 0.00085 mg GF-2687/L	Ground appl. (3% drift): 0.00009 mg GF-2687/L	0.1	Not exceeded
Rooted vascular plants (*Myriophyllum spicatum*)	Water-sediment system	EC_{50}/2: 0.00067 mg GF-2687/L	Ground appl. (3% drift): 0.00009 mg GF-2687/L	0.1	Not exceeded

Table 23 Risk quotients for Aquatic Organisms Determined for Runoff of Halauxifen-Methyl and Transformation Products in Water Bodies 80 Deep

Organism	Exposure	Endpoint value	Refined EEC	RQ	Level of Concern
Halauxifen-Methyl					
Rooted vascular plants (*Myriophyllum spicatum*)	Water-sediment system	EC_{50}/2: 0.0000745 mg a.i./L	0.000025 mg /L	0.3	Not exceeded

Organism	Exposure	Endpoint value	Refined EEC	RQ	Level of Concern
XDE-729 acid (X11393729)					
Rooted vascular plants (*Myriophyllum spicatum*)	Water-sediment system	EC_{50}/2: 0.0004 mg/L	0.00014 mg/L[1]	0.5	Not exceeded

[1]EECs for XDE-729 acid (X11393729) were modelled using a combined residue approach with halauxifen-methyl.

Table 24a Use Claims That Are Supported for GF-2685 Herbicide

Items	Use claims that are supported
Use sites/crops	Spring wheat (including durum), winter wheat and spring barley as proposed.
Appl. rate	2.5 to 10 g a.e./ha, as proposed (rate depending on weed species) + Turbocharge at 0.5% v/v as proposed.
No. of apps	One per season, as proposed.
Use range	Prairie Provinces and Peace River Region of British Columbia and Eastern Canada, as proposed.
Weed claims	Control of cleavers, volunteer flax and lamb's quarters and suppression of hemp-nettle and redroot pigweed using the 2.5 g a.e./ha rate, as per proposed, except for volunteer flax which was proposed for control at 5.0 g a.e./ha. Control of chickweed, cleavers, volunteer flax, hemp-nettle, lamb's quarters and redroot pigweed and suppression of wild buckwheat and kochia using the 5 g a.e./ha rate, as per proposed. In addition to the weeds listed above with 5 g a.e./ha, control of wild buckwheat using the 10 g a.e./ha rate, as proposed.
Appl. timing	Relative to crop: postemergence from the 1-leaf stage to just prior to flag leaf emergence in spring wheat, durum wheat and barley and from the 3-leaf stage to just prior to flag leaf emergence for winter wheat, as proposed. Relative to weeds: postemergence, as proposed.
Appl. method	Apply in a minimum of 50 L of water per hectare by ground equipment and a minimum of 30L of water per hectare for aerial application, as proposed.
Tank mix partners	All application are done postemergence to weeds and crops for the suppression / control of all GF-2685 Herbicide labeled weeds plus control of all tank-mix partners labeled weeds • Refine SG at 10 g a.i./ha thifensulfuron methyl and 5 g a.i./ha tribenuron methyl + Agral 90 at 0.25% v/v, in spring wheat (including durum), winter wheat and barley, as proposed; • 3-way tank-mix with Refine SG + MCPA ester at 280 g a.e./ha in spring wheat (including durum), winter wheat and barley, as proposed; • Axial 100EC at 60 g a.i./ha pinoxaden + Adigor at 0.7 L/ha in spring wheat and barley, as proposed; • Horizon 240EC at 56 g a.i./ha clodinafop-propargyl + Score at 0.8% v/v in spring wheat and durum wheat, as proposed; • Horizon NG at 56 g a.i./ha clodinafop-propargyl in spring wheat and durum wheat, as proposed; • Puma[120] Super or Puma Advance at 92 g a.i./ha fenoxaprop-p-ethyl in spring

