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Proposed Registration Decision

PRD2020-08

# Pydiflumetofen and Saltro

*(publié aussi en français)*

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## Table of Contents

Overview.....	1
Proposed Registration Decision for Pydiflumetofen .....	1
What Does Health Canada Consider When Making a Registration Decision?.....	1
What Is Pydiflumetofen?.....	2
Health Considerations.....	2
Environmental Considerations .....	4
Value Considerations.....	5
Measures to Minimize Risk.....	5
Next Steps.....	6
Other Information .....	6
Science Evaluation.....	7
1.0 The Active Ingredient, Its Properties and Uses .....	7
1.1 Identity of the Active Ingredient .....	7
1.2 Physical and Chemical Properties of the Active Ingredients and End-Use Product ....	7
1.3 Directions for Use.....	9
1.4 Mode of Action.....	9
2.0 Methods of Analysis.....	9
2.1 Methods for Analysis of the Active Ingredient .....	9
2.2 Method for Formulation Analysis .....	9
2.3 Methods for Residue Analysis.....	9
3.0 Impact on Human and Animal Health.....	9
3.1 Toxicology Summary .....	9
3.2 Occupational and Residential Risk Assessment.....	11
3.2.1 Toxicological Reference Values.....	11
3.2.2 Occupational Exposure and Risk.....	11
3.2.3 Residential Exposure and Risk Assessment .....	12
3.3 Food Residues Exposure Assessment.....	13
3.3.1 Residues in Plant and Animal Foodstuffs.....	13
3.3.2 Dietary Risk Assessment .....	13
3.3.3 Maximum Residue Limits.....	14
4.0 Impact on the Environment .....	14
4.1 Fate and Behaviour in the Environment .....	14
4.2 Environmental Risk Characterization.....	14
4.2.1 Risks to Terrestrial Organisms.....	14
5.0 Value.....	17
6.0 Pest Control Product Policy Considerations.....	18
6.1 Toxic Substances Management Policy Considerations.....	18
6.2 Formulants and Contaminants of Health or Environmental Concern .....	18
7.0 Summary.....	19
7.1 Human Health and Safety.....	19
7.2 Environmental Risk .....	20
7.3 Value.....	20
8.0 Proposed Regulatory Decision .....	20

List of Abbreviations .....	21
Appendix I Tables and Figures .....	23
Table 1 Toxicity Profile of Saltro Containing Pydiflumetofen .....	23
Table 2 Exposure and Risk Estimates to Saltro for Workers in Commercial Seed Treatment Facilities and Mobile Treaters .....	24
Table 3 Exposure and Risk Estimate to Workers Using Saltro to Treat and Plant Soybean Seeds On-Farm .....	25
Table 4 Exposure and Risk Estimates to Workers Planting Seed Treated Commercially with Saltro .....	25
Table 5 Screening Level Risk Assessment for Pollinator Exposure to Seed Treated with Pydiflumetofen .....	25
Table 6 Screening Level Risk Assessment for Birds and Mammals .....	26
Table 7 List of Supported Uses .....	27
References .....	28

# Overview

## Proposed Registration Decision for Pydiflumetofen

Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the [Pest Control Products Act](#), is proposing registration for the sale and use of Pydiflumetofen Technical and Saltro, containing the technical grade active ingredient pydiflumetofen, as a seed treatment fungicide to suppress seed-borne blackleg on rapeseed, including canola (Crop Subgroup 20A) and to control early season infection by *Fusarium virguliforme* on soybean.

Pydiflumetofen is currently registered as a foliar treatment on various field food and feed crops, greenhouse food and non-food crops, outdoor ornamentals and turf for the control and suppression of certain diseases. For details, see Proposed Registration Decision PRD2018-06, *Pydiflumetofen*, and Registration Decision RD2018-08, *Pydiflumetofen*.

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

This Overview describes the key points of the evaluation, while the Science Evaluation provides detailed technical information on the human health, environmental and value assessments of pydiflumetofen and Saltro.

## 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<sup>1</sup> 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<sup>2</sup> 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.

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

<sup>2</sup> "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."

These methods and policies also consider the nature of the effects observed and the uncertainties when predicting the impact of pesticides. For more information on how the Health Canada regulates pesticides, the assessment process and risk-reduction programs, please visit the Pesticides section of the [Canada.ca](http://Canada.ca) website.

Before making a final registration decision on pydiflumetofen and Saltro, Health Canada's PMRA will consider any comments received from the public in response to this consultation document.<sup>3</sup> Health Canada will then publish a Registration Decision<sup>4</sup> on pydiflumetofen and Saltro, which will include the decision, the reasons for it, a summary of comments received on the proposed registration decision and Health Canada's response to these comments.

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

## What Is Pydiflumetofen?

Pydiflumetofen is a broad-spectrum fungicide that is registered in Canada in several end-use products as the lone active ingredient or pre-mixed with other active ingredients. These products are applied as foliar treatments on various crops, ornamentals and turf grass to control or suppress certain diseases. Pydiflumetofen inhibits spore germination, mycelial growth and sporulation of the fungus on the leaf surface. The current application is for seed treatment use in rapeseed, including canola (Crop Subgroup 20A) and soybean.

## Health Considerations

### Can Approved Uses of Pydiflumetofen Affect Human Health?

**Saltro, containing pydiflumetofen, is unlikely to affect your health when used according to proposed label directions.**

Potential exposure to pydiflumetofen may occur through the diet (food and drinking water), when handling and applying the end-use products, or when handling and planting treated seeds. 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 selected to protect the most sensitive human population (for example, children and nursing mothers). As such, sex and gender are taken into account in the risk assessment. Only uses for which the exposure is well below levels that cause no effects in animal testing are considered acceptable for registration.

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<sup>3</sup> "Consultation statement" as required by subsection 28(2) of the *Pest Control Products Act*.

<sup>4</sup> "Decision statement" as required by subsection 28(5) of the *Pest Control Products Act*.

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

In laboratory animals, pydiflumetofen was of low acute toxicity by the oral, dermal, and inhalation routes of exposure. Pydiflumetofen was minimally irritating to the eyes and non-irritating to the skin. It did not cause an allergic skin reaction.

The acute toxicity of the end-use product Saltro containing pydiflumetofen, was low via the oral route of exposure and assumed to be low via the dermal route based on the results of the oral study. Saltro was of slight toxicity via the inhalation route of exposure; consequently, the signal word and hazard statement “CAUTION – POISON” are required on the label. It was non-irritating to the eyes and skin, and did not cause an allergic skin reaction.

Registrant-supplied short- and long-term (lifetime) animal toxicity tests were assessed for the potential of pydiflumetofen to cause neurotoxicity, chronic toxicity, cancer, reproductive and developmental toxicity, genetic damage, and various other effects. The most sensitive endpoints for risk assessment were effects on body weight, liver, activity level, and behaviour. There was no evidence that pydiflumetofen damaged genetic material; however, it did cause liver tumours in mice. There was some evidence that the young animal was more sensitive to pydiflumetofen than the adult animal. The risk assessment protects against these and any other potential effects by ensuring that the level of exposure to humans is well below the lowest dose level at which these effects occurred in animal tests.

## **Residues in Water and Food**

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

Acute dietary (food plus drinking water) intake estimates for the general population and all population subgroups were less than 8.5% of the acute reference dose, and are not of health concern. The highest exposed subpopulation was children 3–5 years old.

Aggregate dietary intake estimates (food plus drinking water) revealed that the general population and children (1–2 years old), the subpopulation which would ingest the most pydiflumetofen relative to body weight, are expected to be exposed to less than 30% of the acceptable daily intake. Based on these estimates, the chronic (cancer and non-cancer) dietary risk from pydiflumetofen is not of concern for all population sub-groups.

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 at the established MRL does not pose an unacceptable health risk.

Residue trials conducted throughout Canada and the United States using pydiflumetofen on soybeans and rapeseed (Crop Subgroup 20A) are acceptable. No changes are required to the established pydiflumetofen MRLs regulated under the *Pest Control Products Act* based on the review of the data.

### **Risks in Residential and Other Non-Occupational Environments**

A residential assessment was not required since these products are not permitted for use by residential handlers or for use in residential areas.

