Proposed Registration Decision PRD2016-03

Mandestrobin

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Table of Contents

Overview

Proposed Registration Decision for Mandestrobin

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 Mandestrobin Technical (previously known as S-2200 Fungicide Technical) and the associated end-use products: S-2200 4 SC Fungicide, Intuity Fungicide (previously known as S-2200 4 SC Ag Fungicide), Pinpoint Fungicide (previously known as S-2200 4 SC VPP Fungicide), and S-2200 3.2 FS Fungicide, containing the technical grade active ingredient mandestrobin, for the management of various fungal diseases in canola and other oilseed crops, corn, grape, legume vegetables, strawberry and other low growing berries, as well as turfgrass.

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 S-2200 Fungicide Technical, S-2200 4 SC Fungicide, S-2200 4 SC Ag Fungicide, S-2200 4 SC VPP Fungicide, and S-2200 3.2 FS Fungicide.

What Does Health Canada Consider When Making a Registration Decision?

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

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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."

To reach its decisions, the PMRA applies modern, rigorous risk-assessment methods and policies. These methods consider the unique characteristics of sensitive subpopulations in humans (for example, children) as well as organisms in the environment. These methods and policies also consider the nature of the effects observed and the uncertainties when predicting the impact of pesticides. For more information on how the 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 mandestrobin, the PMRA will consider any comments received from the public in response to this consultation document.[3] The PMRA will then publish a Registration Decision[4] on mandestrobin, which will include the decision, the reasons for it, a summary of comments received on the proposed 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 Mandestrobin?

Mandestrobin is the active ingredient in the following fungicide products that are being proposed for registration in Canada: S-2200 4 SC Fungicide, S-2200 4 SC Ag Fungicide, S-2200 4 SC VPP Fungicide, and S-2200 3.2 FS Fungicide. These products are formulated for either foliar or seed applications and are intended for the management of various fungal diseases in canola and other oilseed crops, corn, grape, legume vegetables, strawberry and other low growing berries, as well as turfgrass. Mandestrobin has preventative and systemic properties and acts by interfering with the cellular mechanisms in susceptible fungal pathogens.

Health Considerations

Can Approved Uses of Mandestrobin Affect Human Health?

Products containing mandestrobin are unlikely to affect your health when used according to label directions.

Potential exposure to mandestrobin may occur through the diet (food and water) or when handling and applying the 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.

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

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

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

In laboratory animals, the technical grade active ingredient mandestrobin was of low acute toxicity by the oral, dermal and inhalation routes. Mandestrobin was minimally irritating to the eye and non-irritating to the skin. Mandestrobin did not cause allergic skin reactions.

The acute toxicity of the end-use products was low via the oral, dermal and inhalation routes of exposure. The products were non-irritating to the skin and minimally irritating to the eyes. They did not cause allergic skin reactions. Consequently, no hazard signal words are required on their labels.

Applicant-supplied short- and long-term (lifetime) animal toxicity tests were assessed for the potential of mandestrobin to cause neurotoxicity, immunotoxicity, chronic toxicity, cancer, reproductive and developmental toxicity, and various other effects. The most sensitive endpoints for risk assessment were adverse effects noted on growth and in the liver, bile duct, and kidneys. There was a low level of concern for sensitivity of the young animal. The risk assessment protects against the finding noted above as well as any other potential effects by ensuring that the level of exposure to humans is well below the lowest dose at which these effects occurred in animal tests.

Residues in 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 children 1-2 years old, the subpopulation which would ingest the most mandestrobin relative to body weight, are expected to be exposed to less than 10% of the acceptable daily intake. Based on these estimates, the chronic dietary risk from mandestrobin is not of health concern for all population subgroups.

Animal studies revealed no acute health effects. Consequently, a single dose of mandestrobin is not likely to cause acute health effects in the general population (including infants and children). Mandestrobin is not carcinogenic; therefore, a cancer dietary risk assessment is not required.

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 Canada (and the United States) using mandestrobin on rapeseed, corn, grapes, strawberries, and soybeans are acceptable. The MRLs for this active ingredient can be found in the Science Evaluation of this consultation document.

Occupational Risks From Handling S-2200 4 SC Fungicide, S-2200 3.2 FS Fungicide, S-2200 4 SC Ag Fungicide, and S-2200 4 SC VPP Fungicide

Occupational risks are not of concern when S-2200 4 SC Fungicide, S-2200 3.2 FS Fungicide, S-2200 4 SC Ag Fungicide and S-2200 4 SC VPP Fungicide are used according to the label directions, which include protective measures.

Farmers, custom applicators, seed treaters and planters who mix, load, apply or treat seeds with S-2200 4 SC Fungicide, S-2200 3.2 FS Fungicide, S-2200 4 SC Ag Fungicide, and S-2200 4 SC VPP Fungicide, as well as field workers re-entering freshly treated fields, can come in direct contact with residues on the skin. Therefore, the label specifies that anyone mixing/loading and applying S-2200 4 SC Fungicide, S-2200 4 SC Ag Fungicide, and S-2200 4 SC VPP Fungicide must wear a long-sleeved shirt, long pants, chemical-resistant gloves, shoes and socks. The field crew and the mixer/loaders for aerial applications of S-2200 4 SC Ag Fungicide must wear coveralls over a long-sleeved shirt, long pants, chemical-resistant gloves, shoes and socks, and goggles or face shield during mixing/loading, cleanup and repair. The label also requires that workers do not enter treated fields for 12 hours after application. Workers treating seeds with S-2200 3.2 FS Fungicide must use closed transfer systems in commercial facilities (excluding mobile treaters), and must wear long pants, a long-sleeved shirt and chemical-resistant gloves, shoes and socks during mixing, loading, treating, bagging, sewing or stacking of bagged treated seed, handling treated seed, and planting treated seed. In addition, seed treatment workers performing cleaning, maintenance, and repair of seed treatment equipment must wear chemical-resistant coveralls. As well, standard label statements to protect against drift during application are on the labels. Taking into consideration these label statements, the use pattern, and the duration of exposure for handlers and workers, risks to these individuals are not a concern.

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 Mandestrobin Is Introduced Into the Environment?

When used according to label directions mandestrobin is not expected to pose an unacceptable risk to the environment.

Mandestrobin enters the environment when applied as a foliar spray, seed treatment or chemigation. Mandestrobin can break down in the presence of microbes in terrestrial systems. Laboratory studies indicate mandestrobin has the potential to be persistent in certain soils, whereas field studies indicate that mandestrobin is less likely to persist in the environment. The properties of mandestrobin and its transformation products, 5-COOH-S-2200 and 2-COOH-S-2200, indicate some potential for downward movement through the soil. However, field studies and modelling indicate that levels of mandestrobin and its transformation products that may reach groundwater are low. In aquatic systems, mandestrobin will move out of the water column and into sediments where it has the potential to persist.

Mandestrobin does not break down by reacting with water, but it can break down rapidly in the presence of sunlight, especially in clear shallow waters. It is not expected to accumulate in the tissues of aquatic organisms. Mandestrobin is not expected to enter the atmosphere nor be transported long distances from where it was applied.

When used according to label directions, mandestrobin is expected to pose a negligible risk to earthworms, bees, beneficial arthropods, birds and small mammals. If exposed to high enough concentrations, mandestrobin may pose a risk to non-target aquatic organisms and terrestrial plants. Risks to non-target aquatic organisms and terrestrial plants can be mitigated with label statements and spray buffer zones to protect sensitive aquatic and terrestrial habitats. Label statements are required on the product labels to inform the users of the potential risks.

Value Considerations

What Is the Value of S-2200 4 SC Fungicide, S-2200 4 SC Ag Fungicide, S-2200 4 SC VPP Fungicide, and S-2200 3.2 FS Fungicide?

These products have demonstrated good efficacy and will provide growers with additional product options for the management of a broad range of common diseases in economically important crops in Canada.

S-2200 4 SC Fungicide, S-2200 4 SC Ag Fungicide, and S-2200 4 SC VPP Fungicide are formulated for foliar spray applications to control or suppress a range of diseases on oil seed crops, grape, low growing berries including strawberry, and turfgrass. S-2200 3.2 FS Fungicide is applied as a seed treatment to control various common fungi that cause seed rots in corn, legume vegetables, and oil seed crops. Mandestrobin is most effective when applied preventatively or at the early stages of disease development. Appropriate use of these products will help growers maximize the quality and yield of their crops.

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 S-2200 4 SC Fungicide, S-2200 3.2 FS Fungicide, S-2200 4 SC Ag Fungicide, and S-2200 4 SC VPP Fungicide 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 S-2200 4 SC Fungicide, S-2200 3.2 FS Fungicide, S-2200 4 SC Ag Fungicide, and S-2200 4 SC VPP Fungicide on the skin or through inhalation of spray mists, anyone mixing, loading and applying S-2200 4 SC Fungicide, S-2200 4 SC Ag Fungicide, and S-2200 4 SC VPP Fungicide must wear a long-

sleeved shirt, long pants, chemical-resistant gloves, shoes and socks. The field crew and the mixer/loaders for aerial applications of S-2200 4 SC Ag Fungicide must wear coveralls over a long-sleeved shirt, long pants, chemical-resistant gloves, shoes and socks, and goggles or face shield during mixing/loading, cleanup and repair. The label also requires that workers do not enter treated fields for 12 hours after application.

Workers treating seeds with S-2200 3.2 FS Fungicide must use closed transfer systems in commercial facilities (excluding mobile treaters), and must wear long pants, a long-sleeved shirt and chemical-resistant gloves, shoes and socks during mixing, loading, treating, bagging, sewing or stacking of bagged treated seed, handling treated seed, and planting treated seed. In addition, seed treatment workers performing cleaning, maintenance, and repair of seed treatment equipment must wear chemical-resistant coveralls. Standard label statements to protect against drift during application are also on the labels.

Environment

Mandestrobin can pose a risk to non-target aquatic organisms and terrestrial plants. To mitigate potential exposures to mandestrobin via spray drift, spray buffer zones of 0 to 15 metres are required to protect sensitive terrestrial and aquatic habitats, depending on the method of application. These spray buffer zones are to be specified on the product labels.

Next Steps

Before making a final registration decision on mandestrobin, the PMRA will consider any 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

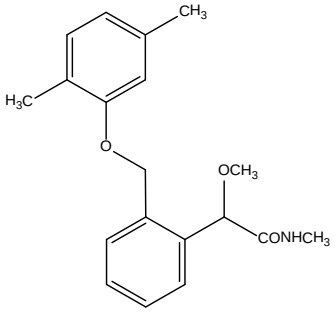
When the PMRA makes its registration decision, it will publish a Registration Decision on mandestrobin (based on the Science Evaluation of this consultation document). In addition, the test data referenced in this consultation document will be available for public inspection, upon application, in the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

Science Evaluation

Mandestrobin

1.0 The Active Ingredient, Its Properties and Uses

1.1 Identity of the Active Ingredient

Active substance	Mandestrobin
Function	Fungicide
Chemical name	
1. International Union of Pure and Applied Chemistry (IUPAC)	*rac-(*2*R*)-2-{2-[(2,5-dimethylphenoxy)methyl]phenyl}-2-methoxy-*N*-methylacetamide
2. Chemical Abstracts Service (CAS)	2-[(2,5-dimethylphenoxy)methyl]-α-methoxy-*N*-methylbenzeneacetamide
CAS number	173662-97-0
Molecular formula	$C_{19}H_{23}NO_3$
Molecular weight	313.4
Structural formula	
Purity of the active ingredient	88.8%

1.2 Physical and Chemical Properties of the Active Ingredient and End-Use Products

Technical Product—S-2200 Fungicide Technical

Property	Result		
Colour and physical state	White solid		
Odour	Odourless		
Melting point	102°C		
Boiling point	296°C		
Relative density	1.2015		
Vapour pressure at 20°C	3.36×10^{-8} Pa (extrapolated)		
Ultraviolet (UV)-visible spectrum	Solution	λmax (nm)	Molar absorptivity, (ε) $(mol/L)^{-1}cm^{-1}$
	Methanol	273	2140
	Acidic	273	1920
	Basic	273	1880
	Neutral	273	1740
Solubility in water at 20°C	15.8 mg/L		
Solubility in organic solvents at 20°C	Solvent	Solubility (g/L)	
	Dichloromethane	395	
	Acetone	332	
	Ethyl acetate	274	
	Methanol	182	
	Toluene	147	
	n-Octanol	63.6	
	Hexane	2.00	
n-Octanol-water partition coefficient (K_{ow})	Log K_{ow} = 3.51 at 25°C		
Dissociation constant (pK_a)	No dissociative activity in the pH range 2-10		
Stability (temperature, metal)	Stable for 14 days when exposed to normal and elevated (54°C) temperatures and metals and metal ions (iron, nickel, iron (II) acetate and nickel (II) acetate).		