Items	Use claims that are supported
	wheat, durum wheat and barley, as proposed; • Liquid Achieve SC at 200 g a.i./ha tralkoxydim + Turbocharge at 0.5% v/v in spring wheat, durum wheat and barley, as proposed; • Everest at 2.0 14.3 – 28.6 g a.i./ha flucarbazone + Ag-Surf or Agral 90 at 0.25% v/v in spring wheat and durum wheat, as proposed; • Traxos Herbicide at 30 g a.i./ha pinoxaden and 30 g a.i./ha clodinafop-propargyl in spring wheat and durum wheat, as proposed; • 3-way tank-mix with Refine SG + Axial 100EC + Adigor at 0.7 L/ha in spring wheat and barley, as proposed; • 3-way tank-mix with Refine SG + Horizon 240EC + Score at 0.8% v/v in spring wheat and durum wheat, as proposed; • 3-way tank-mix with Refine SG + Horizon NG in spring wheat and durum wheat, as proposed. • 3-way tank-mix with Refine SG + Everest 2.0 + Ag-Surf or Agral 90 at 0.25% v/v in spring wheat and durum wheat, as proposed; • 4-way tank-mix with Refine SG + MCPA ester + Axial 100EC + Adigor at 0.7 L/ha in spring wheat and barley, as proposed; and • 4-way tank-mix with Refine SG + MCPA ester + Everest 2.0 + Ag-Surf or Agral 90 at 0.25% v/v in spring wheat and durum wheat, as proposed
Rotational crops (months after application)	Spring wheat (10 months), barley (10 months), oats (10 months), field corn (10 months), canola (10 months), flax (10 months), Juncea canola (10 months), Abyssinian, oriental, brown and yellow mustard (10 months), field peas (10 months), soybeans (10 months), sunflower (10 months) and lentils (22 months) or fields can be summer fallowed, as proposed.
Rainfastness	Applications of GF-2685 are rainfast within 1 hour of application, as proposed.

Table 24b Use Claims That Are Supported for Paradigm Herbicide

Items	Use claims that are supported
Use sites/crops	Spring wheat (including durum), winter wheat and spring barley as proposed.
Appl. rate	10 g a.e./ha (5 g a.e./ha halauxifen-methyl + 5 g a.i./ha florasulam) + Turbocharge at 0.5% v/v, as proposed.
No. of apps	One per season, as proposed.
Use range	Prairie Provinces and Peace River Region of British Columbia, as proposed.
Weed claims	Control of wild buckwheat, volunteer canola, chickweed, cleavers, volunteer flax and lamb's quarters, wild mustard, redroot pigweed, shepherd's purse, smartweed (green smartweed, lady's thumb) and stinkweed; suppression of hemp-nettle, kochia, annual sow thistle and perennial sow thistle using the 10 g a.e./ha rate, as proposed. Control includes Group 2 resistant biotypes of chickweed, lamb's quarters and hemp-nettle, as proposed.
Appl. timing	Relative to crop: postemergence from the 2-leaf stage to just prior to flag leaf emergence in spring wheat, durum wheat and barley and from the 3-leaf stage to just prior to flag leaf emergence for winter wheat, as proposed. Relative to weeds: postemergence, as proposed.
Appl. method	Apply in a minimum of 50 L of water per hectare by ground equipment only, as proposed.
Tank mix	All application are done postemergence to weeds and crops for the suppression /