### **Occupational Risks From Handling Saltro**

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

Workers in commercial seed treatment facilities, mobile treaters, on-farm treaters and planters and those planting and handling seed treated with Saltro can come into direct contact with pydiflumetofen through residues on the skin and through inhalation. Therefore, workers treating seeds in commercial seed treatment facilities or mobile treaters must use a closed-transfer system only, including closed mixing, loading, calibrating and closed treatment equipment. Workers cleaning or repairing seed treatment equipment must wear chemical-resistant coveralls over a long-sleeved shirt, long pants, chemical-resistant gloves, socks, chemical-resistant footwear and a dust mask. All other workers in a seed treatment facility must wear coveralls over a long-sleeved shirt, long pants, chemical-resistant gloves, socks, shoes and a dust mask. Workers completing on-farm seed treatment must wear a long-sleeved shirt, long pants, chemical-resistant gloves, socks and shoes. Workers planting treated seed must wear a long-sleeved shirt, long pants, chemical-resistant gloves, shoes and socks. Closed-cab planting is required for soybean seed.

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 Pydiflumetofen Is Introduced Into the Environment?**

**When pydiflumetofen is used according to the label directions, the risks to the environment are acceptable.**

Pydiflumetofen can enter the environment when it is applied as a fungicide seed treatment product to control or suppress plant diseases. Birds and mammals may be exposed to pydiflumetofen when consuming treated seeds, while bees may be exposed to dust generated during the seeding process. When pydiflumetofen is used according to the label directions as a seed treatment on soybean and all crops within Crop Subgroup 20A, including canola, the risk to pollinators and birds are acceptable.



Pydiflumetofen applied as a seed treatment may pose a risk to non-target wild mammals. As such, the label will require a precautionary statement about the risk to wild mammals and that spilled and exposed seeds must be incorporated into the soil or cleaned up from the soil surface.

## **Value Considerations**

### **What Is the Value of Saltro?**

**Saltro will provide Canadian users with a new mode of action on rapeseed, including canola (Crop Subgroup 20A) and a new product on soybean to manage two important diseases.**

Saltro is effective for suppressing seed-borne blackleg on rapeseed, including canola (Crop Subgroup 20A) and for controlling early season infection by *Fusarium virguliforme* (the pathogen of sudden death syndrome) on soybean.

### **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 Pydiflumetofen Technical and Saltro to address the potential risks identified in this assessment are as follows.

#### **Key Risk-Reduction Measures**

##### **Human Health**

As there can be direct contact with pydiflumetofen on the skin or through inhalation of dust, workers treating seed with pydiflumetofen in commercial facilities (including mobile treaters) or performing clean-up and repair activities must wear chemical-resistant coveralls over a long-sleeved shirt, long pants, chemical-resistant gloves, socks, and chemical-resistant footwear and a dust mask. Workers bagging, sewing or stacking seed treated with pydiflumetofen in commercial facilities must wear coveralls over a long-sleeved shirt, long pants, chemical-resistant gloves, socks, and shoes and a dust mask. On-farm treaters and planters must wear a long-sleeved shirt, long pants, shoes, socks and chemical-resistant gloves. Furthermore, commercial seed treatment is restricted to closed-transfer systems. Closed-cab tractors for planting soybean seed are required.

##### **Environment**

Standard label statements are required to inform users of the toxicity of pydiflumetofen to wild mammals.

Standard statements on the label and the treated seed tags are required to inform users that spilled or exposed seeds must be incorporated into the soil or cleaned up from soil surface.

## **Next Steps**

Before making a final registration decision on pydiflumetofen and Saltro, Health Canada's PMRA will consider any comments received from the public in response to this consultation document. Health Canada will accept written comments on this proposal up to 45 days from the date of publication of this document. Please forward all comments to PMRA Publications (contact information on the cover page of this document). Health Canada will then publish a Registration Decision, which will include its decision, the reasons for it, a summary of comments received on the proposed decision and Health Canada's response to these comments.

## **Other Information**

When the Health Canada makes its registration decision, it will publish a Registration Decision on Pydiflumetofen and Saltro (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

## Pydiflumetofen and Saltro

### 1.0 The Active Ingredient, Its Properties and Uses

#### 1.1 Identity of the Active Ingredient

**Active substance** Pydiflumetofen

**Function** Fungicide

#### Chemical name

**1. International Union of Pure and Applied Chemistry (IUPAC)** 3-(difluoromethyl)-*N*-methoxy-1-methyl-*N*-[(*RS*)-1-methyl-2-(2,4,6-trichlorophenyl)ethyl]pyrazole-4-carboxamide

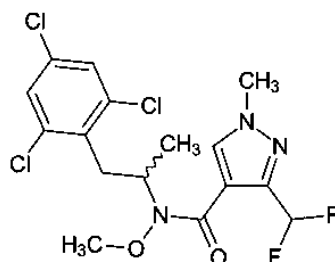
**2. Chemical Abstracts Service (CAS)** 3-(difluoromethyl)-*N*-methoxy-1-methyl-*N*-[1-methyl-2-(2,4,6-trichlorophenyl)ethyl]-1*H*-pyrazole-4-carboxamide

**CAS number** 1228284-64-7

**Molecular formula** C<sub>16</sub>H<sub>16</sub>Cl<sub>3</sub>F<sub>2</sub>N<sub>3</sub>O<sub>2</sub>

**Molecular weight** 426.7

#### Structural formula



**Purity of the active ingredient** 98.7%

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

#### Technical Product—Pydiflumetofen Technical

Property	Result
Colour and physical state	Off-white solid
Odour	Odourless
Melting range	112.7 °C

Property	Result																		
Boiling point or range	Decomposes on heating from approximately 283 °C																		
Density	1.55 g/cm <sup>3</sup>																		
Vapour pressure	1.84 × 10 <sup>-7</sup> Pa (20°C); 5.30 × 10 <sup>-7</sup> Pa (25°C)																		
Ultraviolet (UV)-visible spectrum	<table border="1"> <thead> <tr> <th>pH</th> <th>λ<sub>max</sub> (nm)</th> <th>ε (L.M<sup>-1</sup>cm<sup>-1</sup>)</th> </tr> </thead> <tbody> <tr> <td rowspan="2">Acidic</td> <td>230</td> <td>18 323</td> </tr> <tr> <td>295</td> <td>59.5</td> </tr> <tr> <td rowspan="2">Basic</td> <td>230</td> <td>18 633</td> </tr> <tr> <td>295</td> <td>53.2</td> </tr> <tr> <td rowspan="2">Neutral</td> <td>230</td> <td>18 777</td> </tr> <tr> <td>295</td> <td>1290</td> </tr> </tbody> </table>	pH	λ <sub>max</sub> (nm)	ε (L.M <sup>-1</sup> cm <sup>-1</sup> )	Acidic	230	18 323	295	59.5	Basic	230	18 633	295	53.2	Neutral	230	18 777	295	1290
pH	λ <sub>max</sub> (nm)	ε (L.M <sup>-1</sup> cm <sup>-1</sup> )																	
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Neutral	230	18 777																	
	295	1290																	
Solubility in water at 25 °C	1.5 mg/L																		
Solubility in organic solvents at 25 °C	<table border="1"> <thead> <tr> <th>Solvent</th> <th>Solubility (g/L)</th> </tr> </thead> <tbody> <tr> <td>Dichloromethane</td> <td>&gt; 500</td> </tr> <tr> <td>Acetone</td> <td>220</td> </tr> <tr> <td>Ethyl acetate</td> <td>130</td> </tr> <tr> <td>Toluene</td> <td>67</td> </tr> <tr> <td>Methanol</td> <td>26</td> </tr> <tr> <td>Octanol</td> <td>7.2</td> </tr> <tr> <td>Hexane</td> <td>0.270</td> </tr> </tbody> </table>	Solvent	Solubility (g/L)	Dichloromethane	> 500	Acetone	220	Ethyl acetate	130	Toluene	67	Methanol	26	Octanol	7.2	Hexane	0.270		
Solvent	Solubility (g/L)																		
Dichloromethane	> 500																		
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Ethyl acetate	130																		
Toluene	67																		
Methanol	26																		
Octanol	7.2																		
Hexane	0.270																		
<i>n</i> -Octanol-water partition coefficient ( <i>K</i> <sub>ow</sub> )	<i>K</i> <sub>ow</sub> = 7000 Log <i>K</i> <sub>ow</sub> = 3.8																		
Dissociation constant (p <i>K</i> <sub>a</sub> )	Not applicable; no dissociation in the pH range of 2.0–12.0																		
Stability (temperature, metal)	Stable for 2 weeks at 54 °C; stable for 2 weeks in the presence of metals (aluminum flakes, iron granules) and metal ions (aluminum acetate and iron acetate) at 20 °C and 40 °C.																		