End-Use Product—S-2200 3.2 FS Fungicide

Property	Result
Colour	White, opaque
Odour	Faint, paint-like odour
Physical state	Liquid
Formulation type	Suspension
Guarantee	383 g/L

Property	Result
Container material and description	High-density polyethylene (HDPE)
Density at 20°C	1.091 g/mL
pH of 1% dispersion in water	5.7 at 25°C
Oxidizing or reducing action	No oxidizing or reducing action
Storage stability	In progress
Corrosion characteristics	In progress
Explodability	Not explosive

End-Use Product—S-2200 4 SC Fungicide, S-2200 4 SC Ag Fungicide and S-2200 4 SC VPP Fungicide

Property	Result
Colour	White, opaque
Odour	Sweet odour
Physical state	Liquid
Formulation type	Suspension
Guarantee	43.4%
Container material and description	High-density polyethylene (HDPE)
Density at 20°C	1.095 g/mL
pH of 1% dispersion in water	6.8 at 25°C
Oxidizing or reducing action	No oxidizing or reducing action
Storage stability	In progress
Corrosion characteristics	In progress
Explodability	Not explosive

1.3 Directions for Use

S-2200 4 SC Fungicide, S-2200 4 SC Ag Fungicide, and S-2200 4 SC VPP Fungicide are to be applied by foliar application to labelled crops on a preventative basis or at the earliest signs of infection. The application rates range from 439 to 986 mL/ha. When repeated treatments are required and permitted, reapplication intervals range from seven to 28 days.

S-2200 3.2 FS Fungicide is applied once, directly to seed before planting. Application rates per 100 kg of seed range from 15.6 to 26 mL depending on the treated crop. Because S-2200 3.2 FS Fungicide does not contain a colourant, the product must be applied in combination with an appropriate colourant.

1.4 Mode of Action

Mandestrobin belongs to the quinone outside inhibitors class of fungicides. These fungicides provide control of target pathogens by interfering with their ability to produce energy, which in turn inhibits development of spores and mycelia. Mandestrobin is a broad spectrum fungicide with preventive and systemic properties. It is most effective when applied prior to infection.

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

2.3 Methods for Residue Analysis

For environmental media, high-performance liquid chromatography methods with tandem mass spectrometry (HPLC-MS/MS) were developed and proposed for data generation and enforcement purposes. These methods fulfilled the requirements with regards to selectivity, accuracy and precision at the respective method limit of quantitation. Acceptable recoveries (70–120%) were obtained in environmental media. Methods for residue analysis of environmental media are summarized in Appendix I, Table 1a.

For crops, high performance liquid chromatography methods with tandem mass spectrometric detection (HPLC-MS/MS; Method RM-48C-2A) in plant matrices was developed and proposed for data gathering and enforcement purposes for the determination of mandestrobin residues. The method fulfilled the requirements with regards to specificity, accuracy and precision at the respective method limit of quantitation (0.02 ppm). Acceptable recoveries (70–120%) were obtained in plant matrices. The proposed enforcement method was successfully validated in plant matrices by an independent laboratory. In addition the extraction solvents used in the method were similar to those used in the metabolism studies. Method RM-48M-1 was developed and proposed for enforcement purposes for poultry muscle only. Methods for residue analysis of crops are summarized in Appendix I, Table 1b.

3.0 Impact on Human and Animal Health

3.1 Toxicology Summary

A detailed review of the toxicological database for mandestrobin was conducted. The database is complete, consisting of the full array of toxicity studies required for hazard assessment purposes. The studies were carried out in accordance with 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 mandestrobin. Mechanistic studies were also provided to support a proposed mode of action (MOA) for the thyroid effects in rats, and to investigate a possible effect of mandestrobin and its major metabolites on human estrogen and androgen receptors, as well as a possible effect of mandestrobin on the steroidogenesis of testosterone and estrogen. Acute oral toxicity and mutagenicity assays were also provided for five of the metabolites of mandestrobin observed in the rat.

Mandestrobin (S-2200TG, RS-Mandestrobin) is a racemic mixture of isomers R-mandestrobin (S-2167) and S-mandestrobin (S-2354). The metabolism and pharmacokinetics of mandestrobin were characterised after single oral gavage administration (racemic mixture at low and high doses and separate isomers at a low dose) and multiple oral gavage administration (14-day treatment at a low dose). All forms of mandestrobin, radiolabelled on either benzyl (mandestrobin, R-isomer and S-isomer) or phenoxy (mandestrobin) ring, were rapidly absorbed after a single gavage dose in rats. Area under the curve was proportionally higher at the low dose than at the high dose, indicating saturation of oral absorption at the high dose. Peak plasma levels were reached by 1.2 to 2.6 hours after an oral low dose, and 7.0 to 9.1 hours after a high dose. The labeled compound was widely distributed throughout tissues, but was detected primarily in the gastrointestinal (GI) tract, liver and kidney. Pancreas, uterus and ovaries also had higher levels than most other tissues. Mandestrobin isomers had similar tissue distribution, except the S-isomer was more prevalent in the GI tract than the R-isomer. There were no sex differences in tissue distribution, with the exception of the repeat-dose study in which females retained a larger portion of the dose in the cecum/large intestine/intestinal contents, and reached peak levels in tissues outside the GI tract later than males.

There was no evidence of accumulation of mandestrobin or its metabolites in tissues following repeated dosing. Clearance of a single dose of mandestrobin from plasma was almost complete by 120 hours post-dose. Clearance of the S-isomer was less rapid than the R-isomer. In the repeated-dose study, the majority of the administered dose was excreted by 14 days after last dose. Bile-cannulated rats excreted the radiolabelled compound more quickly than non-cannulated rats, suggesting enterohepatic recirculation. Excretion was consistent with all mandestrobin treatments. Fecal excretion via bile was the primary route, and renal excretion was also important. Excretion in expired air was negligible.

Mandestrobin was almost completely metabolized in rats via (1) oxidation followed by glucuronidation, or (2) demethylation followed by oxidation, or (3) oxidation followed by demethylation. There was no cleavage of benzyl and phenoxy rings. The major metabolites excreted were: 5-CA-S-2200-NHM and 4-OH-S-2200 in feces; 4-OH-S-2200-Glucuronide A in bile; and 5-CA-S-2200-NHM in urine. The same metabolites were identified for both isomers however at different proportions. Treatment with the R-isomer resulted in the following fecal/urinary metabolites in decreasing order of magnitude: 5-CA-S-2200-NHM, 5-CA-MCBX-NDM, 5-CA-2-HM-S-2200-NHM and 5-CA-S-2200-NDM; while S-isomer produced mostly 4-OH-S-2200 and 5-COOH-S-2200. In the multiple-dose study, fecal metabolites found at slightly higher levels in males than females included 5-CA-S-2200-NHM, 5-COOH-S-2200, 5-CA-2-HM-S-2200-NHM, 5-CA-2-HM-MCBX and 5-CA-MCBX-NDM. Results from cannulated rats suggest that 4-OH-S-2200 and its A glucuronide (GlucA) underwent enterohepatic circulation.

In acute toxicity testing, mandestrobin was demonstrated to be of low toxicity via the oral, dermal and inhalation routes in rats. Mandestrobin was minimally irritating to the eye and non-irritating to the skin of rabbits. Mandestrobin was not a dermal sensitizer in guinea pigs (Maximization Test).

The acute toxicity of the end-use products containing mandestrobin was low via the oral, dermal and inhalation routes in rats. The products were non-irritating to the skin and minimally irritating to the eyes of rabbits. They did not elicit a sensitization reaction in mice in the Local Lymph Node Assay.

In a short-term dermal toxicity study in rats, no adverse effects were noted at the limit dose. In repeated-dose dietary short-term studies, the liver and bile duct were the target organs of toxicity; the thyroid gland was also affected. Hepatic effects were noted in dogs and rats including hepatocellular hypertrophy accompanied by increased liver weight. At the lowest observed adverse effect level (LOAEL), increased incidences and severity of hepatocyte hypertrophy accompanied by centrilobular degeneration, liver agonal congestion and/or hemorrhage, large and dark liver, bile duct brown pigmentation and periductular inflammation, increased total cholesterol and serum liver enzymes and increased incidence and severity of thyroid follicular hypertrophy were observed. It was concluded based on the results of special mechanistic studies that, the effects on the thyroid gland were secondary to the liver effects, and were not observed without liver hypertrophy. The liver and thyroid effects were not observed in mice.

Rats and mice received a repeated dose of the test substance in the diet over most of their life span. Liver and thyroid gland effects were noted in rats at a lower dose than what was observed in short-term studies. Liver vacuolation was observed at the high dose in male rats and at the mid-high dose in female rats. Mice seemed less sensitive to the liver effects with adverse effects noted at the highest dose tested only. In long-term studies, the kidneys were a target organ of toxicity in male mice and female rats, which showed an increased incidence of corticomedullary mineralisation. According to scientific publications, the clinical significance of this observation is unclear.

However, this effect was observed in two species and different sexes in a dose-response manner, it was considered treatment-related and adverse. In female rats, renal corticomedullary mineralisation was accompanied by body weight effects, but liver and thyroid effects were only apparent at a higher dose.

MOA studies were provided to explain the liver and thyroid changes observed mostly in rats and dogs. Seven- and 14-day dietary treatments with mandestrobin caused an early induction of liver enzymes at the low dose, and, at mid-high and high dose, increased liver and thyroid gland weight and hepatocyte DNA synthesis, diffuse hepatocellular hypertrophy and diffuse thyroid follicular cell hypertrophy. In addition, effects on thyroxine, triiodothyronine, thyroid-stimulating hormone levels and T4-UDP-glucuronosyltransferase activity consistent with increased clearance of thyroxine were observed.

To evaluate reversibility of these findings, a 7-day dietary treatment followed by a 7-day recovery period was performed. The results demonstrated that most of these effects were transient and reversible. Taken together, the liver MOA studies demonstrated that the thyroid gland effects were secondary to the liver effects.

There was an increased incidence of benign ovary sex cord-stromal tumours in female rats in the long term toxicity study. Although this effect showed a dose-response relationship, it was considered as equivocal evidence of oncogenicity as this type of tumour is commonly observed in aging rats. The first tumour was observed late in the study in the control group (week 91) and later in treatment groups (week 98). No malignant tumors of this type were observed. The concern for this finding was tempered by its occurrence at a relatively high dose.

MOA studies were provided to investigate the ovary sex-cord stromal tumours observed in female rats. A reporter gene assay performed on HeLa cells derived from human uterine cervix carcinoma suggested that mandestrobin and its major metabolites (5-COOH-S-2200, 4-OH-S-2200, 5-CH2OH-S-2200 and 5-CA-S-2200-NHM) did not have agonistic or antagonistic effects on the human estrogen receptor alpha (hERa) and the human androgen receptor (hAR). Confidence in these assays was limited given that they were performed only once. The effect of mandestrobin on the production of testosterone and estradiol was evaluated in a well conducted steroidogenesis assay and the results were negative.

Although these mechanistic studies provide useful input to the mandestrobin toxicology database, they do not constitute an acceptable MOA to explain the incidence of ovary sex cord-stromal tumors in female rats.

Mandestrobin tested negative for genotoxicity in several assays, including bacterial reverse mutation assay, a forward mutation assay in mammalian cells, a chromosomal aberration assay, and an in vivo micronucleus assay.

In a two-generation dietary reproductive toxicity study in rats, there was no treatment-related effect on reproductive performance. Effects observed in parental animals were consistent with those reported in other repeated-dose dietary studies in rats and included increased liver weight and increased incidence of hypertrophy, brown pigmentation of the bile duct and periductular inflammatory cell infiltration. At a higher dose level, offspring of F_1 and F_2 generations exhibited reduced body weights beginning on postnatal day seven. In this study, there was no evidence of sensitivity of the young.

In a gavage developmental toxicity study in rats, developmental effects included increased incidences of litters with distended ureter or delayed skull ossification. These findings occurred at the limit dose of testing in the absence of maternal toxicity, thus providing evidence of sensitivity of the young. The incidences in control animals for these variations were on the low end of the historical control range. Also, clear signs of toxicity were observed at a lower dose in adult animals in other short-term studies. For these reasons the level of concern for these variations was low. No adverse effects were observed in rabbit dams exposed to mandestrobin via gavage or in their fetuses.

In an acute gavage neurotoxicity study in rats, decreased overall locomotor activity was noted in both sexes at 0-30 minutes on study day zero at the highest dose tested. This effect was considered an indicator of general toxicity rather that of specific neurotoxicity. In a 90-day dietary neurotoxicity study, decreased body weight and food consumption were noted, but no signs of neurotoxicity were noted at any time during the study. Overall, the evidence did not suggest that mandestrobin was a frank neurotoxicant.

In a 28-day dietary immunotoxicity study conducted in rats, there was an increase in spleen weight at a dose exceeding the limit dose of testing. Mandestrobin was not considered immunotoxic.

Oral acute studies and mutagenicity studies were also provided for some of the metabolites of mandestrobin. From the results of these studies, it was concluded that the metabolites 2-CH2OH-S-2200, 2-COOH-S-2200, 4-OH-S-2200, 5-COOH-S-2200 and De-Xy-S-2200 should be considered of comparable toxicity to the parent.

The code names for mandestrobin isomers and metabolites can be found in Appendix I, Table 2. Results of the toxicology studies conducted on laboratory animals with mandestrobin and its associated end-use products are summarized in Appendix I, Tables 3, 4, 5 and 6. The toxicology endpoints for use in the human health risk assessment are summarized in Appendix I, Table 7.