Items	Use claims that are supported
partners	control of all Paradigm Herbicide labeled weeds plus control of all tank-mix partners labeled weeds • MCPA ester at 350 g a.e./ha in spring wheat, durum wheat, winter wheat and barley, as proposed; • Curtail M at 495 g a.e./ha (75 g a.e./ha clopyralid + 420 g a.e./L MCPA ester) spring wheat, durum wheat, winter wheat and barley, as proposed; • Axial 100EC at 60 g a.i./ha pinoxaden + Adigor at 0.7 L/ha in spring wheat and barley, as proposed; • Everest 2.0 at 14.3 – 28.6 g a.i./ha flucarbazone + Ag-Surf or Agral 90 at 0.25% v/v in spring wheat and durum wheat, as proposed; • Simplicity Herbicide at 15 g a.i./ha pyroxsulam + Ag-Surf or Agral 90 at 0.25% v/v in spring wheat and durum wheat, as proposed; • 3-way tank-mix with MCPA ester + Axial 100EC + Adigor at 0.7 L/ha in spring wheat and barley, as proposed; • 3-way tank-mix with MCPA ester + Everest 2.0 + Ag-Surf or Agral 90 at 0.25% v/v in spring wheat and durum wheat, as proposed; • 3-way tank-mix with MCPA ester + Simplicity + Ag-Surf or Agral 90 at 0.25% v/v in spring wheat and durum wheat, as proposed; • 3-way tank-mix with Curtail M + Everest 2.0 + Ag-Surf or Agral 90 at 0.25% v/v in spring wheat and durum wheat, as proposed; and • 3-way tank-mix with Curtail M + Simplicity + Ag-Surf or Agral 90 at 0.25% v/v in spring wheat and durum wheat, as proposed.
Rotational crops (months after application)	Spring wheat (10 months), barley (10 months), canola (10 months), flax (10 months), Juncea canola (10 months), oriental, brown and yellow mustard (10 months), field peas (10 months), soybeans (10 months), sunflower (10 months) and lentils (22 months) or fields can be summer fallowed, as proposed. Oats was removed from the list of proposed rotational since it does not appear as a rotational crop with florasulam.
Rainfastness	Applications of Paradigm Herbicide are rainfast within 1 hour of application, as proposed.

Table 24c Use Claims That Are Supported for Pixxaro A Herbicide

Items	Use claims that are supported
Use sites/crops	Spring wheat (including durum), winter wheat and spring barley as proposed.
Appl. rate	82 g a.e./ha (5 g a.e./ha halauxifen-methyl + 77 g a.e. /ha fluroxypyr) + Turbocharge at 0.5% v/v, as proposed.
No. of apps	One per season, as proposed.
Use range	Prairie Provinces and Peace River Region of British Columbia, as proposed.
Weed claims	Control of wild buckwheat, chickweed, cleavers, volunteer flax, hemp-nettle, kochia, lamb's quarters and redroot pigweed and suppression of wild mustard using the 82 g a.e./ha rate, as proposed. Control includes Group 2 resistant biotypes, as proposed.

Items	Use claims that are supported
Appl. timing	Relative to crop: postemergence from the 1-leaf stage to just prior to flag leaf emergence in spring wheat, durum wheat and barley and from the 3-leaf stage to just prior to flag leaf emergence for winter wheat, as proposed. Relative to weeds: postemergence, as proposed.
Appl. method	Apply in a minimum of 50 L of water per hectare by ground equipment and a minimum of 30L of water per hectare for aerial application, as proposed.
Tank mix partners	All application are done postemergence to weeds and crops for the suppression / control of all Pixxaro A Herbicide labeled weeds plus control of all tank-mix partners labeled weeds • MCPA ester at 350-420 g a.i./ha in spring wheat (including durum), winter wheat and barley, as proposed; • Curtail M at 495 g a.e./ha (75 g a.e./ha clopyralid + 420 g a.e./ha MCPA ester) in spring wheat (including durum), winter wheat and barley, as proposed; • Axial 100EC at 60 g a.i./ha pinoxaden + Adigor at 0.7 L/ha in spring wheat and barley, as proposed; • Horizon 240EC at 56 g a.i./ha clodinafop-propargyl + Score at 0.8% v/v in spring wheat and durum wheat, as proposed; • Horizon NG at 56 g a.i./ha clodinafop-propargyl in spring wheat and durum wheat, as proposed; • Puma^{120} Super or Puma Advance at 92 g a.i./ha fenoxaprop-p-ethyl in spring wheat, durum wheat and barley, as proposed; • Liquid Achieve SC at 200 g a.i./ha tralkoxydim + Turbocharge at 0.5% v/v in spring wheat, durum wheat and barley, as proposed; • Everest 2.0 at 14.3 – 28.6 g a.i./ha flucarbazone + Ag-Surf or Agral 90 at 0.25% v/v in spring wheat and durum wheat, as proposed; • Traxos Herbicide at 30 g a.i./ha pinoxaden and 30 g a.i./ha clodinafop-propargyl in spring wheat and durum wheat, as proposed; • 3-way tank-mix with MCPA ester or Curtail M + Axial 100EC + Adigor at 0.7 L/ha in spring wheat and barley, as proposed; • 3-way tank-mix with MCPA ester or Curtail M + Horizon 240EC + Score at 0.8% v/v in spring wheat and durum wheat, as proposed; • 3-way tank-mix with MCPA ester or Curtail M + Horizon NG in spring wheat and durum wheat, as proposed. • 3-way tank-mix with MCPA ester or Curtail M + Puma120 Super or Puma Advance in spring wheat, durum wheat and barley, as proposed; • 3-way tank-mix with MCPA ester or Curtail M + Liquid Achieve SC + Turbocharge at 0.5% v/v in spring wheat, durum wheat and barley, as proposed; • 3-way tank-mix with MCPA ester or Curtail M + Everest 2.0 + Ag-Surf or Agral 90 at 0.25% v/v in spring wheat and durum wheat, as proposed; • 3-way tank-mix with MCPA ester or Curtail M + Traxos Herbicide in spring wheat and durum wheat, as proposed;
Rotational crops (months after application)	Spring wheat (10 months), barley (10 months), oats (10 months), canola (10 months), flax (10 months), mustard (10 months), field peas (10 months) and lentils (22 months) or fields can be summer fallowed, as proposed
Rainfastness	Applications of Pixxaro A Herbicide are rainfast within 1 hour of application, as proposed.