### End-Use Product—Saltro

Property	Result
Colour	white
Odour	slight aromatic odour
Physical state	Liquid
Formulation type	Suspension
Label concentration	Pydiflumetofen 500 g/L
Container material and description	Plastic jug and tote, 1 to 1050 L
Density	1.19 g/mL at 20 °C
pH of 1% dispersion in water	7.5–9.5 (1% in water)
Oxidizing or reducing action	No oxidizing or reducing action
Storage stability	Stable for 2 weeks when stored at 54 °C in HDPE packaging

Property	Result
Corrosion characteristics	Non-corrosive to the packaging material
Explosibility	Not explosive

### 1.3 Directions for Use

Saltro is applied as a seed treatment for the control of early season infection by *Fusarium virguliforme* (the causal agent of sudden death syndrome) on soybean at 100 mL/100 kg seed, or for the suppression of seed and air-borne blackleg on rapeseed, including canola (Crop Subgroup 20A) at 80 mL/100 kg seed. Saltro may be mixed with other fungicide, insecticide or nematocide seed treatment products.

### 1.4 Mode of Action

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

## 2.0 Methods of Analysis

### 2.1 Methods for Analysis of the Active Ingredient

Please refer to PRD2018-06, *Pydiflumetofen*, for the methods for analysis of the active ingredient.

### 2.2 Method for Formulation Analysis

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

### 2.3 Methods for Residue Analysis

Please refer to PRD2018-06, *Pydiflumetofen*, for the methods for residue analysis.

## 3.0 Impact on Human and Animal Health

### 3.1 Toxicology Summary

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

A detailed review of the toxicity studies conducted previously with pydiflumetofen was published in PRD2018-06, *Pydiflumetofen*. No new toxicological data were submitted and published scientific literature was searched, but did not reveal any new information. The scientific quality of the data is acceptable and the database is considered adequate to characterize

the potential health hazards associated with pydiflumetofen. The toxicological reference values that were previously established in PRD2018-06, *Pydiflumetofen*, remain unchanged. Only consideration of cumulative risk assessment was required in the context of this major new use review.

The results of acute toxicity studies conducted with Saltro are summarized in Appendix I, Table 1. Saltro was of low acute toxicity via the oral route and of slight acute toxicity via the inhalation route in rats. Based on the results of the oral study, low acute dermal toxicity was assumed. Saltro was non-irritating to the eyes and skin of rabbits, and was not a dermal sensitizer in a local lymph node assay in mice.

After repeated oral dosing with pydiflumetofen, the liver was the primary target of toxicity in all species tested. Decreases in body weight and food consumption were frequently observed. In rats and mice, the key treatment-related effects were changes in liver metabolism, which led to altered clinical chemistry parameters and increased hypertrophy in the liver. In mice, oncogenicity was observed in the liver. In dogs, liver and thyroid weights were increased. The available data supported a non-genotoxic, threshold mode of action for the development of these tumours. In the two-generation reproductive toxicity study, the first generation had slightly reduced body weights in the absence of maternal toxicity, however the same effect was not present in the second generation. No evidence of sensitivity was noted in gavage developmental toxicity studies in rats or rabbits. In two acute oral neurotoxicity studies, female rats exhibited transient changes to activity level and behaviour.

Results of the toxicology studies conducted on laboratory animals with pydiflumetofen and toxicology reference values for use in the human health risk assessment are summarized in PRD2018-06, *Pydiflumetofen*, Appendix I, Tables 3 and 4, respectively.

### **Incident Reports**

As of 24 September 2019, no human or domestic animal incident reports involving pydiflumetofen had been submitted to the PMRA.

### **Cumulative Assessment**

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

Other effects on the liver and body weight are considered to represent a more generalized toxicity, and a common mechanism of toxicity has not been identified. Therefore, a cumulative health risk assessment is not required at this time.

## **3.2 Occupational and Residential Risk Assessment**

### **3.2.1 Toxicological Reference Values**

Occupational exposure to pydiflumetofen is characterized as short- to intermediate-term in duration and is predominantly by the dermal and inhalation routes for treaters (commercial, mobile and on-farm), baggers, sewers, stackers, cleaners and planters.

#### **3.2.1.1 Dermal Absorption**

The dermal absorption value for pydiflumetofen of 50% was previously established in PRD2018-06, *Pydiflumetofen*.

### **3.2.2 Occupational Exposure and Risk**

#### **3.2.2.1 Dust-off Study**

The dust off from seeds treated with Saltro were less than the average dust generated from the seeds treated with the products used in the surrogate exposure studies. This supports the use of the surrogate exposure studies without underestimating the exposures to workers handling seeds treated with Saltro.

#### **3.2.2.2 Commercial Treater (including Mobile Treater) Exposure and Risk Assessment**

Pydiflumetofen is proposed as a seed treatment of canola and soybean in commercial facilities. Workers in these facilities have the potential for exposure to pydiflumetofen while treating seed in commercial seed treatment facilities and by mobile treaters as well as during bagging, sewing and stacking of treated seed and during clean-up and repair of treatment equipment. Occupational exposure to Saltro is characterized as short-term for mobile treaters and farmers and intermediate-term for seed treatment workers and occurs predominately via the dermal and inhalation routes.

To estimate exposure to treaters and other workers in commercial facilities a canola passive dosimetry study was used. This study was conducted using a closed-transfer system. Exposure to workers in commercial treatment facilities is also considered as being representative of that of mobile treaters because of the larger seed throughput capacities in commercial facilities. The unit exposure values for treaters and cleaners were based on subjects wearing chemical-resistant coveralls over a single layer (long-sleeved shirt and long pants) and chemical-resistant gloves.

For workers bagging, sewing, stacking and driving forklifts, unit exposure values were based on subjects wearing cotton coveralls over a single layer (long-sleeved shirt and long pants) and chemical-resistant gloves.

Dermal and inhalation exposures were calculated by combining unit exposure values with the maximum application rate and the AHETF throughput values for canola and soybean. Exposures were normalized to mg/kg bw/day by using 80 kg adult body weight. The calculated margin of exposure (MOE) was greater than the target MOE of 100 for both dermal and inhalation routes combined (Appendix I, Table 2). As such, no health risks of concern are expected for workers in commercial treatment facilities or mobile treaters provided the PPE recommended on the proposed label is worn.

### **3.2.2.3 On-Farm Treater and Planter Exposure and Risk Assessment**

Exposures to workers treating and planting soybean seeds on-farm was represented through a surrogate passive dosimetry study which monitored workers wearing a single layer and chemical-resistant gloves. Exposure was estimated by combining the application rate, seeding rate for soybean and the maximum area planted per day with unit exposure values. The exposure and risk estimates for on-farm treating and planting are presented in Appendix I, Table 3. As the calculated MOE for the dermal and inhalation routes combined is greater than the target MOE of 100, there are no health risks of concern for on-farm treaters, planters or anyone handling treated seed when wearing a long-sleeved shirt, long pants, chemical-resistant gloves, socks and shoes. As the dermal and inhalation unit exposure values are derived from a study which used closed-cab tractors, this restriction has been added to the label.

### **3.2.2.4 Planting of Commercially Treated Seed Exposure and Risk Assessment**

Exposure to workers handling and planting commercially treated canola and soybean seed was represented through a surrogate passive dosimetry study which monitored workers wearing a single layer and chemical-resistant gloves. Exposure was estimated by combining the application rate, seeding rate for canola and soybean, and the maximum area planted per day with the unit exposure values. The exposure and risk estimated for planting commercially treated seed are presented in Appendix I, Table 4. As the calculated MOE for the dermal and inhalation routes combined is greater than the target MOE of 100, there are no health risks of concern for planters or anyone handling treated seed when wearing a long-sleeved shirt, long pants, chemical-resistant gloves, socks and shoes. As the dermal and inhalation unit exposure values are derived from a study which used closed-cab tractors, this restriction has been added to the label for soybeans. However, given the magnitude of the calculated MOE for canola, a closed-cab is not required for planting canola seed.