Incident Reports

Since 26 April 2007, registrants have been required by law to report incidents to the PMRA, including adverse effects to Canadian health or the environment. Mandestrobin is a new active ingredient pending registration for use in Canada. No human or domestic animal incidents involving the active ingredient mandestrobin have been reported to the PMRA and the applicant did not submit any additional data.

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, the database contains the standard complement of required studies including gavage developmental toxicity studies in rats and rabbits and a two-generation dietary reproductive toxicity study in rats.

With respect to potential prenatal and postnatal toxicity, there was no indication of increased susceptibility of fetuses or offspring compared to parental animals in the reproductive toxicity study in rats and prenatal developmental toxicity study in rabbits. Minor developmental variations (increased incidence of delayed skull ossification and distended ureters) were observed in the rat developmental toxicity study in the absence of maternal toxicity. The concern

for this finding was low in view of the fact that it occurred at the limit dose of testing and toxicity was evident at this dose in other short-term studies (body weight effects, liver and thyroid effects). Furthermore, the incidences of these variations just slightly exceeded the laboratory historical data range.

Overall, the database is adequate for determining the sensitivity of the young. Concern for sensitivity was low and there were no serious endpoints were noted. On the basis of this information, the 10-fold *Pest Control Products Act* factor was reduced to 1-fold.

3.2 Acute Reference Dose (ARfD)

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

3.3 Acceptable Daily Intake

To estimate risk of repeated dietary exposure, a no observed adverse effect level (NOAEL) of 27 mg/kg bw/day from the combined dietary chronic toxicity/carcinogenicity study in rats was selected for risk assessment. At the LOAEL of 135 mg/kg bw/day, decreased body weight and body weight gain and increased incidence of renal corticomedullary mineralization were observed in female rats. This study provides the lowest NOAEL in the database. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied. As discussed in the *Pest Control Products Act* Hazard Characterization section, the *Pest Control Products Act* factor was reduced to 1-fold. The composite assessment factor (CAF) is thus 100.

The Acceptable Daily Intake (ADI) is calculated according to the following formula:

$$\text{ADI} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{27 \text{ mg/kg bw/day}}{100} = 0.3 \text{ mg/kg bw/day of mandestrobin}$$

This ADI provides a margin of greater than 1500 to the dose resulting in increased incidence of benign ovary sex cord-stromal tumours in female rats and greater than 3300 to the dose resulting in increased incidence of fetal variations in the rat.

Cancer Assessment

As previously discussed, an increase in benign sex cord-stromal tumours in females in the rat oncogenicity study with mandestrobin was considered equivocal based on the weight of evidence. Overall, the endpoints selected for the non-cancer risk assessment are protective of these equivocal findings.

3.4 Occupational and Residential Risk Assessment

3.4.1 Toxicological Endpoints

Occupational exposures to S-2200 4 SC Fungicide, S-2200 4 SC Ag Fungicide, S-2200 4 SC VPP Fungicide, and S-2200 3.2 FS Fungicide are characterized as short- to intermediate-term in duration and are predominantly by the dermal and inhalation routes.

3.4.1.1 Short- and Intermediate-term Dermal

For short- and intermediate-term dermal risk assessment, the 28-day dermal toxicity study in rats was selected. No adverse effects were observed up to the limit dose of testing. A NOAEL of 1000 mg/kg bw/day was established.

The target margin of exposure (MOE) for these scenarios is 100, which includes uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability. The selection of this study and MOE is considered to be protective of all populations, including nursing infants and the unborn children of exposed female workers.

3.4.1.2 Short- and Intermediate-term Inhalation

For short- and intermediate-term inhalation scenarios, the reproductive toxicity study in rat was selected. For the inhalation scenarios, no repeat-dose inhalation toxicity study was available. Since an oral NOAEL was selected, an inhalation absorption factor of 100% was used in a route-to-route extrapolation. At the LOAEL of 166 mg/kg bw/day, increased brown pigmentation of the bile duct and periductular inflammatory cell infiltration in F_1 parental animals were observed. A NOAEL of 56 mg/kg bw/day was established.

The target MOE for these scenarios is 100, which includes uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability. The selection of this study and MOE is considered to be protective of all populations, including nursing infants and the unborn children of exposed female workers. A *Pest Control Products Act* factor of 1-fold was applied for the reasons outlined in the *Pest Control Products Act* Hazard Characterization section.

3.4.1.3 Non-dietary Oral Ingestion

For short-term incidental oral scenarios, the reproductive toxicity study in rat was selected. At the LOAEL of 166 mg/kg bw/day, increased brown pigmentation of the bile duct and periductular inflammatory cell infiltration in F_1 parental animals were observed. A NOAEL of 56 mg/kg bw/day was established.

The target MOE for this scenario is 100, which includes uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability. The selection of this study and MOE is considered to be protective of all populations, including nursing infants and the unborn children of exposed female workers. A *Pest Control Products Act* factor of 1-fold was applied for the reasons outlined in the *Pest Control Products Act* Hazard Characterization section.

3.4.1.4 Dermal Absorption

No in vivo or in vitro, rat or human, dermal absorption studies and/or data were submitted.

A dermal absorption value was not required for route-to-route extrapolation, as the NOAEL from the short-term 28-day dermal toxicity study is appropriate for assessing short- to intermediate-term exposures (no effects up to the limit dose of 1000 mg/kg bw/day).

3.4.2 Occupational Exposure and Risk

3.4.2.1 Mixer/loader/applicator Exposure and Risk Assessment

Individuals have potential for exposure to S-2200 4 SC Fungicide, S-2200 4 SC Ag Fungicide, and S-2200 4 SC VPP Fungicide during mixing, loading and application (ground and aerial), and exposure to S-2200 3.2 FS Fungicide during treatment of seeds (including mixing, loading, treating, and handling of treated seeds including bagging, sewing and stacking). Dermal and inhalation exposure estimates for workers were generated from PHED and surrogate worker exposure studies and data belonging to exposure task forces (AHETF, ARTF, SEEDTROPEX, and ORETF).

Exposures to workers mixing, loading and applying S-2200 4 SC Fungicide, S-2200 4 SC Ag Fungicide, S-2200 4 SC VPP Fungicide, and S-2200 3.2 FS Fungicide are expected to be short- to intermediate-term duration and to occur primarily by the dermal and inhalation routes. Exposure estimates were derived for mixers/loaders/applicators applying S-2200 4 SC Fungicide or S-2200 4 SC Ag Fungicide to canola (representing Crop Group 20A (Rapeseed Subgroup)) using groundboom (open-cab), aerial, and sprinkler chemigation equipment; to grape (representing Crop Group 13-07F (Small fruit vine climbing subgroup except fuzzy kiwifruit)) using airblast (open-cab) and sprinkler chemigation equipment; and to strawberry (representing Crop Group 13-07G (Low growing berry subgroup)) using groundboom and sprinkler chemigation.

Exposure estimates were derived for mixers/loaders/applicators applying S-2200 4 SC Fungicide or S-2200 4 SC VPP Fungicide to turfgrass (golf courses, lawns and landscape areas around residential, institutional, public, commercial and industrial buildings, recreational areas and to sod (sod farms)) using groundboom, backpack, manually- and mechanically-pressurized handwands, and turf handgun equipment. The exposure estimates are based on mixers/loaders/applicators wearing a long-sleeved shirt, long pants, and chemical-resistant gloves for foliar and turf uses. In addition, mixers and loaders for aerial application wear coveralls.

Exposure estimates were derived for seed treaters (including treaters, baggers, and cleaners) applying S-2200 3.2 FS Fungicide to canola seeds (representing Crop Group 20A (Rapeseed Subgroup)) and corn seeds (field corn, sweet corn, and popcorn) using closed transfer commercial treating equipment; and to legume vegetable seeds (represented by soybean and pea seeds) using closed transfer commercial or open transfer on-farm treating equipment. The exposure estimates are based on treaters wearing a long-sleeved shirt, long pants, and chemical-resistant gloves with seed treatment equipment cleaners also wearing chemical-resistant coveralls.

Chemical-specific data for assessing human exposures during pesticide handling activities were not submitted.

Dermal exposures were estimated by coupling the unit exposure values with the amount of product handled per day. Inhalation exposures were estimated by coupling the unit exposure values with the amount of product handled per day with 100% inhalation absorption. Exposures were 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 MOE; the target MOE is 100 for each of the dermal and inhalation routes. Routes of exposure cannot be combined since the toxic effects are different.

Table 3.4-1 Estimated Exposures of Mixers, Loaders, and Applicators From Foliar Applications of S-2200 4 SC Fungicide to Canola (Subgroup 20A), Grapes (Subgroup 13-07F), Strawberry (Subgroup 13-07G), and Turfgrass and Sod

Scenario	Application rate (g a.i./ha)	ATPD (ha/day)	Amount of a.i. handled per day [1] (kg a.i./day)	PHED (unless otherwise stated) dermal (µg a.i./kg a.i. handled)	Dermal Exposure [2] (mg a.i./kg bw/day)	Dermal MOE [3]	PHED (unless otherwise stated) Inhalation (µg a.i./kg a.i. handled)	Inhalation Exposure [2] (mg a.i./kg bw/day)	Inhalation MOE [4]
GROUND Applications									
Canola (covers strawberry (26 ha/day)): All Liquids Open M/L [5] (long pants, long sleeves, and gloves); Open cab groundboom (long pants, long sleeves, and no gloves)									
Farmer M/L/A	420	107	44.94	84.12	0.04725	21164	2.56	0.001438	38943
Custom M/L/A		360	151.2	84.12	0.15899	6290	2.56	0.004838	11575
Grapes: All Liquids Open M/L (long pants, long sleeves, and gloves); open-cab airblast (long pants, long sleeves, and gloves)									
Farmer, Custom M/L/A	420	20	8.4	3820.44 [b]	0.40115	2493	10.68 [b]	0.001121	49955
Turfgrass and sod: Backpack equipment; All Liquids Open M/L/A (long pants, long sleeves, and gloves)									
M/L/A	472	0.1875	0.0885	5445.85	0.00602	166113	62.1[a]	0.000069	782609

Scenario	Application rate (g a.i./ha)	ATPD (ha/day)	Amount of a.i. handled per day [1] (kg a.i./day)	PHED (unless otherwise stated) dermal (µg a.i./kg a.i. handled)	Dermal Exposure [2] (mg a.i./kg bw/day)	Dermal MOE [3]	PHED (unless otherwise stated) Inhalation (µg a.i./kg a.i. handled)	Inhalation Exposure [2] (mg a.i./kg bw/day)	Inhalation MOE [4]
Turfgrass and sod: Turf handgun; All Liquids Open M/L/A (long pants, long sleeves, and gloves)									
Custom M/L/A	472	2	0.944	785 [c]	0.00926	107991	4 [c]	0.000047	1148936
Turfgrass and sod: All Liquids Open M/L (long pants, long sleeves, and gloves); Open cab groundboom (long pants, long sleeves, and no gloves)									
Golf course M/L/A	472	16	7.552	84.12	0.00794	125945	2.56	0.000242	223140
Sod farm M/L/A		30	14.16	84.12	0.01489	67159	2.56	0.000453	119205
Turfgrass and sod: Mechanically-pressurized handgun; All Liquids Open M/L/A (long pants, long sleeves, and gloves)									
Custom M/L/A	472	4.75 [d]	2.242	5585.49	0.15653	6389	151	0.004232	12760
AERIAL (canola only): All Liquids Open M/L (coveralls, long pants, long sleeves, and gloves); Applicator (long pants, long sleeves, and no gloves)									
Farmer, Custom M/L	420	400	168	32.77	0.06882	14531	1.6	0.003360	16667
Farmer, Custom A		400	168	9.66	0.02029	49285	0.07	0.000147	380952
CHEMIGATION (canola, grapes, strawberry): All Liquids Open M/L (long pants, long sleeves, and gloves)									
Sprinkler Chemigation M/L	420	140	58.8	51.14	0.03759	26603	1.6	0.001176	47619

1. Amount of a.i. handled per day calculated using the maximum application rate × ATPD
2. Exposure was calculated using the amount of a.i. handled per day × unit exposure value/body weight (80 kg) (dermal or inhalation). No dermal absorption value required; assumed 100% inhalation systemic absorption
3. Estimates of dermal exposure for M/L and A were compared to a dermal NOAEL of 1000 mg/kg bw/day, target MOE = 100.
4. Estimates of inhalation exposure for M/L and A were compared to a NOAEL of 56 mg/kg bw/day, target MOE = 100.
5. Farmer mixer/loader is sufficient to represent the expected exposures of workers for chemigation

a. Moderate inhalation rate

b. Revised open-cab airblast unit exposures

c. ORETF (commercial) professional low pressure nozzle gun sprayer. 3800L/day default volume per day ÷ (min. 8 L spray volume/100 m^2 × 10000 m^2/ha)

Table 3.4-2 Risk Estimates for Workers Treating Seeds in Commercial Facilities with S-2200 3.2 FS Fungicide