Table 25 Toxic Substances Management Policy Considerations – Comparison to TSMP Track 1 Criteria

TSMP Track 1 Criteria	TSMP Track 1 Criterion value		Halauxifen-Methyl Endpoints
Toxic or toxic equivalent as defined by the *Canadian Environmental Protection Act*	Yes		Yes
Predominantly anthropogenic[2]	Yes		Yes
Persistence[3]:	Soil	Half-life ≥ 182 days	Laboratory studies: DT_{50} of 0.9 to 2.8 days in aerobic and anaerobic soil Field studies: DT_{50} of 1.54 to 14.8 days
	Water	Half-life ≥ 182 days	DT_{50} of 0.47 to 4.0 days in the water phase of aerobic and anaerobic water-sediment systems. Total system DT_{50} values range from 0.5 to 5 days in aerobic and anaerobic water-sediment systems.
	Sediment	Half-life ≥ 365 days	DT_{50} of 0.2 to 7.4 days in the sediment phase of aerobic and anaerobic water-sediment systems. Total system DT_{50} values range from 0.5 to 5 days in aerobic and anaerobic water-sediment systems.
	Air	Half-life ≥ 2 days or evidence of long range transport	Volatilisation is not an important route of dissipation and long-range atmospheric transport is unlikely to occur based on the vapour pressure (5.9×10^{-9} Pa at 20°C) and Henry's law constant (1.2×10^{-11} atm·m^3/mol at 20°C). Supplemental information indicates the photochemical oxidation half-life in air reported is 2.2 days.
Bioaccumulation[4]	Log $K_{OW} \geq 5$		pH 5: 3.75 pH 7: 3.76 pH 9: 3.92
	BCF ≥ 5000		183-214
	BAF ≥ 5000		Not available
Is the chemical a TSMP Track 1 substance (all four criteria must be met)?			No, does not meet TSMP Track 1 criteria.

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

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

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

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

Appendix II Supplemental Maximum Residue Limit Information—International Situation and Trade Implications

Differences Between Maximum Residue Limits in Canada and in Other Jurisdictions

Halauxifen-methyl is a new active ingredient which was jointly reviewed by Canada, the United States and Australia. The maximum residue limits proposed for halauxifen-methyl in Canada are the same as corresponding proposed tolerances in the United States (American tolerances listed in the Electronic Code of Federal Regulations, 40 CFR Part 180).

Currently, there are no Codex maximum residue limits[9] listed for halauxifen-methyl in or on any commodity on the Codex Alimentarius Pesticide Residues in Food website.