## **3.2.3 Residential Exposure and Risk Assessment**

### **3.2.3.1 Handler Exposure and Risk**

As Saltro is proposed as a commercial class seed treatment product, a residential handler risk assessment is not required.

### **3.2.3.2 Postapplication Exposure and Risk**

As Saltro is not proposed for use in residential areas, a postapplication residential risk assessment is not required.



### **3.2.3.3 Bystander Exposure and Risk**

Bystander exposure is expected to be negligible since the potential for drift is expected to be minimal and a label restriction to minimize drift has been added to the proposed label.

## **3.3 Food Residues Exposure Assessment**

PRD2018-06, *Pydiflumetofen*, provides a summary of data reviewed and the rationale for the regulatory decision. No new data were submitted with the current petition. Previously reviewed data, summarized under PRD2018-06, *Pydiflumetofen*, were used to support the seed treatment use of pydiflumetofen in/on soybeans and on all crops within Crop Subgroup 20A. Please refer to PRD2018-06, *Pydiflumetofen*, for further details.

### **3.3.1 Residues in Plant and Animal Foodstuffs**

Please refer to PRD2018-06, *Pydiflumetofen*, for residues in plant and animal foodstuffs.

### **3.3.2 Dietary Risk Assessment**

A chronic (cancer and non-cancer) dietary risk assessment was conducted using the Dietary Exposure Evaluation Model (DEEM-FCID™, Version 4.02, 05-10-c) program which incorporates food consumption data from the National Health and Nutritional Examination Survey, What We Eat in America (NHANES/WWEIA) dietary survey for the years 2005–2010 available through CDC's National Center for Health Statistics (NCHS).

#### **3.3.2.1 Acute Dietary Exposure Results and Characterization**

The following assumptions were applied in the basic acute analysis for pydiflumetofen: 100% crop treated, default processing factors, residues in/on crops and animal commodities at MRL levels. The basic acute dietary exposure (food alone) for all supported pydiflumetofen registered commodities is estimated to be 6.6% (0.066315 mg/kg bw/day) of the acute reference dose (ARfD) for the general population (95<sup>th</sup> percentile, deterministic). Aggregate exposure from food and drinking water is not of health concern. Specifically 7.0% (0.070362 mg/kg bw/day) of the ARfD was obtained for the general population and 8.5% of the ARfD was obtained for children 3–5 years old.

#### **3.3.2.2 Chronic Dietary Exposure Results and Characterization**

For the chronic dietary exposure assessment, MRL-level residues were used for all domestic and imported crops and livestock commodities. It was assumed that 100% of the crops were treated. The basic chronic dietary exposure from all supported pydiflumetofen food uses (alone) for the total population, including infants and children, and all representative population subgroups is 17.7% of the acceptable daily intake. Aggregate exposure from food and water is not of health concern. The PMRA estimates that chronic dietary exposure to pydiflumetofen from food and water is 21.1% (0.018983 mg/kg bw/day) of the acceptable daily intake (ADI) for the total population. The highest exposure and risk estimate is for children of 1–2 years old at 29.7% (0.026694 mg/kg bw/day) of the ADI.

### 3.3.3 Maximum Residue Limits

The pydiflumetofen MRLs regulated under the *Pest Control Products Act* may be found on Health Canada's [MRL Database](#).

## 4.0 Impact on the Environment

### 4.1 Fate and Behaviour in the Environment

The fate and environmental behaviour of pydiflumetofen has been previously assessed. For full details, please refer to PRD2018-06, *Pydiflumetofen*.

### 4.2 Environmental Risk Characterization

An environmental risk assessment for foliar-applied pydiflumetofen has been previously completed for use on agricultural and greenhouse food crops, greenhouse and outdoor-grown ornamentals, and on turf. For full details see PRD2018-06, *Pydiflumetofen*.

The proposed maximum seed treatment rate for Saltro is on soybean at 0.0756 mg a.i./seed (63 g a.i./ha). This rate is much lower than the registered foliar use pattern for other pydiflumetofen end-use products, but the application scenario and the exposure pathway are different. Applying pydiflumetofen as a seed treatment is expected to have lower exposure to aquatic environments compared with applying as a foliar application.

As Saltro is adhesively coated on the surface of the seeds during treatment, the drift of dust during planting of treated seed is expected to be reduced. When seeds are incorporated into the soil or otherwise cleaned-up from the soil surface, the potential for pydiflumetofen to reach off-site non-target organisms such as terrestrial plants and aquatic organisms is significantly reduced. In addition, risk to off-site non-target organisms at the higher foliar application rate was acceptable in the previous risk assessment. Therefore, when the foliar application rate is compared to the lower seed treatment rate, risk to non-target organisms off-site is also expected to be acceptable.

Terrestrial organisms such as birds and wild mammals could be exposed to pydiflumetofen from ingesting the treated seed. Pollinators could be exposed to the dust generated during the planting of treated seed. As a result, the environmental risk assessment for the pydiflumetofen seed treatment, Saltro, will be limited to the following terrestrial organisms: pollinators, birds, and mammals. These organism groups were assessed because potential exposure was expected based on the exposure pathway when pydiflumetofen is applied as a seed treatment.

#### 4.2.1 Risks to Terrestrial Organisms

**Pollinators:** Pydiflumetofen is not systemic. Therefore, pollinators are not expected to be exposed to residues of pydiflumetofen in the pollen and nectar of plants grown from treated seed. Pollinators may be exposed to pydiflumetofen contaminated dust generated from seeding equipment.

Adult bee pollinators may come in contact with or ingest dust deposited on foraging sources after planting seed treated with pydiflumetofen. Since the toxicity to adult bees was previously assessed as acceptable for the registered foliar application method, the risk from exposure to contaminated dust generated from seeding equipment is acceptable when considering that the application rate of a seed treatment is much lower than the foliar application rate. However, a risk to bee larvae was identified for Saltro at the screening level (Appendix I, Table 5).

A screening level risk that exceeded the level of concern for bee larvae was seen in both the original risk assessment for pollinators based on foliar applications, as well as the proposed seed treatment use of pydiflumetofen. In the original risk assessment, two higher tiered semi-field (Tier II tunnel) studies applying a foliar end-use product during bloom were used to further characterize the risk. No colony-level effects at any measured endpoint or a dose-response relationship were seen in either of the two studies. The studies were conducted at a maximum foliar rate of 200 g a.i./ha, which is more than three times higher than the maximum proposed seed treatment rate of 63 g a.i./ha. Since exposure to bee larvae from dust-off is expected to be lower than the exposure resulting from direct foliar application to blooming, attractive crops; the risks to adult and larval pollinators from the use of pydiflumetofen as a seed treatment is also determined to be acceptable.

**Birds:** Birds may be exposed to pydiflumetofen through ingestion of seeds treated with Saltro.

The screening level risk assessment for seed treatment products uses a conservative approach by assuming that the daily diet of birds consists of 100% treated seed. To represent the crops in Crop Subgroup 20A, canola is used in this risk assessment since it is expected to have the largest use pattern of this crop grouping.

The calculated risk quotients (RQs) from the screening level (Appendix I, Table 6) showed that under this conservative assumption, acute oral risk from soybean and canola seed is acceptable to all sizes of birds. The risk of reproductive effects to large birds exposed to canola treated seed was also acceptable.

However, the level of concern for reproductive effects was exceeded for small, medium and large birds exposed to soybean treated seed, and for small and medium sized birds exposed to canola treated seed. Therefore, the risk was further characterized by looking at the number of seeds that would be needed to be consumed per day to reach the effects endpoints, the size of the forage area needed to find enough seeds to reach an adverse effect, and bird biology (Appendix I, Table 6).