Worker task	Unit exposure (µg/kg a.i. handled)[1]		Appl. rate	Seed treated (kg seed/ day)[3]	Dermal Exposure (mg/kg bw/day)[4]	Dermal MOE[5]	Inhalation (mg/kg bw/day)[4]	Inhalation MOE[5]
	Dermal	Inhalation	(kg a.i./ kg seed)					
Closed mix, load, transfer commercial facilities								
Corn (field, sweet, and pop)								
Treater	0.88	0.016	0.00006	125,000	8.25E-05	1.21E+07	1.50E-06	3.73E+07
Bagger	17.67	0.89	0.00006	125,000	1.66E-03	6.02E+05	8.34E-05	6.71E+05
Cleaner (normalized)*	17.1	5.1	0.00006	-	1.29E-03	7.75E+05	3.83E-04	1.46E+05
Treater + Cleaner †	-	-	0.00006	-	1.37E-03	7.30E+05	3.85E-04	1.45E+05
Canola								
Treater	0.88	0.016	0.0001	67,000	7.37E-05	1.36E+07	1.34E-06	4.18E+07

Worker task	Unit exposure (µg/kg a.i. handled)[1]		Appl. rate (kg a.i./ kg seed)	Seed treated (kg seed/ day)[3]	Dermal Exposure (mg/kg bw/day)[4]	Dermal MOE[5]	Inhalation (mg/kg bw/day)[4]	Inhalation MOE[5]
	Dermal	Inhalation						
Bagger	17.67	0.89	0.0001	67,000	1.48E-03	6.76E+05	7.45E-05	7.52E+05
Cleaner (normalized)*	17.1	5.1	0.0001	-	2.15E-03	4.65E+05	6.38E-04	8.78E+04
Treater + Cleaner †	-	-	0.0001	-	2.22E-03	4.50E+05	6.39E-04	8.76E+04
Soybean								
Treater	0.88	0.016	0.0001	63,000	6.93E-05	1.44E+07	1.26E-06	4.44E+07
Bagger	17.67	0.89	0.0001	63,000	1.39E-03	7.19E+05	7.01E-05	7.99E+05
Cleaner (normalized)*	17.1	5.1	0.0001	-	2.15E-03	4.65E+05	6.38E-04	8.78E+04
Treater + Cleaner †	-	-	0.0001	-	2.22E-03	4.50E+05	6.39E-04	8.76E+04
Legumes (other than soybean)								
Treater	0.88	0.016	0.0001	216,000	2.38E-04	4.20E+06	4.32E-06	1.30E+07
Bagger	17.67	0.89	0.0001	216,000	4.77E-03	2.10E+05	2.40E-04	2.33E+05
Cleaner (normalized)*	17.1	5.1	0.0001	-	2.15E-03	4.65E+05	6.38E-04	8.78E+04
Treater + Cleaner †	-	-	0.0001	-	2.39E-03	4.18E+05	6.42E-04	8.72E+04

* Normalized Cleaner unit exposure (µg/g a.i./100kg seed/day)
= 240.02 µg/day / 14.04 g a.i./100 kg seed, application rate in the exposure study
† Assuming that a worker both treats and cleans in the same workday; using normalized cleaner, and considered conservative
1. For closed transfer commercial facilities, the arithmetic mean values were used from the surrogate exposure study; long-sleeved shirt and long pants (plus nitrile gloves for mixer/loader/calibrators); plus Tyvek coveralls and nitrile gloves for cleaners.
2. Highest PMRA-supported application rate on the label
3. Default seed treatment throughput for beans (PMRA seed treatment database)
4. Exposure (mg/kg bw/day) = unit exposure (µg/kg a.i. handled) × application rate (g a.i./100 kg seed) × seeds treated (kg seed/day) × 0.001(mg/µg) / body weight (kg bw)
Cleaner Normalized Exposure (mg/kg bw/day) = (unit exposure (µg/g a.i./100 kg seed) × (0.0001 or 0.00006) kg a.i./kg seed × 100 kg seed × 1000 g/kg)/(80 kg bw × 1000 µg/mg)
5. Margin of Exposure (MOE) = NOAEL/Exposure; NOAEL = 1000 mg/kg bw/day, target MOE = 100; inhalation NOAEL = 56 mg/kg bw/day, target MOE = 100

Table 3.4-3 Risk Estimates for On-Farm Treatment (Mobile Treaters) of Legume Seeds with S-2200 3.2 FS Fungicide

Unit exposure values [1,2] (µg/kg a.i.)		Amount of a.i. handled per day [3] (kg a.i./day)	Dermal Exposure [4,5] (mg/kg bw/day)	Dermal MOE [6]	Inhalation Exposure [4,5] (mg/kg bw/day)	Inhalation MOE [6]
Dermal	Inhalation					
90th percentile	90th percentile					
141.9	7.825	1.9	0.00337	296736	0.00019	284211

1. Surrogate mixer/loader/applicator study
2. Workers wearing a single layer (a long-sleeved shirt, long pants, and chemical-resistant gloves)
3. Amount a.i. handled per day based on peas (except cowpea and field pea; representing legumes, including soybean) = application rate (0.0001 kg a.i./kg seed) × seeding rate (190 kg seed/ha) × area planted per day (100 ha/day).
4. No adjustment for dermal absorption required; both dermal and inhalation exposures considered 100% systemically available
5. Daily exposure (mg/kg bw/day)
= (Unit exposure × Amount of a.i. handled/day) / (80 kg bw × 1000 µg/mg)
6. Margin of Exposure (MOE) = NOAEL (route-specific)/Exposure; short- to intermediate term durations, target MOE = 100

Table 3.4-4 Exposure and Risk Estimates for Farmers Treating and Planting Legume Seeds with S-2200 3.2 FS Fungicide

PPE: single layer + chemical-resistant gloves								
Crop	Unit exposure (µg/kg bw/day) [1]		Seed treated and Planted [2] (kg seed/day)	Rate (kg a.i./kg seed)	Dermal Exposure [3] (mg/kg bw/day)	Dermal MOE (target = 100)[4]	Inhalation Exposure [3] (mg/kg bw/day)	Inhalation MOE (target = 100)[4]
	Dermal	Inhalation						
Legume vegetable seeds	407.34	223.03	19000	0.0001	0.0096743	103366	0.005297	10572

1 Unit exposures in the surrogate seed treatment study for workers wearing a long-sleeved shirt, long pants, and chemical-resistant gloves
2 From the Seed Treated/Planted Per Day tables (2009)
3 Exposure = (Unit exposure × Seed treated/planted × Rate)/(1000 µg/mg × 80 kg bw)
4 Dermal NOAEL = 1000 mg/kg bw/day, target MOE= 100; inhalation NOAEL = 56 mg/kg bw/day, target MOE = 100

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 S-2200 4 SC Fungicide, S-2200 4 SC Ag Fungicide, S-2200 4 SC VPP Fungicide, and workers planting seeds treated with S-2200 3.2 FS Fungicide. Given the nature of activities performed, the primary route of exposure for workers re-entering treated areas would be through the dermal route, and through the dermal and inhalation routes for planting treated seeds. The durations of exposure are considered to be short-term in duration when entering treated crops, turf, and handling and planting seeds.

Dermal exposures to workers entering treated areas (Table 3.4-5) are estimated by coupling dislodgeable foliar residue values for foliar treatments, or turf transferable residue values for turf, with activity-specific transfer coefficients. Chemical-specific dislodgeable foliar residue data were not submitted. Therefore, a default dislodgeable foliar residue value of 25%, or default turf transferable residue value of 1% of the application rate on the day of the final treatment, was used in the exposure assessment.

Dermal and inhalation exposures of workers planting treated seeds (Table 3.4-6) are estimated by coupling unit exposures for planting treated seeds with the amount of seeds planted, and size of areas planted.

No dermal absorption value was required since the dermal endpoint was based on a dermal study. Inhalation absorption is considered 100%. Exposures were normalized to mg/kg bw/day by using 80 kg adult body weight.

Exposure estimates were compared to the toxicological end point to obtain the MOE; the target MOE is 100.

Table 3.4-5 Postapplication Occupational Exposure and Risk Estimates for Re-Entry Tasks Performed in Crops Treated with S-2200 4 SC Fungicide

Crop	Tasks	Maximum Application Rate (µg/cm^2)	Number of Applications at Maximum Rate	Minimum Application Interval (days)	Dislodgeable Foliar Residue or Turf Transferable Residue (µg/cm^2)[A]; DALA = 0	Highest of Crop Group Transfer Coefficients[B] (cm^2/hour)	Dermal Exposure (mg/kg bw/day)	MOE
Canola	Scouting, solid stand	4.2	1	-----	1.050	1100	0.1155	8658
Grape	Girdling, turning	4.2	3	10	1.544	19300	2.9799	336
	Hand harvesting, leaf pulling, tying and training	4.2	3	10	1.544	8500	1.3124	762
Strawberry	Hand harvesting	4.2	4	7	1.907	1100	0.2098	4766
Turfgrass/ Sod	Golf course maintenance: transplanting; sod slab harvesting	4.72	4	14	0.061	6700	0.0409	24450
	Golf course/Sod mowing, watering, etc.					3500	0.0214	46729
	Aerating, scouting, fertilizing, hand pruning, mechanical weeding, seeding					1000	0.0061	163934

DALA = Days after last application
[A] Use default dislodgeable foliar residue for canola, grapes, and strawberry; turf transferable residue for turfgrass
[B] PMRA Transfer Coefficients based on ARTF database (2012)
[C] Dermal NOAEL = 1000 mg/kg bw/day, target MOE= 100

Table 3.4-6 Exposure and Risk Estimates for Planting Canola, Corn, Soybean, and Pea Seeds Treated with S-2200 3.2 FS Fungicide

Scenario	Unit exposure (µg/kg a.i. handled)[1]		Seeds planted per day [2] (kg)	Appl. rate (kg a.i./kg seed)	Amount of a.i. handled per day [3] (kg a.i./day)	Exposure [4] (mg/kg bw/day)		MOE [5]	MOE [5]
Planting	Dermal	Inhalation				Dermal	Inhalation	Dermal	Inhalation
canola	1515	82.83	600	0.0001	0.06	0.0011	0.00006	909091	933333
corn			1350	0.00006	0.081	0.0015	0.00008	666667	700000
Legumes (excluding soybean)			19000	0.0001	1.9	0.0360	0.00197	27778	28426
soybean			9000	0.0001	0.9	0.0170	0.00093	58824	60215

Note: Exposure estimates based on passive dosimetry study during planting of treated maize corn.
[1] Unit exposure values for planters wearing a single layer + chemical-resistant gloves and using closed-cab planting equipment
[2] Seed Treated Planted Per Day Table
[3] Kg a.i. handled per day = kg seed treated per day × application rate (kg a.i./kg seed)
[4] Exposure (mg/kg bw/day) = $\frac{\text{Unit exposure (µg/kg a.i. handled per day)} \times \text{kg a.i. handled per day} \times 0.001\text{mg/µg}}{\text{80 kg bw}}$
[5] Dermal NOAEL = 1000 mg/kg bw/day, target MOE= 100; inhalation NOAEL = 56 mg/kg bw/day, target MOE = 100

Risks to workers entering treated crops, turfgrass and sod, are not of concern. The default restricted entry interval (REI) of 12 hours is adequate to protect workers. Risks to workers planting treated seeds are not of concern when following the treated seed label precautions.

3.4.3 Residential Exposure and Risk Assessment

3.4.3.1 Handler Exposure and Risk

No homeowner applicator scenario is proposed.

3.4.3.2 Postapplication Exposure and Risk

3.4.3.2.1 Postapplication Dermal Exposures

Section 3, Lawns and Turf, of the 2012 United States Environmental Protection Agency (USEPA) Residential Standard Operating Procedure (SOP) was used to determine postapplication exposures to people re-entering treated lawns in residential areas.

The duration of exposure is considered to be short-term (up to 30 days) for golfing and for residential turf activities. No product-specific turf transferable residue (TTR) study was provided; therefore, the current default peak (day 0) DFR value of 1% of the application rate, transfer coefficients, exposure time, and algorithms were based on the SOP for turf. Body weights used were 80 kg for adults, 57 kg for youth, 32 kg for children (6<11years old), and 11 kg for children (1<2 years old).

Table 3.4-7 Postapplication Dermal Exposure and Risk Estimates for Re-Entry onto Turf Treated with S-2200 4 SC Fungicide

Lifestage (years of age)	TTR_t (µg/cm^2)	Transfer Coefficient (cm^2/hour)	Hours of Exposure (hour/day)	Exposure (mg/day)	Absorbed Dose (mg/kg/day)	Dermal MOE
High Contact Lawn Activities						
Adult 18+	0.05	180,000	1.5	12.74	0.1593	6277
Youth 11 <16		148,000	1.3	9.08	0.1593	6277
Children 1 <2		49,000	1.5	3.47	0.3154	3171
Mowing Turf						
Adult 18+	0.05	5,500	1	0.2596	0.003245	308166
Youth 11 <16		4,500	1	0.2124	0.003726	268362
Golfing (Treated greens, tees, and fairways)						
Adult 18+	0.05	5,300	4	1.0006	0.012508	79949
Youth 11 <16		4,400	4	0.8307	0.01457	68615
Children 6 <11		2,900	4	0.5475	0.01711	58445

3.4.3.2.2 Child Incidental Oral Ingestion

A child may place a hand in his/her mouth a number of times, as well as place an object in their mouth a number of times during a certain period of time. Each of these events could result in a potential transfer of residue, but could also result in a soil ingestion event as soil may be present on the hand or object during mouthing (USEPA Residential SOP 2012). Table 3.4-8 shows estimates of the exposures for each scenario. Risks from each of the three non-dietary oral ingestion scenarios are considered not to be of concern (greater than the target MOE of 100).