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

References

A. List of Studies/Information Submitted by Registrant

1.0 Chemistry

PMRA Document Number	Reference
2226395	2012, OECD Document J for XDE-729 methyl and a representative formulation GF-2685, DACO: 2.11.1,2.11.3,2.11.4,Document J CBI
2226399	2012, Batch Analysis Study for XDE-729 ME Technical, DACO: 2.13.3,IIA 1.11.1
2226401	2011, Determination of Color, Physical State, Odor, Melting Point and Decomposition Temperatures of XDE-729 Methyl Pure Active Ingredient, DACO: 2.14.1,2.14.13,2.14.2,2.14.3,2.14.4,2.14.5,IIA 2.1.1,IIA 2.1.2,IIA 2.1.3,IIA 2.4.1,IIA 2.4.2 CBI
2226402	2011, XDE-729 Methyl TGAI: Determination of Density for Solids, DACO: 2.14.6,IIA 2.2 CBI
2226403	2011, Determination of Vapour Pressure for XDE-729 methyl, DACO: 2.14.9,IIA 2.3.1 CBI
2226404	2011, Calculation of the Henry's Law Constants for XDE-729 methyl from Unbuffered and pH 5, 7, and 9 Buffered Water, DACO: 2.16,IIA 2.3.2 CBI
2226405	2011, Determination of Color, Odor, Physical State, Oxidizing and Reducing Action, Explodability, pH and Bulk Density of XDE-729 Methyl Technical Grade Active Ingredient, DACO: 2.14.1,2.14.2,2.14.3,IIA 2.4.1,IIA 2.4.2 CBI
2226407	2012, X11393728: XDE-729 Methyl: Determination of Spectral Characteristics (UV/Visible Absorption and Molar Absorptivity, Mass Spectrum, Infrared Spectrum, and NMR) Amended Final Report, DACO: 2.13.2,2.14.12,IIA 2.5.1.1,IIA 2.5.1.2,IIA 2.5.1.3,IIA 2.5.1.4,IIA 2.5.1.5 CBI
2226408	2011, Determination of Water Solubility for XDE-729 Methyl, DACO: 2.14.7,IIA 2.6 CBI
2226409	2011, Determination of Organic Solvent Solubility for XDE-729 Methyl TGAI, DACO: 2.14.8,IIA 2.7 CBI
2226412	2011, Determination of Octanol/Water Partition Coefficient for XDE-729 Methyl by Shake Flask Method, DACO: 2.14.11,IIA 2.8.1,IIA 2.8.2 CBI
2226415	2011, Determination of Dissociation Constant of XDE-729 methyl Using UV-Visible Spectrophotometry, DACO: 2.14.10,8.2.3.2,IIA 2.9.5 CBI
2226417	2011, Determination of the Stability of XDE-729 methyl Technical to Normal and Elevated Temperatures, Metals and Metal Ions Amended Report, DACO: 2.14.13,IIA 2.17.2 CBI
2226429	2012, Analytical method and Validation for the Determination of Active Ingredient in XDE-729 ME Technical by Liquid Chromatography, DACO: 2.13.1,IIA 4.2.1
2226430	2012, Analytical Method and Validation for the Determination of Active Ingredient and Impurities in XDE-729 ME Technical by Liquid Chromatography, DACO: 2.13.4,IIA 4.2.3 CBI