### **Soybean**

Soybean seeds are not an attractive food source or palatable for most birds. They are also too large for small birds to consume. Therefore, the reproductive risk to small birds is acceptable because the likelihood of small birds consuming large-sized, unpalatable treated seed is very minimal. Medium- and large-sized birds need to consume 36 and 356 seeds/day and forage over a minimum area of 76 and 762 m<sup>2</sup>, respectively, to reach a reproductive risk that exceeded the level of concern.

It is very unlikely that a medium- or large-sized bird would consume only treated seed, that is considered unpalatable, over a large area and not fly to a new foraging location. The minimal risk to birds can be further mitigated with the requirement to clean up spilled or exposed seeds. Therefore, the reproductive risk to medium and large birds is acceptable.

### **Canola**

Small- and medium-sized birds need to consume a minimum of 243 and 1217 seeds/day respectively, to reach a reproductive risk that exceeded the level of concern. It is very unlikely that a small- or medium-sized bird would consume such a large amount of treated seed. The minimal risk to birds can be further mitigated with the requirement to clean up spilled or exposed seeds. Therefore, the reproductive risk to small- and medium-sized birds is acceptable.

Overall, the risk to birds from the use of pydiflumetofen as a seed treatment on soybean and Crop Subgroup 20A is acceptable.

**Mammals:** Mammals may be exposed to pydiflumetofen through ingestion of seeds treated with Saltro.

The screening level risk assessment for seed treatment products uses a conservative approach by assuming that the daily diet of mammals consists of 100% treated seed. To represent the crops in Crop Subgroup 20A, canola is used in this risk assessment since it is expected to have the largest use pattern of this crop grouping.

The calculated RQs from the screening level (Appendix I, Table 6) showed that under this conservative assumption, risk is acceptable to large mammals from acute oral and reproductive exposure. For canola seed treatment the risk to medium-sized mammals was acceptable from acute exposure.

However, the level of concern for both acute and reproductive effects on small mammals was exceeded for both soybean and canola. For medium-sized mammals exposed to canola, the reproductive effects were exceeded, and for soybean, both the acute oral and reproductive effects exceeded the level of concern. Therefore, the risk was further characterized by looking at the number of seeds needed to reach an endpoint, the size of the forage area needed to reach an adverse effect, and mammalian biology (Appendix I, Table 6).

### **Soybean**

Small- and medium-sized mammals need to consume a minimum of 7 and 17 seeds/day respectively, to reach a risk that exceeded the level of concern. Considering that the screening level assessment is based on an average-sized small (15 g) and medium (35 g) mammal, and that each soybean seed weighs 0.1 g; small- and medium-sized mammals would need to consume 5% (0.7 and 1.7 g worth of seed, respectively) of their body size to reach to reach an effects endpoint. Therefore, a risk to mammals may still exceed the level of concern.

## **Canola**

Small- and medium-sized mammals need to consume a minimum of 677 and 1579 seeds/day, respectively, to reach a risk that exceeded the level of concern. It is very unlikely that a small- or medium-sized mammal would consume such a large amount of treated seeds. Therefore, the risk to small- and medium-sized mammals is acceptable.

Overall, the risks to large mammals are acceptable. Risks to small- and medium-sized mammals exceed the level of concern after further characterization. Therefore standard mammalian hazard label language is recommended, along with the requirement that any spilled or exposed seeds must be incorporated into the soil or otherwise cleaned-up from the soil surface.

## **Overall conclusion about potential risks to terrestrial organisms**

Overall, the risk to pollinators and birds from the use of pydiflumetofen as a seed treatment is acceptable. Pydiflumetofen may pose a risk to wild mammals; however, the risk to wild mammals can be mitigated with hazard statements and a requirement to clean up spilled or exposed seeds. Therefore, the risk to wild mammals is acceptable with these mitigation measures.

## **Incident Reports**

Environmental incident reports are obtained from two main sources, the Canadian Pesticide Incident Reporting System (including both mandatory reporting from the registrant and voluntary reporting from the public and other government departments) and the USEPA Ecological Incident Information System (EIIS). Specific information regarding the mandatory reporting system regulations that came into force 26 April 2007 under the *Pest Control Products Act* can be found on the Report a Pesticide Incident page of the Canada.ca website (<http://www.hc-sc.gc.ca/cps-spc/pest/part/protect-proteger/incident/index-eng.php>).

As of 24 September 2019, no environmental incidents involving pydiflumetofen were reported to the PMRA.

## **5.0 Value**

The availability of Saltro will provide Canadian users with a new mode of action on rapeseed, including canola (Crop Subgroup 20A) and a new product on soybean to manage two economically important fungal diseases. While there are multiple products registered in Canada for the control or suppression of blackleg on rapeseeds and early season *Fusarium virguliforme* infection on soybean, the value of Saltro is that it has a long period of duration, suppressing seed-borne and air-borne blackleg pathogen up to 109 days after planting.

Efficacy data from field trials and a controlled environment study demonstrated that Saltro can be expected to control early season *F. virguliforme* infection on soybean, and suppress blackleg on rapeseeds.

As no phytotoxicity or other adverse effects were observed on either soybean or canola in the trial studies, application of Saltro is not expected to result in injury to soybean and rapeseed when used according to label directions. Details of the supported uses are provided in Appendix 1, Table 7.

## **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, that is, those that meet all four criteria outlined in the policy: persistent (in air, soil, water and/or sediment), bio-accumulative, primarily a result of human activity and toxic as defined by the *Canadian Environmental Protection Act*. The *Pest Control Products Act* requires that the TSMP be given effect in evaluating the risks of a product.

Pydiflumetofen and its transformation products have been previously assessed in accordance with DIR99-03<sup>5</sup> and evaluated against the Track 1 criteria. The PMRA reached the conclusion that pydiflumetofen and its transformation products do not meet all of the TSMP Track 1 criteria. Please refer to PRD2018-06, *Pydiflumetofen* for further information on the TSMP assessment.

### **6.2 Formulants and Contaminants of Health or Environmental Concern**

During the review process, contaminants in the active ingredient as well as formulants and contaminants in the end-use products are compared against Parts 1 and 3 of the List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern.<sup>6</sup> The list is used as described in NOI2005-01<sup>7</sup> and is based on existing policies and regulations, including the Toxic Substances Management Policy<sup>5</sup> and DIR2006-02,<sup>8</sup> 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 conclusion that pydiflumetofen and its end-use product, Saltro, do not contain any formulants or contaminants identified in the *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern*.

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<sup>5</sup> PMRA Regulatory Directive DIR99-03, *The Pest Management Regulatory Agency's Strategy for Implementing the Toxic Substances Management Policy*.

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

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

<sup>8</sup> PMRA's Regulatory Directive DIR2006-02, *Formulants Policy and Implementation Guidance Document*.

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

## **7.0 Summary**

### **7.1 Human Health and Safety**

The toxicology database submitted for pydiflumetofen is adequate to characterize the potential toxic effects that may result from exposure. Pydiflumetofen is not selectively neurotoxic. In short-term and chronic studies on laboratory animals, the primary target was the liver. The key effects were decreases in body weight and changes in clinical chemistry and liver histopathology. There was also evidence of liver carcinogenicity in mice after longer-term dosing. A non-genotoxic, threshold mode of action for the development of these tumours was supported and consequently a threshold approach was applied for the cancer risk assessment. Pydiflumetofen did not cause developmental effects in rats or rabbits, and did not cause any adverse effects on reproduction in rats. There was some evidence of increased sensitivity of the offspring; however, concern is low due to the less serious nature of the observed effects. The risk assessment protects against the toxic effects noted above by ensuring that the level of human exposure is well below the lowest dose level at which these effects occurred in animal tests.

Workers in commercial seed treatment facilities, mobile treaters, on-farm workers treating and planting and workers planting and/or handling treated canola and soybean seeds are not expected to be exposed to levels of pydiflumetofen that will result in health risks of concern when used according to label directions. The PPE for commercial treaters, including mobile treaters and cleaners in commercial seed treatment facilities is chemical-resistant coveralls over a long-sleeved shirt, long pants, chemical-resistant gloves, socks, chemical-resistant footwear and a dust mask. Closed transfer systems must be used in commercial facilities. Baggers, sewers, stackers and forklift drivers in commercial seed treatment facilities must wear coveralls over a long-sleeved shirt, long pants, chemical-resistant gloves, socks, shoes and a dust mask. On-farm seed treatment is limited to soybean seed. On-farm treaters and workers handling treated seed must wear a long-sleeved shirt, long pants, chemical-resistant gloves, socks and shoes. Workers planting treated seed must wear a long-sleeved shirt, long pants, chemical-resistant gloves, socks and shoes. A closed-cab tractor must be used when planting treated soybean seed.