Table 3.4-8 Postapplication Residential Child Oral Exposure and Risk Assessment for Entry onto Turfgrass Treated with S-2200 4 SC Fungicide

Lifestage (years of age)	Route of ingestion	Residue loading (mg/cm^2)	Oral Exposure (mg/kg bw/day)	MOE
Children 1 <2	Hand-to-mouth	0.00069	0.0065	8660
	Object-to-mouth	0.04720	0.00020	285171
	Incidental soil ingestion	3.1624 (µg/g)	1.4E-05	3.9E+06

3.4.3.2.3 Residential Aggregate Assessment

Adults and youth are considered to conduct multiple postapplication activities on treated turf. The public (including children) may enter treated recreational turf areas on the day of treatment. Table 3.4-9 shows the activities that are considered to co-occur when adults and youth are active on treated turf. Golfing is not part of the aggregate assessment. Risks for adults and youth are not considered to be of concern (greater than the target MOE of 100).

Table 3.4-9 Residential Dermal Aggregate Risks of Entry onto Turfgrass Treated with S-2200 4 SC Fungicide (or S-2200 4 VPP Fungicide)

	Scenario		Dermal MOE
	Absorbed Dose (mg/kg bw/day)		
Lifestage (years of age)	High Contact Lawn Activities [1]	Mowing Turf [1]	Aggregate [2]
Adult 18+	0.1593	0.003245	6154
Youth 11 <16	0.1593	0.003726	6135

1. Exposures taken from Table 3.4-7
2. Based on SPN2003-04; target MOE is 100

Postapplication exposure scenarios that are likely to co-occur over a short term are the dermal and hand-to-mouth scenarios (2012, USEPA Residential SOP, Turf and Lawns) (Table 3.4-10). However, there is no common toxic effect for aggregation of dermal and oral exposures; therefore, the dermal route is not included. The PMRA also includes dietary exposure in this aggregate because these exposures are by the oral route. Aggregate oral exposure risks to children are not considered to be of concern.

Table 3.4-10 Aggregate Oral (Non-Dietary and Dietary) Ingestion of Mandestrobin Residues by Children 1<2 yrs

Route of ingestion	Oral Exposure (mg/kg bw/day)
Hand-to-mouth [1]	0.0065
Chronic dietary exposure [2]	0.027593
Aggregate MOE [3] (target = 100)	1644

1. From Table 3.4-8; hand-to-mouth activity is not expected to under-estimate non-dietary intake of children 1<2 years of age
2. From Dietary Exposure Assessment (food + water)
3. Using PMRA SPN2003-04

3.4.3.2.4 Pick-Your-Own Acute Aggregate Exposure Assessment

Strawberry and lowbush blueberry are considered to be pick your own (PYO) crops. The public may be exposed to residues of S-2200 4 SC Fungicide on these crops at PYO operations. This exposure is expected to be acute and to occur by the dermal and oral routes. The acute dermal exposures for adults, youth, and children in PYO facilities are addressed by the dermal exposures of workers re-entering treated fields for hand harvesting, and not considered to be of concern. Exposure by the oral route is addressed by the dietary exposure assessment. Therefore, the public picking strawberries and lowbush blueberries at PYO facilities is acceptable at the pre-harvest interval on the label.

3.4.3.3 Bystander Exposure and Risk

Bystander exposure should be negligible since the potential for drift is expected to be minimal. Application is limited to agricultural crops 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 Residues in Plant and Animal Foodstuffs

The residue definition for risk assessment and enforcement in plant products is mandestrobin. The data gathering/enforcement analytical method is valid for the quantitation of mandestrobin (S-2200) residues in crops. The residue definition for risk assessment and enforcement in animal commodities will be determined once a livestock feeding study and enforcement method are submitted to the Agency.

The residues of mandestrobin are stable in rapeseed (seed, oil and meal), lettuce, barley (grain, straw), soybean seed, and corn (grain, forage, K+CWHR) for up to 12 months; in corn stover for up to 9 months; in grapes for up to 8 months; in grape juice for up to 7 months; and in strawberries and raisins for up to 5 months, when stored in a freezer at -18°C. Freezer storage stability studies are on-going for rapeseed (seed, oil, and meal), strawberries and grapes (fruit, raisins). Mandestrobin residues concentrated in the following processed commodities: raisin (1.9-fold), and grape juice (1.4-fold). Quantifiable residues are not expected to occur in livestock

matrices with the current use pattern. Crop field trials conducted throughout Canada and the United States using end-use products containing mandestrobin at approved rates in or on corn, grapes, rapeseed, soybeans, and strawberries are sufficient to support the proposed maximum residue limits.

3.5.2 Concentrations in Drinking Water

Estimated environmental concentrations (EECs) of mandestrobin combined residue 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 mandestrobin 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 average concentrations in the top one metre of the water table. EECs of mandestrobin combined residue in surface water were calculated using the SWCC model, which simulates pesticide runoff from a treated field into an adjacent water body and the fate of a pesticide within that water body. Pesticide concentrations in surface water were estimated in a vulnerable drinking water source, a small reservoir.

Drinking water modelling of mandestrobin includes four transformation products, 5-COOH-S-2200, MCBX, S-2200-OR and S-2200-ORC as well as mandestrobin itself. Degradation rates for drinking water modelling were calculated from the overall degradation of these five compounds, and for groundwater modelling, the more conservative K_d from 5-COOH-S-2200 was used.

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 EEC estimate is expected to allow for future use expansion into other crops at this application rate. Table 3.5-1 lists the application information and main environmental fate characteristics used in the simulations. Twenty-seven initial application dates between May and September were modelled. The model was run for 50 years for all scenarios. The largest EECs of all selected runs are reported in Table 3.5-2 below.

Table 3.5-1 Major groundwater and surface water model inputs for Level 1 assessment of mandestrobin

Type of Input	Parameter	Value
Application Information	Crop(s) to be treated	Beans, Blueberries, Canola, Chick peas, Corn, Flaxseed, Gooseberries, Grapes, Lentils, Lupins, Mustard seed, Peas, Radish, Soybeans, Strawberries, Turf
	Maximum allowable application rate per year (g a.i./ha)	1890
	Maximum rate each application (g a.i./ha)	472 (turf) and 420 (for other crops)
	Maximum number of applications per year	4

Type of Input	Parameter	Value
	Minimum interval between applications (days)	14 (turf) and 7 (for other crops)
	Method of application	Field sprayer or aerial application equipment
Environmental Fate Characteristics	Hydrolysis half-life at pH 7 (days)	stable
	Photolysis half-life in water (days)	4.5 days (mandestrobin only) 10.7 days (mandestrobin with four transformation products)
	Adsorption K_{OC} or K_d (mL/g)	Mandestrobin K_{OC} of 365 used for surface water modelling; 5-COOH-S2200 K_d of 1.24 used for groundwater modelling
	Aerobic soil biotransformation half-life (days)	264 days @ 20°C for eco 306 days @ 20°C for drinking water
	Aerobic aquatic biotransformation half-life (days)	693 days @ 20°C for eco 4320 days @ 20°C for drinking water
	Anaerobic aquatic biotransformation half-life (days)	2345 days @ 20°C for eco 6335 days @ 20°C for drinking water

Table 3.5-2 Level 1 estimated environmental concentrations of mandestrobin in potential drinking water sources

Compound	Groundwater EEC (µg a.i./L)		Surface Water EEC (µg a.i./L)	
			Reservoir	
	Daily[1]	Yearly[2]	Daily[3]	Yearly[4]
Mandestrobin combined residue	225	225	82	21

Notes:
[1] 90th percentile of daily average concentrations
[2] 90th percentile of 365 day moving-average concentrations
[3] 90th percentile of the peak concentrations from each year
[4] 90th percentile of yearly average concentrations

3.5.3 Dietary Risk Assessment

Chronic (non-cancer) dietary risk assessments were conducted using the Dietary Exposure Evaluation Model (DEEM–FCID™ NHANES, Version 4.02), 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 2003-2008 available through CDC's National Center for Health Statistics (NCHS).

3.5.3.1 Chronic Dietary Exposure Results and Characterization

The following criteria were applied to the basic chronic non-cancer analysis for mandestrobin: 100% crop treated, default processing factors and proposed MRLs of rapeseed (CSG 20A), grape (CSG 13-07F), strawberry (CSG 13-07G, except cranberry), soybean (CG 6, except cowpea and field pea) and corn. The basic chronic dietary exposure from all supported mandestrobin food uses (alone) for the total population, including infants and children, and all representative population subgroups is less than 1.3% of the acceptable daily intake (ADI). Aggregate exposure from food and drinking water is considered acceptable. The PMRA estimates that chronic dietary exposure to mandestrobin from food and drinking water is 2.8% (0.0084 mg/kg bw/day) of the ADI for the total population. The highest exposure and risk estimate is for children 1-2 years old at 9.2% (0.028 mg/kg bw/day) of the ADI.

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.

3.5.4 Aggregate Exposure and Risk

The aggregate risk for mandestrobin consists of exposure from food and drinking water sources.

3.5.5 Maximum Residue Limits

Table 3.5-3 Proposed Maximum Residue Limits

Commodity	Recommended Maximum Residue Limit (ppm)
Raisins	7.0
Small fruit vine climbing (Crop Subgroup 13-07F, except fuzzy kiwifruit)	5.0
Low growing berry (Crop Subgroup 13-07G, except cranberry)	3.0
Rapeseed (Crop Subgroup 20A)	0.5
Legume vegetables (succulent or dried) (Crop Group 6, except cowpea and field pea), corn (field, popcorn, sweet)	0.02

Maximum Residue Limits (MRLs) are proposed for each commodity included in the listed crop groupings in accordance with the Residue Chemistry Crop Groups webpage in the Pesticides and Pest Management section of Health Canada's website.

For additional information on maximum residue limits 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, Tables 1, 8 and 9.

4.0 Impact on the Environment

The active substance mandestrobin is a racemic mixture of the two isomers (S-2200 *R*-isomer and S-2200 *S*-isomer) in a ratio of 50:50. The results presented in this section are for the mixture unless stated otherwise.

4.1 Fate and Behaviour in the Environment

The fate and behaviour of mandestrobin and its major transformation products are summarized in Appendix I, Table 10. The chemical name and structure of transformation products formed in the environment, as well as a summary of their occurrence in environmental fate studies, are presented in Appendix I, Table 11.

Mandestrobin is introduced in the environment when it is applied as a seed treatment, foliar spray and chemigation to a variety of seeds, field crops and non-crops. Mandestrobin could reach the soil upon application or through wash-off from the leaves. Abiotic transformation processes are not expected to contribute significantly to the dissipation of mandestrobin in soil as this compound is stable to hydrolysis and phototransformation. Biotransformation may be an important route of dissipation for mandestrobin in the terrestrial environment.

In both aerobic and anaerobic soils, mandestrobin transformed to the major products 5-COOH-S-2200, DX-CA-S-2200, 2-$CONH_2$-S-2200, 5-$CONH_2$-S-2200, MCBX and De-Xy-S-2200. Mandestrobin is slightly persistent to persistent in aerobic soil and will also persist in anaerobic soil.

Based on results from adsorption studies, mandestrobin exhibited medium to low mobility in soil, transformation products 5-COOH-S-2200 and 2-COOH-S-2200 exhibited very high to low mobility. The groundwater ubiquity scores (GUS) calculated for mandestrobin and its transformation products 5-COOH-S-2200 and 2-COOH-S-2200 based on their persistence and mobility indicate that mandestrobin is a borderline leacher and that 5-COOH-S-2200 and 2-COOH-S-2200 are probable leachers. In field dissipation studies, no residues of mandestrobin and its transformation products were detected beyond a 30 cm soil depth. Mandestrobin will not carry over to the next growing season.

Mandestrobin could reach surface water through spray drift and runoff. Once in the aquatic environment, mandestrobin is not expected to hydrolyze, but will undergo rapid phototransformation in clear shallow water to the major transformation products S-2200-OR, S-2200-ORC, S-2200-PR and CO_2. Biotransformation is not a primary route of transformation for mandestrobin in water and large amounts of mandestrobin were shown to partition into sediment. MCBX and 5-COOH-S-2200 were the only major biotransformation products identified in aquatic systems. Mandestrobin does not accumulate to a large degree in fish and depuration occurs rapidly.

Residues of mandestrobin and its transformation products are not expected to be found in air. Mandestrobin exhibits low volatility based on its low vapour pressure.

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 derived using standard models which take into consideration the application rate(s), chemical properties and environmental fate properties, including the dissipation of the pesticide between applications. Ecotoxicology information includes acute and chronic toxicity data for various organisms or groups of organisms from both terrestrial and aquatic habitats, including invertebrates, vertebrates, and plants. Toxicity endpoints used in risk assessments may be adjusted to account for potential differences in species sensitivity as well as varying protection goals (in other words, protection at the community, population, or individual level).