PMRA Document Number	Reference
2226431	2012, Analytical Method and Validation for the Determination of Residual Solvents and Process Impurities in XDE-729 ME Technical by Gas Chromatography, DACO: 2.13.4,IIA 4.2.3 CBI
2226443	2011, PAM I Multiresidue Protocol Testing for XDE-729, DACO: 2.16,8.6,IIA 4.9 CBI
2306233	2011, Certificate of Analysis - XDE-729 methyl, Test Item No. TSN301574., DACO: 2.13.3,4.8,IIA 5.5.4,IIA 5.8 CBI
2306235	2011, Certificate of Analysis Characterization of TSN030751-0006, DACO: 2.13.3,4.3.1,IIA 5.3.2 CBI
2306236	2009, Certificate of Analysis Characterization of TSN030751-0005, DACO: 2.13.3,4.3.1,IIA 5.3.2 CBI
2319626	2010, XDE-729 Methyl CoA (PAI_AS), DACO: 2.13.3,IIA 1.11.1 CBI
2319627	2011, [CBI REMOVED] CoA, DACO: 2.13.3,IIA 1.11.1 CBI
2319629	2011, [CBI REMOVED] CoA, DACO: 2.13.3,IIA 1.11.1 CBI
2319630	2010, [CBI REMOVED] CoA, DACO: 2.13.3,IIA 1.11.1 CBI
2319631	2010, [CBI REMOVED] CoA, DACO: 2.13.3,IIA 1.11.1 CBI
2319632	2011, [CBI REMOVED] CoA, DACO: 2.13.3,IIA 1.11.1 CBI
2319633	2011, [CBI REMOVED] CoA, DACO: 2.13.3,IIA 1.11.1 CBI
2319634	2011, [CBI REMOVED] CoA, DACO: 2.13.3,IIA 1.11.1 CBI
2319635	2011, [CBI REMOVED] CoA, DACO: 2.13.3,IIA 1.11.1 CBI
2319636	2011, [CBI REMOVED] CoA, DACO: 2.13.3,IIA 1.11.1 CBI
2319637	2011, [CBI REMOVED] CoA, DACO: 2.13.3,IIA 1.11.1 CBI
2319638	2011, [CBI REMOVED] CoA, DACO: 2.13.3,IIA 1.11.1 CBI
2319639	2011, [CBI REMOVED] CoA, DACO: 2.13.3,IIA 1.11.1 CBI
2319640	2011, [CBI REMOVED] CoA, DACO: 2.13.3,IIA 1.11.1 CBI
2319641	2011, [CBI REMOVED] CoA, DACO: 2.13.3,IIA 1.11.1 CBI
2366698	2013, One Year Ambient Storage Stability of Halauxifen-methyl Technical in Foil Laminate, LLDPE, and Saranex, DACO: 2.14.14,IIA 2.17.1 CBI
2226437	2012, Method Validation Study for the Determination of Residues of X11393728 (XDE-729 Methyl), X11393729 (XDE-729 Acid) and X11449757 (des-Methyl XDE-729 Acid) in Soil using HPLC with Positive-Ion Electrospray Ionization Mass Spectrometry Detection, DACO: 8.2.2.1,IIA 4.4
2226438	2012, ILV of Analytical Method Study Number 110716 for the Determination of XDE-729 Methyl Ester and its Metabolite Residue in Soil, DACO: 8.2.2.1,IIA 4.4
2226439	2012, Method Validation Study for the Determination of Residues of XDE-729 and its Metabolites in Surface Water, Ground Water and Drinking Water by Liquid Chromatography with Tandem Mass Spectrometry (Amended), DACO: 8.2.2.3,IIA 4.5
2226440	2012, XDE-729 Methyl Ester - Independent Laboratory Validation of Analytical Method 110718 for the Determination of XDE-729 Methyl Ester and its Metabolites Residues in Water, DACO: 8.2.2.3,IIA 4.5
2226283	2012, Analytical method and Validation for the Determination of Fluoroxypyr-meptyl, XDE-729 Methyl [CBI REMOVED] in GF-2688, DACO: 3.4.1,IIIA 5.2.1

PMRA Document Number Paradigm Herbicide	Reference
2226232	2011, Determination of Color, Odor, Physical State, Oxidizing and Reducing Action, Bulk Density, Explodability, and pH of GF-2687, and End-Use Product Containing XDE-729 methyl and Florasulam, DACO: 3.5.12,3.5.6,3.5.7,3.5.8,IIIA 2.2.1,IIIA 2.2.2,IIIA 2.4.2,IIIA 2.6.2
2226233	2011, Analytical methods for the determination of the a.s. in product, DACO: 3.4.1,IIIA 5.2.1
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3.0 Environment

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