Bystander and residential exposure is not of concern.

The nature of the residues in plants and animals is adequately understood. The residue definition for enforcement is pydiflumetofen in plant products and in animal matrices. The proposed seed treatment use of pydiflumetofen on crops within Crop Subgroup 20A and soybeans does not constitute a risk of 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. Based on the review of the data, no changes are required to the following established pydiflumetofen MRLs.



Commodity	Established MRL (ppm)
Rapeseeds (Revised) (Crop Subgroup 20A)	0.9
Dry soybeans	0.4

## 7.2 Environmental Risk

Current environmental assessment methodology was used to conduct a risk assessment of the proposed use of the end-use product Saltro on soybean and crop subgroup 20A as a seed treatment. Using previously evaluated information, it has been determined that when pydiflumetofen is used according to label directions, the risk to aquatic and most terrestrial organisms, including pollinators and birds, is acceptable. Pydiflumetofen may pose a risk to wild mammals; however, the risk to wild mammals can be mitigated with hazard statements and a requirement to clean up spilled or exposed seeds. Therefore, the risk to wild mammals is acceptable with these mitigation measures.

## 7.3 Value

Pydiflumetofen, the active ingredient of Saltro, is effective against early season *Fusarium virguliforme* infection on soybean and seed-borne and air-borne blackleg on rapeseed, including canola (Crop Subgroup 20A) when used in accordance with the label. Saltro can be tank-mixed with other seed treatment pesticides to provide broad-spectrum protection against other diseases, insects or nematodes. The availability of Saltro will provide Canadian users with a new mode of action on rapeseed, including canola and a new product on soybean to manage these important diseases.

## 8.0 Proposed Regulatory Decision

Health Canada's PMRA, under the authority of the *Pest Control Products Act*, is proposing registration for the sale and use of Pydiflumetofen Technical and Saltro, containing the technical grade active ingredient pydiflumetofen, to be used as a seed treatment fungicide to suppress seed-borne blackleg on rapeseed, including canola (Crop Subgroup 20A) and to control early season infection by *Fusarium virguliforme* on soybean.

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



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## List of Abbreviations

↑	increased
↓	decreased
♂	male
♀	female
°C	degree Celsius
a.i.	active ingredient
AD	administered dose
ADI	acceptable daily intake
AHETF	Agriculture Handler Exposure Task Force
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ARfD	acute reference dose
AUC	area under the curve
BQ	7-benzyloxyquinoline
BROD	benzyloxyresorufin O-dealkylase
bw	body weight
bwg	bodyweight gain
CAF	composite assessment factor
CAR	constitutive androstane receptor
CAS	Chemical Abstracts Service
cm	centimetres
C <sub>max</sub>	maximum concentration
CR	chemical-resistant
DEEM-FCID	Exposure Evaluation Model
DIR	Directive
DNA	deoxyribonucleic acid
EEC	Estimated environmental concentration
EIIS	Ecological Incident Information System
F <sub>1</sub>	first generation
fc	food consumption
FDA	<i>Food and Drugs Act</i>
fe	food efficiency
FRAC	Fungicide Resistance Action Committee
g	gram
ha	hectare(s)
HDPE	high-density polyethylene
IUPAC	International Union of Pure and Applied Chemistry
kg	kilogram
K <sub>ow</sub>	<i>n</i> -octanol-water partition coefficient
L	litre
LC <sub>50</sub>	lethal concentration 50%
LD <sub>50</sub>	lethal dose 50%
LLNA	local lymph node assay
LOAEL	lowest observed adverse effect level
m <sup>2</sup>	meter(s) squared

mg	milligram
mL	millilitre
MAS	maximum average score
MAX	maximum
MIN	minimum
MOA	mode of action
MOE	margin of exposure
MRL	maximum residue limit
NCHS	National Center for Health Statistics
NHANES/WWEIA	National Health and Nutritional Examination Survey, What We Eat in America
nm	nanometer
NOAEL	no observed adverse effect level
NOEL	no observed effect level
NOI	Notice of Intent
pH	measure of the acidity or basicity of an aqueous solution
pKa	dissociation constant
PMRA	Pest Management Regulatory Agency
PPE	Personal protective equipment
ppm	parts per million
PRD	Proposed Registration Decision
PROD	pentoxeresorufin O-dealkylase
R <sub>ac</sub>	mean accumulation ratios
RD	Registration Decision
RQ	risk quotient
SDHI	succinate dehydrogenase inhibitor
TCP	trichlorophenol
TSMP	Toxic Substances Management Policy
UDPGT	uridine diphosphate glucuronyltransferase
UF	uncertainty factor
USEPA	United States Environmental Protection Agency
UV	ultraviolet
wt	weight
µg	microgram
µm	micrometre

## Appendix I Tables and Figures

**Table 1 Toxicity Profile of Saltro Containing Pydiflumetofen**

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/PMRA #	Study Results
Acute Oral Toxicity (gavage) Wistar rats PMRA 2888558	LD <sub>50</sub> > 2000 mg/kg bw One death at 5000 mg/kg bw Decreased activity, irritability, hunched back, incoordination, and piloerection were all observed on the day of treatment. All clinical signs cleared by day 3.
Acute Dermal Toxicity PMRA 2888559	Assumed low toxicity based on results of the acute oral toxicity study
Acute Inhalation Toxicity Sprague-Dawley rats PMRA 2888560	LC <sub>50</sub> > 0.51 mg/L There were no mortalities at 0.51 mg/L, though four females were hypoactive and all animals exhibited irregular respiration. All symptoms cleared by day 3.
Eye Irritation New Zealand White Rabbit PMRA 2888561	MAS = 0/110 Non-irritating
Eye Irritation Isolated chicken eye assay PMRA 2888562	Not a severe irritant or a non-irritant
Skin Irritation EpiSkin assay PMRA 2888563	Non-irritant
Skin Irritation New Zealand White Rabbit PMRA 2888564	MAS = 0/8 Non-irritating

Study Type/Animal/PMRA #	Study Results
Skin Sensitization Local lymph node assay CBA/J mice PMRA 2888565	Negative

**Table 2 Exposure and Risk Estimates to Saltro for Workers in Commercial Seed Treatment Facilities and Mobile Treater**

Scenario	kg a.i. handled per day <sup>1</sup>	Unit Exposure <sup>3</sup> (µg/kg a.i. handled)		Total Exposure <sup>4</sup> (mg/kg bw/day)	MOE <sup>6</sup>
		Dermal	Inhalation		
<b>Canola</b>					
Treater/applicator (CR coveralls over single layer + CR gloves)	26.8	7.36	0.27	0.0013233	27206
Bagger/sewer/stacker (Cotton Coveralls over single layer + CR gloves)		1.29	0.25	0.0002998	120070
Forklift Operator (Cotton Coveralls over single layer + CR gloves)		0.72	0.105	0.0001558	231103
Cleaner (CR coveralls over single layer + CR gloves) <sup>4</sup>	40 g a.i. / 100 kg seed <sup>2</sup>	5.31	0.37	0.0015125	23802
<b>Soybean</b>					
Treater/applicator (CR coveralls over single layer + CR gloves)	31.5	7.36	0.27	0.0015553	23146
Bagger/sewer/stacker (Cotton Coveralls over single layer + CR gloves)		1.29	0.25	0.0003524	102155
Forklift Operator (Cotton Coveralls over single layer + CR gloves)		0.72	0.105	0.0001831	196621
Cleaner (CR coveralls over single layer + CR gloves) <sup>4</sup>	50 g a.i./100 kg <sup>2</sup>	5.31	0.37	0.0018906	19041

<sup>1</sup>Estimated amount (kg) a.i. handled per day = Throughput (kg seed/day) × Application Rate (kg a.i./kg seed)

<sup>2</sup>Cleaner exposure estimates based on application rate

<sup>3</sup> Unit exposure values from surrogate worker exposure studies on file with the PMRA