Initially, a screening level risk assessment is performed to identify pesticides and/or specific uses that do not pose a risk to non-target organisms, and to identify those groups of organisms for which there may be a potential risk. The screening level risk assessment uses simple methods, conservative exposure scenarios (for example, direct application at a maximum cumulative application rate) and sensitive toxicity endpoints. A risk quotient (RQ) is calculated by dividing the exposure estimate by an appropriate toxicity value (RQ = exposure/toxicity), and the risk quotient is then compared to the level of concern (LOC = 1 in most cases except for bees and certain beneficial arthropods where the level of concern is 0.4 and 2, respectively). If the screening level risk quotient is below the level of concern, the risk is considered negligible and no further risk characterization is necessary. If the screening level risk quotient is equal to or greater than the level of concern, then a refined risk assessment is performed to further characterize the risk. A refined assessment takes into consideration more realistic exposure scenarios 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.

4.2.1 Risks to Terrestrial Organisms

A risk assessment for mandestrobin and its transformation products was undertaken for terrestrial organisms based on available toxicity data. A summary of terrestrial toxicity data is presented in Appendix I, Table 12. Results of the accompanying risk assessment are presented in Appendix I, Tables 13-15.

Earthworms: Earthworms could be exposed to mandestrobin when this compound reaches the soil upon application. The expected environmental concentration is, therefore, calculated based on a direct application of mandestrobin to bare soil at the maximum seasonal labelled application rate.

At levels higher than those expected in the Canadian environment, the acute exposure of earthworms to mandestrobin has been shown to cause mortality and decreased weight. Chronic exposure to mandestrobin also resulted in significant reduction in reproduction and body weight. However, given the low expected environmental concentration, risk quotients calculated for acute and chronic exposure to mandestrobin do not exceed the level of concern. The 5-COOH-S-2200 and 2-COOH-S-2200 transformation products were not acutely toxic to earthworms. There is therefore no concern from acute exposure to these transformation products.

Bees (pollinators): Foraging bees could be exposed directly to mandestrobin spray droplets during application or to mandestrobin residues found on the surface of leaves (contact exposure). Foraging bees could also be exposed to mandestrobin through the ingestion of pollen and nectar contaminated from direct spray or the systemic movement in the plant (oral exposure). In addition, brood may be exposed to mandestrobin and its transformation products as foraging bees bring contaminated pollen and nectar back to the hive.

In laboratory tests, mandestrobin was non-toxic to adult honey bees when applied directly on bees or through diet consumption. When honey bee larvae were incubated with a diet treated with mandestrobin, no mortality was observed at the highest dose tested. All risk quotients calculated for mandestrobin did not exceed the level of concern.

Beneficial arthropods: The risk assessment for beneficial arthropods considers that the main route of exposure for these non-target organisms is from contact with treated plant material both on the treated area (from direct spray on the crop) and at the margins of the treated field (from spray drift). The expected concentration of mandestrobin residues on foliage within the treated field is calculated as the cumulative application rate, which takes into account the maximum labelled application rate, the application interval and the dissipation of the compound on the surface of the leaves.

In laboratory tests carried out with freshly dried residues on a glass plate, S-2200 25SC Fungicide caused no statistically significant adverse acute effects on the parasitic wasp and predatory mite. Significant effects on the reproduction of the parasitic wasp were observed, but at levels higher than those expected in the environment. The screening level risk quotients calculated for both the predatory mite and the parasitic wasp were below the level of concern.

Birds and mammals: At the highest dose, acute oral exposure to mandestrobin caused no mortality in bobwhite quail and canary. When mandestrobin was administered in the diet no adverse effects to bobwhite quail and mallard duck were observed. In reproductive tests, no subchronic or reproductive effects were observed at the highest concentrations tested for either bobwhite quail or mallard duck.

Laboratory studies indicated that mandestrobin was not acutely toxic to rats. Among chronic effects observed in a two-generation dietary reproduction study with rats, was a decreased body weight in offspring.

For birds and mammals, risk quotients calculated at the screening level for mandestrobin did not exceed the level of concern on an acute or reproductive basis for both foliar application (up to 4 times a year for a maximum total rate of 1888 g a.i./ha/year) and seed treatment (up to 10 g a.i./100 kg seeds or 0. 9 g ai/ha).

Non-target plants: For the risk assessment, the cumulative application rate is compared to plant toxicity endpoints. The cumulative application rate takes into account the maximum labelled application rate, the application interval and the dissipation of the compound on the surface of the leaves. For the off-field assessment, the rate is adjusted according to the projected drift deposition at one metre downwind from the site of application.

The toxicity of S-2200 4 SC Fungicide to non-target plants was determined through vegetative vigour and seedling emergence assays using standard crop species. No significant adverse effects were observed in any plant species at the highest application rate tested (560 g a.i./ha). However, given that the study was conducted at the one-time application rate of 560 g a.i./ha, whereas the seasonal maximum application rate (4 × 472 g a.i./ha) is 1888 g a.i./ha, the screening risk quotient exceeded the level of concern. The risk to terrestrial plants was, thus, further assessed.

For an ASAE (American Society of Agricultural Engineers) ‘coarse’ droplet size, the maximum spray drift deposition at one metre downwind from the point of application is 17% for aerial application. Based on the risk quotients using the off-field EECs from drift, the level of concern for terrestrial vascular plants is not exceeded.

There is still uncertainty with regards to potential effects on the vegetative vigour and seedling emergence of plants after exposure to multiple applications. Due to this uncertainty, it was determined that drift mitigation measures are necessary.

4.2.2 Risks to Aquatic Organisms

A risk assessment of mandestrobin, its *R*- and *S*-isomers and transformation products 2-COOH-S-2200, 5-COOH-S-2200, S-2200-OR and S-2200-ORC was undertaken for freshwater and marine organisms based on available toxicity data. A summary of aquatic toxicity data is presented in Appendix I, Table 16. The accompanying risk assessment is presented in Appendix I, Tables 17-20.

Freshwater invertebrates: Mandestrobin was moderately toxic and S-2200 *R*-isomer was highly toxic to daphnids on an acute basis. Acute exposure to S-2200 *S*-isomer and other transformation products did not affect daphnids. In general, the *S*-isomer was shown to be of lower toxicity to aquatic organisms than mandestrobin, while the *R*-isomer was shown to be of comparable toxicity. Chronic exposure to mandestrobin reduced parental survival, reproduction and growth in daphnids, reduced the survival in chironomids, and reduced body length in amphipods.

The screening level risk quotients for freshwater invertebrates from acute and chronic exposure to mandestrobin do not exceed the level of concern. The risk quotients for daphnids from acute exposure to S-2200 *R* and *S*-isomers and the transformation products, 2-COOH-S-2200, 5-COOH-S-2200, S-2200-OR and S-2200-ORC do not exceed the level of concern at the screening level.

Freshwater fish: Mandestrobin was demonstrated to be of moderate toxicity to bluegill sunfish and sheepshead minnow, but showed high toxicity to rainbow trout and fathead minnow. The S-2200 *R*-isomer was highly toxic to rainbow trout on an acute basis. Acute exposure to S-2200 *S*-isomer and other transformation products did not affect rainbow trout.

The risk quotients for rainbow trout resulting from acute exposure to S-2200 *S*-isomer and transformation products 2-COOH-S-2200, 5-COOH-S-2200, S-2200-OR did not exceed the level of concern at the screening level. The screening level risk quotients for freshwater fish resulting from acute and chronic exposure to mandestrobin, and from acute exposure to S-2200 *R*-isomer and S-2200-ORC exceeded the level of concern. The risk to freshwater fish from acute and chronic exposure to mandestrobin, S-2200 *R*-isomer and S-2200-ORC was further assessed (see Section 4.2.3).

Amphibians: To assess the risk to amphibians, fish toxicity endpoints are used as surrogate data, when amphibian data are not available, to represent aquatic life-stages of amphibians. The difference between fish and amphibian risk assessments is related to the water depth used for the estimated environmental concentrations (water depth of 15 cm for amphibians). The screening level risk quotients for acute and chronic exposures of amphibians to mandestrobin exceeded the level of concern. The risk to amphibians was thus further assessed (see Section 4.2.3).

Freshwater algae and vascular plants: Mandestrobin showed adverse effects on cell density, growth rate and yield in green algae, blue-green algae and diatoms. S-2200 *R*-isomer and 2-COOH-S-2200 reduced the growth rate and biomass in test with green algae. S-2200 *S*-isomer and other transformation products had no adverse affects on green algae. Mandestrobin reduced the frond number and biomass of duckweed.

The risk quotient for freshwater algae resulting from acute exposure to mandestrobin and the S-2200 *R*-isomer exceeded the level of concern at the screening level. The risk quotients for freshwater green alga from exposure to S-2200 *S*-isomer and the transformation products 2-COOH-S-2200, 5-COOH-S-2200, S-2200-OR and S-2200-ORC did not exceed the level of concern at the screening level. The risk quotient for duckweed from exposure to mandestrobin did not exceed the level of concern. The risk to freshwater algae from acute exposure to mandestrobin and S-2200 *R*-isomer was thus further assessed (see Section 4.2.3).

Marine/estuarine invertebrates: Mandestrobin was acutely toxic to the mysid shrimp and moderately toxic to the eastern oyster. Exposure to mandestrobin for 36 days affected the first generation growth and survival of the mysid shrimp. Mandestrobin had no chronic effects on the sediment dwelling estuarine amphipod.

The risk quotient for marine invertebrates (mysid shrimp) resulting from acute and chronic exposure to mandestrobin exceeded the level of concern at screening level. The risk to marine invertebrates was, thus, further assessed (see Section 4.2.3).

Marine/estuarine fish: Acute exposure to mandestrobin had no adverse effects to the sheepshead minnow at the highest test concentration. Exposure to mandestrobin during early life stages of sheepshead minnows resulted in significant reductions in total length, wet weight and dry weight.

The screening level risk quotient for marine fish resulting from acute exposure to mandestrobin exceeded the level of concern. The risk quotients for marine fish resulting from chronic exposure to mandestrobin did not exceed the level of concern at the screening level. The acute risk to marine fish was, thus, further assessed (see Section 4.2.3).

Marine/estuarine algae: Mandestrobin exhibited acute adverse effects on cell density, growth rate and yield of the marine diatom.

The risk quotient for marine diatom resulting from acute exposure to mandestrobin did not exceed the level of concern at the screening level.

4.2.3 Further characterization of risk to aquatic organisms

4.2.3.1 Assessment of potential risk from spray drift

To further characterize the risk to fish, amphibians, crustaceans and algae, refined EECs for aerial application were calculated using a maximum drift deposition percent at one metre downwind from the point of application. The maximum percent drift deposition for aerial and ground application and an ASAE 'coarse' droplet size (as specified on the product labels) is 17% and 3% of the application rate, respectively. The EECs were calculated for water bodies 15-cm and 80-cm deep.

The refined risk quotients for fish, crustacean (mysid shrimp) and marine diatom indicate that the level of concern from exposure to mandestrobin, S-2200 *R*-isomer and S-2200-ORC due to spray drift is not exceeded. The refined risk quotients for amphibians and freshwater algae indicate that the level of concern from mandestrobin exposure due to spray drift is exceeded for aerial application, but not exceeded for ground application. It was determined that drift mitigation measures in the form of spray buffer zones were necessary.

4.2.3.2 Assessment of potential risk from run-off

The risk from exposure to run-off into a body of water directly adjacent to the application field was determined using the run-off 90th percentile of the EECs predicted by PRZM-EXAMS. The risk quotients for exposure to mandestrobin, S-2200 *R*-isomer and the transformation product S-2200-ORC were calculated using toxicity endpoints and EECs representing the 90th percentile of 96-hour concentration.

The risk quotients for aquatic organisms resulting from exposure to S-2200 *R*-isomer and S-2200-ORC through runoff do not exceed the level of concern. However, the risk quotients from exposure of mandestrobin to amphibians, freshwater algae and marine crustaceans through runoff marginally exceeded the level of concern (RQ $\leq$ 2.5). Standard precautionary label statements are required on the product label to inform users of best practices to minimize potential run-off from treated fields.

5.0 Value

5.1 Consideration of Benefits

Registration of mandestrobin, and the end-use products that contain this new active ingredient, will provide Canadian growers and turf managers with additional products on the market with which to address major disease problems.

A number of fungicides, including some from the same mode of action group, are registered on the subject crops to control or suppress the plant diseases indicated on the mandestrobin product labels. Refer to Appendix I, Table 22 for further information on the currently available alternatives grouped according to their modes of action.

With broad-ranging efficacy and two methods of application, mandestrobin represents a valuable addition to an effective integrated pest management approach for various cropping systems. As multiple alternative fungicides from different mode of action groups are currently registered for most diseases appearing on the foliar product and seed treatment labels, appropriate resistance management strategies can be implemented. The use patterns being registered for mandestrobin will allow application of this active ingredient in combination with good agricultural practices, including cultural methods that help to lower disease pressure.

5.2 Effectiveness Against Pests

S-2200 4 SC Fungicide; S-2200 4 SC AG Fungicide; S-2200 4 VPP Fungicide (foliar products)

Efficacy data from a total of 33 small scale trials conducted between 2006 and 2012 were reviewed to support the value of nine different disease claims on the foliar-applied mandestrobin products. A complete list of supported uses with additional details is provided in Appendix I, Table 23. Most trials were located either in Canada or northern United States. Depending on the crop disease combinations, the levels of efficacy demonstrated across the different trials were consistent with performance standards expected from claims of either control or suppression. In addition, low water spray volumes were used for ground applications in six of the trials provided with the intention of simulating aerial applications. No reduction in efficacy was observed from these treatments, thereby supporting directions for aerial applications on canola.

S-2200 3.2 FS Fungicide (seed treatment product)

Twenty small scale field and greenhouse efficacy trials, conducted in Canada between 2011 and 2013, were reviewed in support of the claims on the mandestrobin-containing seed treatment product S-2200 3.2 FS Fungicide. Evidence of efficacy from four bioassays was also considered in support of the product's label. Mandestrobin was demonstrated to be effective in reducing the severity and incidence of seed decay and seedling diseases caused by various seed- and soil-borne pathogens, including *Fusarium* and *Rhizoctonia*. In the majority of tested crop/pathogen combinations, mandestrobin was effective in controlling the diseases in question. However, when assessing seed decay caused by the pathogen *Phomopsis* in soybean, mandestrobin seed treatments resulted in disease suppression rather than control.

5.3 Non-Safety Adverse Effects

Phytotoxicity resulting from applications of mandestrobin-containing products was not reported in any of the available trial data. There is no indication that non-safety adverse effects would result from S-2200 4 SC Fungicide, S-2200 4 SC AG Fungicide, S-2200 4 SC VPP Fungicide or S-2200 3.2 FS Fungicide when applied to crops in accordance with label directions and restrictions.

5.4 Supported Uses

A complete list of supported uses is provided in Appendix I, Table 23.

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, mandestrobin 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:

- Mandestrobin does not meet all Track 1 criteria, and is not considered a Track 1 substance. See Appendix I, Table 21 for comparison with Track 1 criteria.

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

- Mandestrobin does not form any transformation products that meet all Track 1 criteria. Major transformation products S-2200-OR, S-2200-ORC and S-2200-PR are formed only by aqueous phototransformation. 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.

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 conclusion:

- Technical grade mandestrobin (S-2200 Fungicide Technical) and the end-use products S-2200 4 SC Fungicide, S-2200 3.2 FS Fungicide, S-2200 4 SC Ag Fungicide and S-2200 4 SC VPP Fungicide do not contain any formulants or contaminants of health or environmental concern identified in the *Canada Gazette.*

  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 mandestrobin is adequate to define the majority of toxic effects that may result from exposure. The main targets were the liver (mice, rats, dogs), thyroid gland (rats) and kidneys (mice, rats) in several short- and long-term studies. There was evidence of increased susceptibility of the young in the toxicity studies submitted, but the level of concern was low. There was equivocal evidence of oncogenicity in rats following longer-term dosing. The risk assessment protects against the toxic effects noted by ensuring that the level of human exposure is well below the lowest dose at which these effects occurred in animal tests.

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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.*

Mixers, loaders, and applicators handling S-2200 4 SC Fungicide, S-2200 4 SC Ag Fungicide, S-2200 4 SC VPP Fungicide, and S-2200 3.2 FS Fungicide, and workers re-entering treated areas of rapeseed, climbing vine fruit, low-growing berries, turfgrass and sod, and planting treated corn, legumes, and rapeseed seeds are not expected to be exposed to levels of mandestrobin that will result in an unacceptable risk when these products are used according to label directions. The personal protective equipment and restricted entry interval on the product labels are adequate to protect workers. The S-2200 3.2 FS Fungicide label also includes the requirement to treat seeds in commercial facilities using closed mix, load, and transfer seed treating equipment.

Residential exposures to individuals contacting treated turf, including golfing, are not expected to result in risks of concern when S-2200 4 SC VPP Fungicide is used according to label directions. Exposure to the public entering pick-your-own strawberry and lowbush blueberry farms, following treatment with S-2200 4 SC Ag Fungicide, is also not expected to result in risks of concern.

The nature of the residues in plants is adequately understood. The residue definition for enforcement and risk assessment is mandestrobin in plant matrices. The proposed use of mandestrobin on rapeseed (canola), corn, grapes, strawberries, and soybeans does not constitute a risk of concern from chronic 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 mandestrobin.

Commodity	Recommended MRL (ppm)
Raisins	7.0
Small fruit vine climbing (Crop Subgroup 13-07F, except fuzzy kiwifruit)	5.0
Low growing berry (Crop Subgroup 13-07G, except cranberry)	3.0
Rapeseed (Crop Subgroup 20A)	0.5
Legume vegetables (Crop Group 6, except cowpea and field pea), corn (field, popcorn, sweet)	0.02

7.2 Environmental Risk

To mitigate risks to non-target organisms, spray buffer zones to protect sensitive aquatic and terrestrial habitats from spray drift and label statements to inform users of potential risks to the environment are required. With these measures in place, risks to the environment from the use of mandestrobin are considered to be acceptable.

7.3 Value

The value information submitted was sufficient to support the registration of 16 fungal disease claims for four new end-use products containing the new fungicidal active ingredient mandestrobin. Intended either for foliar applications or seed treatments, the supported uses cover a broad range of diseases in economically important field and horticultural crops including turfgrass. Registration of these products will provide Canadian growers and producers additional disease management products with a new active ingredient from a mode of action group with a well-established efficacy profile.

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 Mandestrobin Technical (previously known as S-2200 Fungicide Technical) and the associated end-use products: S-2200 4 SC Fungicide, Intuity Fungicide (previously known as S-2200 4 SC Ag Fungicide), Pinpoint Fungicide (previously known as S-2200 4 SC VPP Fungicide), and S-2200 3.2 FS Fungicide, containing the technical grade active ingredient mandestrobin, for the management of various fungal diseases in canola and other oilseed crops, corn, grape, legume vegetables, strawberry and other low growing berries, as well as turfgrass.

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

℃	degrees Celsius
♀	female
♂	male
↑	increasing
↓	decreasing
ε	emittance
λ	wavelength
µg	microgram(s)
µM	micromolar(s)
1/n	exponent for the Freundlich isotherm
a.i.	active ingredient
abs	absolute
AD	administered dose
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism and excretion
AHETF	Agricultural Handlers Exposure Task Force
ALP	alkaline phosphatase
ALT	alanine aminotransferase
APTT	activated partial thromboplastin time
appl.	application
AR	applied radioactivity
ARfD	acute reference dose
ARTF	Agricultural Re-entry Task Force
ASAE	American Society of Agricultural Engineers
atm	atmosphere
ATPD	area treated per day
BAF	bioaccumulation factor
BBCH	Biologishe Bundesanstalt, Bundessortenamt and Chemical industry
BCF	bioconcentration factor
bw	body weight
bwg	body weight gain
Bz	benzyl
C_{max}	maximum plasma concentration
CAF	composite assessment factor
CAS	Chemical Abstracts Service
CDC	Center for Disease Control
CDN	Canadian
CEPA	*Canadian Environmental Protection Act*
CG	Crop Group
CHL	chinese hamster lung cell line
cm	centimetre(s)
cm^2	centimetre(s) squared
CO_2	carbon dioxide
conj.	conjugated
CSG	Crop Sub-Group

CYP	cytochrome P450
d	day(s)
DALA	days after last application
DAT	days after treatment
DEEM-FCID	Dietary Exposure Evaluation Model – Food Commodity Intake Database
DFOP	double first-order in parallel
DFR	dislodgeable foliar residue
DIR	Directive
DNA	deoxyribonucleic acid
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
E_bC_{50}	EC_{50} in terms of algal biomass
EC_{25}	effective concentration on 25% of the population
EC_{50}	effective concentration on 50% of the population
E. coli	*Escherichia coli*
EDE	estimated daily exposure
EEC	estimated environmental concentration
ER_{25}	effective rate on 25% of the population
ER_{50}	effective rate on 50% of the population
F_1	first generation
F_2	second generation
fc	food consumption
FDA	*Food and Drugs Act*
FIR	food ingestion rate
FRAC	Fungicide Resistance Action Committee
FS	flowable suspension
g	gram(s)
GAP	Good Agricultural Practice
GC-MS	gas chromatography with mass spectrometry
GI	gastrointestinal
GUS	groundwater ubiquity score
h	hour(s)
H295R	human adrenocarcinoma cell line
ha	hectare(s)
HAFT	highest average field trial value
hAR	human androgen receptor
HCl	hydrochloric acid
HeLa	Henrietta Lacks
hERa	human oestrogen receptor alpha
HDPE	High-density polyethylene
HPLC	high performance liquid chromatography
HPLC-MS/MS	high performance liquid chromatography with tandem mass spectrometry
HPRT	hypoxanthine phosphorybosyl transferase
ID	identification

ILV	independent laboratory validation
IORE	indeterminate order rate equation
IUPAC	International Union of Pure and Applied Chemistry
K+CWHR	kernels and cobs with husk removed
kg	kilogram(s)
K_d	soil-water partition coefficient
K_F	Freundlich adsorption coefficient
K_{FOC}	Freundlich adsorption coefficient normalized to organic carbon
K_{oc}	organic-carbon partition coefficient
K_{ow}	*n*–octanol-water partition coefficient
L	litre(s)
LAFT	lowest average field trial value
LC_{50}	lethal concentration 50%
LC-MS/MS	liquid chromatography with tandem mass spectrometry
LD_{50}	lethal dose 50%
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	square metre(s)
m^3	cubed metre(s)
Max.	maximum
mg	milligram(s)
Min.	minimum
mL	millilitre(s)
M/L/A	mixer/loader/applicator
MAS	maximum average score
MIS	maximum irritation score
MOA	mode of action
MOE	margin of exposure
mol	mole
MQL	minimum quantification limit
MRL	maximum residue limit
m/z	mass-to-charge ratio of an ion
n	number of field trials
N/A or n/a	not applicable
NAFTA	North American Free Trade Agreement
NaOH	sodium hydroxide
NC	not classified
NCHS	National Center for Health Statistics
NHANES/ WWEIA	National Health and Nutritional Examination Survey, What We Eat in America
nm	nanometre(s)
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration

NOEL	no observed effect level
NZW	New Zealand white
OC	organic carbon content
ORETF	Outdoor Residential Exposure Task Force
Pa	Pascal
PBI	plantback interval
PES	post-extraction solids
Ph	phenoxy
PHED	Pesticide Handlers Exposure Database
PHI	preharvest interval
p*K*a	dissociation constant
PLT	platelet
PMRA	Pest Management Regulatory Agency
PND	postnatal day
ppb	parts per billion
PPE	personal protective equipment
ppm	parts per million
PT	prothrombin time
PYO	pick your own
RAC	raw agricultural commodity
REI	restricted entry interval
rel	relative
RQ	risk quotient
R/S	enantiomeric ratio
SC	soluble concentrate
SD	standard deviation
SEEDTROPEX	Seed Treatment Operator Exposure Task Force
SFO	single first order
SOP	Standard Operating Procedure
SPN	Science Policy Notice
S. typhimurium	*Salmonella typhimurium*
$t_{1/2}$	total elimination half-life
T3	tri-iodothyronine
T4	thyroxine
TLC	thin layer chromatography
t_{max}	time to reach maximum plasma concentration
TG	technical grade
$t_{R\ IORE}$	representative half-life dissipation in soil calculated with the IORE model
TRR	total radioactive residue
TRT.	treatment
TSH	thyroid-stimulating hormone
TSMP	Toxic Substances Management Policy
TTR	turf transferable residue
UDP	uridine 5'-diphospho-
UF	uncertainty factor
UGT	UDP-glucuronosyltransfase
UR	unextracted residues

US	United States
USEPA	United States Environmental Protection Agency
UV	ultraviolet
vs.	verses
v/v	volume per volume dilution
v/v/v	volume per volume per volume dilution
w	week(s)
wt(s)	weight(s)

Appendix I Tables and Figures

Table 1a Residue Analysis for Environmental Media

Matrix	Method ID	Analyte	Method Type		LOQ	Reference
Soil	CLE 8213772-01V	S-2200 R isomer	LC-MS/MS	*m/z* 314→192	0.0025 mg/kg	2377924
		S-2200 S isomer		*m/z* 314→192		
		De-Xy-S-2200		*m/z* 210→192	0.005 mg/kg	
		2-COOH-S-2200		*m/z* 344→192		
		5-COOH-S-2200		*m/z* 344→160		
Soil	RM-48S-3	S-2200	HPLC-MS/MS	*m/z* 314→192	0.02 mg/kg	2377958 and 2377849
		DX-CA-S-2200		*m/z* 224→146		
		2-COOH-S-2200		*m/z* 344→192		
		5-COOH-S-2200		*m/z* 344→192		
		2-CONH2-S-2200		*m/z* 343→192		
		5-CONH2-S-2200		*m/z* 343→192		
Water	Not stated	S-2200	HPLC-MS/MS	*m/z* 314→192	0.10 µg/L	2377854 and 2377857

Table 1b Residue Analysis for Crops

Matrix	Method ID	Analyte	Method Type	LOQ (ppm)	Reference
Rapeseed Rotational Crops: Wheat (forage, grain, straw), Lettuce, Beet (roots, leaves)	RM-48C-2A (precedent RM-48C-2) (Enforcement Method-Plant Commodities)	S-2200	LC-MS/MS	0.02	2377885
Rapeseed	RM-48C-2A (ILV of enforcement method – plant)	S-2200	LC-MS/MS	0.02	2377899
Only one transition was monitored for S-2200: *m/z* 314/92; however DFG-S19 method can be used as a confirmatory method for the analysis of S-2200.					
Rapeseed (seeds)	DFG-S19 (Multiresidue method)	S-2200	LC-MS/MS	0.005: *R* and *S*-isomer	2377889
Barley (grain, straw), lettuce	DFG-S19 (Validation of multiresidue method)	S-2200	LC-MS/MS	0.005: *R* and *S*-isomer	2377892
Radiovalidation (plant commodities)	Similar solvents were used for the metabolism studies (acetone/water; 80:20) and the enforcement method (acetone/water; 70:30). In general, extraction efficiencies were similar for both extraction methods (Tissumizer or shaking) with both solvent systems in rapessed forage (80.3-90.9% of the TRR). Seed samples were also extracted with a Tissumizer and a solvent solution of acetone:water, 70:30, v/v, which yielded an average extraction efficiency of 108.1% of the TRR.				2377887
Rapeseed, Corn (Forage and Stover)	RM-48C-1 (Data-Gathering Method – Plant	S-2200	GC-MS	0.02	2377926; 2377153; 2377152

Matrix	Method ID	Analyte	Method Type	LOQ (ppm)	Reference
Corn (Grain and K+CWHR), Soybean	Commodities)			0.01	
Strawberry, Grape	RM-48G (Data-Gathering Method – Plant Commodities)	S-2200	LC-MS/MS	0.02	2377917; 2377911; 2377920; 2377913
Poultry muscle	RM-48M-1 (ILV of Proposed Enforcement Method – Livestock Commodities)	S-2200	LC-MS/MS	0.02	2377859
If livestock feed items increase the dietary burden in cattle and poultry, a validated enforcement method using cattle fat, meat and meat byproducts, milk, and eggs will be necessary, including ILV and radiovalidation.					