<sup>4</sup>Total Exposure Treater/BSS/Forklift Operator (mg/kg bw/day) = (Dermal Unit exposure (µg/kg a.i.) Dermal Absorption (50%) + Inhalation Unit exposure (µg/kg a.i.)) × kg a.i. handled per day / (80 kg bw × 1000 µg/mg)

<sup>5</sup>For Cleanout personnel, unit exposures are normalized for application rate (the proposed application rate was used) therefore:

Total Exposure (mg/kg bw/day) = [(Dermal Unit Exposure (µg/g a.i./100 kg seed) Dermal Absorption + Inhalation Unit Exposure (µg/g a.i./100 kg seed)) × application rate (g a.i./100 kg seed)] / 80 kg bw × 1000 µg/mg

<sup>6</sup>Based on a NOAEL = 36 mg/kg bw/day, target MOE= 100

**Table 3 Exposure and Risk Estimate to Workers Using Saltro to Treat and Plant Soybean Seeds On-Farm**

Seed Type	kg a.i. handled per day <sup>1</sup>	Unit Exposure (µg/kg a.i. handled) <sup>2</sup>		Total Exposure <sup>3</sup> (mg/kg bw/day)	MOE <sup>4</sup>
		Dermal	Inhalation		
Soybeans	8.15	407.34	223.03	0.043	828

<sup>1</sup> Amount of a.i. handled per day (kg a.i.) = seed treating capacity per day (kg) application rate (kg a.i./kg seed)

<sup>2</sup> Unit exposure values from surrogate worker exposure study on file with the PMRA

<sup>3</sup>Total Exposure (mg/kg bw/day) = (Dermal Unit exposure (µg/kg a.i.) Dermal Absorption (50%) + Inhalation Unit exposure (µg/kg a.i.)) × kg a.i. handled per day / (80 kg bw × 1000 µg/mg)

<sup>4</sup> Based on a NOAEL = 36 mg/kg bw/day, target MOE= 100

**Table 4 Exposure and Risk Estimates to Workers Planting Seed Treated Commercially with Saltro**

Seed Type	kg a.i. handled per day <sup>1</sup>	Unit Exposure (µg/kg a.i. handled) <sup>2</sup>		Total Exposure <sup>3</sup> (mg/kg bw/day)	MOE <sup>4</sup>
		Dermal	Inhalation		
Canola	0.24	1515	82.83	0.0025	14280
Soybeans	8.15			0.086	421

<sup>1</sup> Amount of ai handled per day (kg ai) = seed treating capacity per day (kg) application rate (kg ai/kg seed)

<sup>2</sup> Unit exposure values from surrogate worker exposure studies on file with the PMRA

<sup>3</sup>Total Exposure (mg/kg bw/day) = (Dermal Unit exposure (µg/kg ai) Dermal Absorption (50%) + Inhalation Unit exposure (µg/kg ai)) × kg ai handled per day / (80 kg bw × 1000 µg/mg)

<sup>4</sup> Based on a NOAEL = 36 mg/kg bw/day, target MOE= 100

**Table 5 Screening Level Risk Assessment for Pollinator Exposure to Seed Treated with Pydiflumetofen**

Test substance	Exposure	Endpoint value	EEC <sup>1</sup>	RQ	Level of Concern Exceeded? <sup>2</sup>
Pydiflumetofen	Acute oral, adults	LD <sub>50</sub> : >116 µg a.i./bee	0.225 kg a.i./ha * 28.6 µg a.i./bee = 6.44 µg a.i./bee	<0.055	No
	Acute contact, adults	LD <sub>50</sub> : > 100 µg a.i./bee	0.225 kg a.i./ha * 2.4 µg a.i./bee = 0.54 µg a.i./bee	<0.005	No

	Acute oral, larvae	LD <sub>50</sub> : >0.0035 µg a.i./larva/d	0.225 kg a.i./ha * 12.15 µg a.i./bee = 2.73 µg a.i./bee	<781	Yes
	Chronic oral, larvae	NOEL: <0.0035 µg a.i./larva/d	0.225 kg a.i./ha * 12.15 µg a.i./bee = 2.73 µg a.i./bee	>781	Yes

<sup>1</sup> Exposure estimate for bees= application rate (0.225 kg a.i./ha based on foliar assessment in PRD2018-06) adjustment factor (2.4 µg a.i./bee per kg a.i./ha for adult bee contact exposure; 28.6 µg a.i./bee per kg a.i./ha for adult bee oral exposure; and 12.15 µg a.i./bee per kg a.i./ha for larvae)

<sup>2</sup> LOC for bees is set at 0.4 for acute endpoints and 1.0 for chronic endpoints.

**Table 6 Screening Level Risk Assessment for Birds and Mammals**

	Study Endpoint (mg a.i./kg bw/day / UF)	EDE (mg a.i./kg bw/day)	RQ	Limit of Concern Exceeded?	Number of Seeds Needed to Reach an Endpoint		Area Required (m <sup>2</sup> )			
							No Drilling		Precision Drilling	
					MIN	MAX	MIN	MAX	MIN	MAX
<b>Soybean</b>										
<b>Small bird (0.02 kg)</b>										
Acute	200.00	126.97	0.6	No	52.80	52.80	0.57	1.68	113.49	336.84
Reproduction	26.90	126.97	4.7	Yes	<b>7.10</b>	<b>7.10</b>	<b>0.08</b>	<b>0.23</b>	<b>15.23</b>	<b>45.31</b>
<b>Medium bird (0.10 kg)</b>										
Acute	200.00	99.74	0.5	No	264.00	264.00	2.83	8.42	566.28	1684.21
Reproduction	26.90	99.74	3.7	Yes	<b>35.51</b>	<b>35.51</b>	<b>0.38</b>	<b>1.13</b>	<b>76.16</b>	<b>226.53</b>
<b>Large bird (1.00 kg)</b>										
Acute	200.00	29.08	0.1	No	2640.00	2640.00	28.31	84.21	5662.81	16842.11
Reproduction	26.90	29.08	1.1	Yes	<b>355.08</b>	<b>355.08</b>	<b>3.81</b>	<b>11.33</b>	<b>761.65</b>	<b>2265.26</b>
<b>Small mammals (0.015 kg)</b>										
Acute	55.00	72.56	1.3	Yes	<b>10.89</b>	<b>10.89</b>	<b>0.12</b>	<b>0.35</b>	<b>23.36</b>	<b>69.47</b>
Reproduction	36.10	72.56	2.0	Yes	<b>7.15</b>	<b>7.15</b>	<b>0.08</b>	<b>0.23</b>	<b>15.33</b>	<b>45.60</b>
<b>Medium mammals (0.035 kg)</b>										
Acute	55.00	62.40	1.1	Yes	<b>25.41</b>	<b>25.41</b>	<b>0.27</b>	<b>0.81</b>	<b>54.50</b>	<b>162.11</b>
Reproduction	36.10	62.40	1.7	Yes	<b>16.68</b>	<b>16.68</b>	<b>0.18</b>	<b>0.53</b>	<b>35.77</b>	<b>106.40</b>
<b>Large mammals (1.00 kg)</b>										
Acute	55.00	34.36	0.6	No	726.00	726.00	7.79	23.16	1557.27	4631.58
Reproduction	36.10	34.36	1.0	No	476.52	476.52	5.11	15.20	1022.14	3040.00
<b>Canola (representative crop for Crop Subgroup 20A)</b>										
<b>Small bird (0.02 kg)</b>										
Acute	200.00	101.575	0.5	No	1810.00	5000.00	4.53	69.06	905.00	13812.15
Reproduction	26.90	101.575	3.8	Yes	<b>243.45</b>	<b>672.50</b>	<b>0.61</b>	<b>9.29</b>	<b>121.72</b>	<b>1857.73</b>
<b>Medium bird (0.10 kg)</b>										
Acute	200.00	79.789	0.4	No	9050.00	25000.00	22.63	345.30	4525.00	69060.77
Reproduction	26.90	79.789	3.0	Yes	<b>1217.23</b>	<b>3362.50</b>	<b>3.04</b>	<b>46.44</b>	<b>608.61</b>	<b>9288.67</b>

<b>Large bird (1.00 kg)</b>										
Acute	200.00	23.261	0.1	No	90500.00	250000.00	226.25	3453.04	45250.00	690607.73
Reproduction	26.90	23.261	0.9	No	12172.25	33625.00	30.43	464.43	6086.13	92886.74
<b>Small mammals (0.015 kg)</b>										
Acute	55.00	58.048	1.1	Yes	<b>1031.25</b>	<b>373.31</b>	<b>2.58</b>	<b>5.16</b>	<b>515.63</b>	<b>1031.25</b>
Reproduction	36.10	58.048	1.6	Yes	<b>676.88</b>	<b>245.03</b>	<b>1.69</b>	<b>3.38</b>	<b>338.44</b>	<b>676.88</b>
<b>Medium mammals (0.035 kg)</b>										
Acute	55.00	49.921	0.9	No	2406.25	871.06	6.02	12.03	1203.13	2406.25
Reproduction	36.10	49.921	1.4	Yes	<b>1579.38</b>	<b>571.73</b>	<b>3.95</b>	<b>7.90</b>	<b>789.69</b>	<b>1579.38</b>
<b>Large mammals (1.00 kg)</b>										
Acute	55.00	27.487	0.5	No	68750.00	24887.50	171.88	343.75	34375.00	68750.00
Reproduction	36.10	27.487	0.8	No	45125.00	16335.25	112.81	225.63	22562.50	45125.00

**Table 7 List of Supported Uses**

<b>Supported use claims for Saltro</b>
<p>Control of early season infection by <i>Fusarium virguliforme</i> (the causal agent of sudden death syndrome) on soybean at 100 mL/100 kg seed (50 g a.i./100 kg seed).</p> <p>Saltro may be mixed with Apron XL<sup>®</sup> LS, Maxim<sup>®</sup> 480FS, Apron MAXX<sup>®</sup> RTA<sup>®</sup> or Apron MAXX RFC, Vibrance<sup>®</sup> 500FS, Vibrance MAXX RFC and Mertect<sup>®</sup> to control a broad spectrum of soil- and seed-borne pathogens. For protection from various insect pests, Saltro may be mixed with Cruiser<sup>®</sup> 5FS and Fortenza<sup>®</sup>. For combined protection from labeled insect and soil- and seed-borne pathogens, Saltro may be mixed with Cruiser MAXX<sup>®</sup> Beans and Vibrance 500FS. For protection from soybean cyst nematodes, Saltro may be mixed with Clariva<sup>™</sup> PN.</p>
<p>Suppression of seed and air-borne blackleg caused by <i>Leptosphaeria maculans</i> on Crop Subgroup 20A (Rapeseed Subgroup)* at 80 mL/100 kg seed (40 g a.i./100 kg seed).</p> <p>Saltro may be mixed with Vibrance Flexi Canola for control of additional fungal diseases. For insect control, Saltro may be mixed with Rascendo<sup>™</sup>, Fortenza and/or Cruiser 5FS. Saltro may be mixed with Helix<sup>®</sup> Vibrance or Prosper<sup>®</sup> Evergol<sup>®</sup> for control of additional fungal diseases and insect pests.</p>

\* Crop subgroup 20A: borage, crambe, cuphea, echium, flax seed, gold of pleasure, hare's ear mustard, lesquerella, lunaria, mustard seed, milkweed, oil radish, rapeseed/canola, sesame, sweet rocket; cultivars, varieties, and/or hybrids of these.

## References

### PMRA Document Number

### References

#### A. List of Studies/Information Submitted by Registrant

##### 1.0 Chemistry

- 2571065 2015, SYN545974 - Physico-Chemical Studies of the Pure and Technical Substance, DACO: 2.13.2,2.14.1,2.14.10,2.14.11,2.14.12,2.14.13,2.14.14,2.14.2,2.14.3,2.14.4,2.14.5,2.14.6,2.14.7,2.14.8,2.14.9,2.16,8.2.3.2,8.2.3.3.3 CBI
- 2888549 2018, Pydiflumetofen - [CBI removed] Document J - Product Chemistry Volume, DACO: 2.2,3.1.1,3.1.2,3.1.3,3.1.4,3.2.1,3.2.2,3.2.3,3.3.1,3.3.2,3.4.2,4.8 CBI
- 2888550 2018, Pydiflumetofen - [CBI removed] - Document MIII, Section 1 - Product Chemistry Volume, DACO: 10.2.1,10.2.2,10.2.3.1,10.2.3.2,10.3.3,10.6,2.2,3.1.2,3.1.3,3.1.4,3.2.1,3.2.2,3.2.3,3.3.1,3.3.2,3.5.1,3.5.10,3.5.11,3.5.12,3.5.13,3.5.14,3.5.2,3.5.3,3.5.4,3.5.5,3.5.6,3.5.7,3.5.8,3.5.9,3.7,5.14,5.2,8.4.1,8.6 CBI
- 2888551 2018, Pydiflumetofen - [CBI removed] - Document H Product Chemistry Volume, DACO: 3.2.1 CBI
- 2888554 "2018, [CBI removed]- SF-950/1- Determination of SYN545974 in [CBI removed] by UHPLC, DACO: 3.4.1 CBI"
- 2888555 2017, [CBI removed] - Validation of Analytical Method SF-950/1, DACO: 3.4.1 CBI
- 2888556 2018, Pydiflumetofen - [CBI removed] Physico-Chemical Studies of the Formulation, DACO: 3.5.1,3.5.10,3.5.11,3.5.12,3.5.13,3.5.14,3.5.15,3.5.2,3.5.3,3.5.4,3.5.5,3.5.6,3.5.7,3.5.8,3.5.9 CBI
- 2966260 2019, DACO: 3.2.2 CBI

##### 2.0 Human and Animal Health

- 2888558 2018, Pydiflumetofen FS - Acute Oral Toxicity Study in Rats (Up and Down Procedure), DACO: 4.6.1
- 2888560 2018, Pydiflumetofen FS - Acute Inhalation Toxicity in Rats, DACO: 4.6.3
- 2888561 2018, Pydiflumetofen FS - Acute Eye Irritation Study in Rabbits, DACO: 4.6.4
- 2888562 2018, Pydiflumetofen FS - In Vitro Eye Irritation Test in Isolated Chicken Eyes, DACO: 4.6.4
- 2888563 2018, Pydiflumetofen FS - In Vitro Skin Irritation Test in the EPISKINTM Model, DACO: 4.6.5
- 2888564 2018, Pydiflumetofen FS - Primary Skin Irritation Study in Rabbits, DACO: 4.6.5
- 2888565 2018, Pydiflumetofen FS - Local Lymph Node Assay (LLNA) in Mice, DACO: 4.6.6



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- 2888566 2018, Occupational Risk Assessment for Saltro, for Seed Treatment Use on Soybeans and Canola in Canada, DACO: 5.1,5.2,5.3,5.6
- 2888567 2018, Laboratory dust-off measurements of soybean and canola seed treated with Saltro Seed Treatment, DACO: 5.6
- 2926581 2018, Exposure - bridging between seeds, DACO: 5.1,5.2,5.3,5.6

### 3.0 Environment

None

### 4.0 Value

- 2888569 2018, Saltro Fungicide DACO 10 Efficacy Data And Information – Canada, DACO: 10.1,10.3.1,10.3.2
- 2888572 2018, 10.2.3.3-1 - Trial Abstract 1, DACO: 10.2.3.3
- 2888573 2018, 10.2.3.3-2 - Trial Abstract 2, DACO: 10.2.3.3
- 2888574 2018, 10.2.3.3-3 - Trial Abstract 3, DACO: 10.2.3.3
- 2888575 2018, 10.2.3.3-4 - Trial Abstract 4, DACO: 10.2.3.3
- 2888576 2016, 10.2.3.3-5 - Trial Abstract 5, DACO: 10.2.3.3
- 2888577 2016, 10.2.3.3-6 - Trial Abstract 6, DACO: 10.2.3.3
- 2888578 2016, 10.2.3.3-7 - Trial Abstract 7, DACO: 10.2.3.3
- 2888580 2016, 10.2.3.3-8 - Trial Abstract 8, DACO: 10.2.3.3