For further use expansions involving cereal grains (wheat), the applicant is requested to also measure for the metabolite De-Xy-S-2200 in the crop field trials (along with mandestrobin) as it was a major metabolite found in the metabolism studies for wheat grain and straw. The residue definition of mandestrobin may be revised as a result.

Table 2 Chemical Names of Isomers and Metabolites of Mandestrobin

Code/Trivial name	Chemical name
S-2167 (R-isomer of mandestrobin)	(R)-2-methoxy-N-methyl-2-[α-(2,5-xylyloxy)-o-tolyl]acetamide
S-2354 (S-isomer of mandestrobin)	(S)-2-methoxy-N-methyl-2-[α-(2,5-xylyloxy)-o-tolyl] acetamide
2-CH_2OH-S-2200	(2RS)-2-[2-(2-hydroxymethyl-5-methylphenoxymethyl)phenyl]-2-methoxy-N-methylacetamide
2-COOH-S-2200	2-({2-[(1RS)-1-methoxy-2-(methylamino)-2-oxoethyl]benzyl}oxy)-4-methylbenzoic acid
4-OH-S-2200	(2RS)-2-[2-(4-hydroxy-2,5-dimethylphenoxymethyl)phenyl)-2-methoxy-N-methylacetamide
5-COOH-S-2200	3-({2-[(1RS)-1-methoxy-2-(methylamino)-2-oxoethyl]benzyl}oxy)-4-methylbenzoic acid
De-XY-S-2200	(2RS)-2-(2-hydroxymethylphenyl)-2-methoxy-N-methylacetamid

Table 3 Toxicity Profile of S-2200 3.2 FS Fungicide

(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 Sprague-Dawley Rat PMRA # 2378126	$LD_{50♀}$ = 3129 mg/kg bw Low Toxicity
Acute Dermal Toxicity Sprague-Dawley Rat PMRA # 2378127	$LD_{50♂/♀}$ > 5000 mg/kg bw Low Toxicity

Study Type/Animal/PMRA #	Study Results
Acute Inhalation (nose-only) Sprague-Dawley Rat PMRA # 2378128	$LC_{50♂/♀}$ > 2.04 mg/L Low Toxicity
Eye Irritation NZW rabbit PMRA # 2378129	MIS= 8.0/110 MAS (24, 48, 72 hour)= 0.22/110 Minimally irritating
Dermal Irritation NZW Rabbit PMRA # 2378130	MIS= 1/8 MAS (24, 48, 72 hour)= 0/8 Non-irritating
Local Lymph Node Assay (LLNA) CBA/J Mouse PMRA # 2378131	Non-sensitizer

Table 4 Toxicity Profile of S-2200 4 SC Fungicide, S-2200 4 SC AG Fungicide and S-2200 4 SC VPP Fungicide

(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 Sprague-Dawley Rat PMRA # 2377860	$LD_{50♀}$ = 3129 mg/kg bw Low Toxicity
Acute Dermal Toxicity Sprague-Dawley Rat PMRA # 2377862	$LD_{50♂/♀}$ > 5000 mg/kg bw Low Toxicity
Acute Inhalation (nose-only) Sprague-Dawley Rat PMRA # 2377865	$LC_{50♂/♀}$ > 2.04 mg/L Low Toxicity

Study Type/Animal/PMRA #	Study Results
Eye Irritation NZW rabbit PMRA # 2377866	MIS= 3.33/110 MAS (24, 48, 72 hour)= 0.22/110 Minimally irritating
Dermal Irritation NZW Rabbit PMRA # 2377868	MIS= 0/8 MAS (24, 48, 72 hour)= 0/8 Non-irritating
Local Lymph Node Assay (LLNA) CBA/J Mouse PMRA # 2377870	Non-sensitizer

Table 5 Toxicity Profile of Technical Mandestrobin

(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) Effects seen above the LOAEL(s) have not been reported in this table for most studies for reasons of brevity.

Study Type/Animal/PMRA #	Study Results
ADME (single administration [S-2200TG, S-2167, S-2354], multiple administration [S-2200TG]) Wistar Rat PMRA #2377990, 2377989, 2377987	Mandestrobin (benzyl-^{14}C-S-2200TG and phenoxy-^{14}C-S-2200TG, racemic mixtures), R-isomer (benzyl-^{14}C-S-2167), S-isomer (benzyl-^{14}C-S-2354). All forms of mandestrobin were rapidly absorbed (≥ 95% administered single dose (AD); 73-81% by 78 hours). Systemic exposure was proportionally higher at the low dose than at the high dose, indicating saturation of oral absorption at high dose. Peak plasma levels (C_{max}) were reached by 1.2-2.6 hours (t_{max}) after an oral dose of 5 mg/kg, and 7.0-9.1 hours after a dose of 1000 mg/kg. The labeled compound was widely distributed throughout tissues, but was detected primarily in the GI tract, liver and kidney. Pancreas, uterus and ovaries also had higher levels than most other tissues. Isomers had similar tissue distribution except the S-isomer was more prevalent in GI tract than the R-isomer. There was no sex difference in distribution into tissues, except during the multiple dosing period, females kept a larger portion of the dose in the cecum/large intestine/intestinal contents, and reached peak levels in tissues outside the GI tract later than males. There was no evidence of long-term accumulation of S-2200TG or its metabolites in tissues. Clearance of a single dose of S-2200TG from plasma was almost complete by 120 hours post-dose ($t_{½}$ = 18-23 hours at the low dose; $t_{½}$= 25-29 hours at the high dose). Clearance of the S-isomer was less rapid than the R-isomer. In the repeated dose study, 85-89% of the AD was excreted by 14 days after last dose. Bile cannulated rats excreted S-2200TG faster than non-cannulated rats (97-99% vs. 49-51% of a single dose by 24 hours), suggesting enterohepatic recirculation. Excretion was consistent with all S-2200TG treatments. Fecal excretion (60-75% of AD) via bile was the primary excretion route, and renal excretion (15-21% of AD) was also important. Excretion in expired air was negligible. S-2200TG is almost completely metabolized in rats via (1) oxidation followed by glucuronidation, (2) demethylation followed by oxidation, or (3) oxidation followed by demethylation. The molecule core remains essentially intact, with no cleavage of benzyl and phenoxy rings. The major metabolites excreted are: 5-CA-S-2200-NHM and 4-OH-S-2200 in feces; 4-OH-S-2200-GlucA in bile; and 5-CA-S-2200-NHM in urine. The same metabolites were identified for both isomers however at different proportions. In order of magnitude, R-isomer produced mostly 5-CA-S-2200-NHM, 5-CA-MCBX-NDM, 5-CA-2-HM-S-2200-NHM

	and 5-CA-S-2200-NDM; while S-isomer produced mostly 4-OH-S-2200 and 5-COOH-S-2200. In the multiple dose study, fecal metabolites found at slightly higher levels in male than females were 5-CA-S-2200-NHM, 5-COOH-S-2200, 5-CA-2-HM-S-2200-NHM, 5-CA-2-HM-MCBX and 5-CA-MCBX-NDM. Results from cannulated rats suggest that 4-OH-S-2200 and its A glucuronide (GlucA) undergo enterohepatic circulation.
Acute Oral Toxicity Wistar Rat PMRA # 2377929	$LD_{50♀}$ > 2000 mg/kg bw Low Toxicity
Acute Dermal Toxicity Wistar Rat PMRA # 2377936	$LD_{50♂♀}$ > 2000 mg/kg bw Low Toxicity
Acute Inhalation (nose-only) Wistar Rat PMRA # 2377937	$LC_{50♂♀}$ > 4.96 mg/L Low Toxicity
Eye Irritation NZW rabbit PMRA # 2377939	MIS= 10.3/110 MAS (24, 48, 72 hour)= 4.0/110 Minimally irritating
Dermal Irritation NZW Rabbit PMRA # 2377940	MIS= 0/8 MAS (24, 48, 72 hour)= 0/8 Non-irritating
Sensitization Study (Maximization Test) Guinea Pig PMRA # 2377941	Non-sensitizer
28-Day dermal toxicity Wistar Rat PMRA # 2377957	NOAEL = 1000 mg/kg bw/day LOAEL was not determined due to absence of effects up to the limit dose.
90-Day oral toxicity (diet) CD-1 Mouse PMRA # 2377946	NOAEL= 807/529 mg/kg bw/day in ♂/♀ LOAEL was not determined in ♂ LOAEL ♀ = 1111 mg/kg bw/day; effects included decreased bw and lower bwg
90-Day oral toxicity (diet) Wistar Rat PMRA # 2377948	NOAEL= 283/320 mg/kg in ♂/♀ LOAEL= 743/789 mg/kg bw/day in ♂/♀; effects included ↑ incidence hepatocyte hypertrophy and severity, ↑ total cholesterol, ↑ incidence of thyroid follicular cell hypertrophy; ↑ liver wts, ↑ incidence large liver, ↑ incidence liver agonal congestion/ hemorrhage, ↑ severity thyroid follicular hypertrophy (♂); ↑ rel liver wt (♀)
90-Day oral toxicity (diet) Beagle Dog	NOAEL= 91/103 mg/kg bw/day in ♂/♀ LOAEL= 268/304 mg/kg bw/day in ♂/♀; effects included ↑ incidence liver centrilobular degeneration and severity, ↑ incidence dark liver; ↑ incidence large liver (♂) ; ↑ ALP (♀)

PMRA # 2377954	
1-Year oral toxicity (diet) Beagle Dog PMRA # 2377952	NOAEL= 92 mg/kg bw/day LOAEL= 181/226 mg/kg bw/day in ♂/♀; effects included ↓ bw, ↑ liver wt, ↑ incidence liver centrilobular degeneration, agonal congestion/hemorrhage, hepatocyte hypertrophy and severity, hepatocyte pigment, ↑ ALP, ↑ ALT, ↑ PLT; ↓ bwg (♂); ↓ PT and APTT, thin appearance and reduced muscle tone (1/4) (♀)
78- week Oncogenicity (diet) CD-1 Mouse PMRA #2377960	NOAEL = 239/994 mg/kg bw/day in ♂/♀ LOAEL not determined in ♀ LOAEL = 824 mg/kg bw/day in ♂; effects included ↑ incidence of corticomedullary mineralization (♂) No evidence of oncogenicity
2-Year combined oral chronic toxicity /carcinogenicity (diet) Wistar rat PMRA # 2377961	NOAEL = 130/27 mg/kg bw/day in ♂/♀ LOAEL = 449/135 mg/kg bw/day in ♂/♀; effects included ↑ liver wt, liver hypertrophy, thyroid follicular cell hypertrophy (♂); ↓ bw, ↓ bwg, rel liver wt, hepatocyte hypertrophy, ↑ incidence of corticomedullary mineralization (♀) Equivocal evidence of oncogenicity based on a treatment-related increase in ovary sex cord-stromal benign tumors in female rats (2, 0, 1, 4, 6).
2-generation reproductive toxicity study BrlHan:WIST@Jcl (GALAS) Rats PMRA # 2377964	NOAEL (parental) = 1000 ppm (56/63 mg/kg bw/day in ♂/♀) LOAEL (parental) = 3000 ppm (166/195 mg/kg bw/day in ♂/♀); effects included ↑ bile duct brown pigmentation and periductular inflammatory cell infiltration (with liver weight and hypertrophy at the same dose) NOAEL (offspring) = 3000 ppm (195 mg/kg bw/day) LOAEL (offspring) = 10000 ppm (628 mg/kg bw/day); effects included ↓ bw F1/F2 from PND 7 NOAEL (reproductive) = 10000 ppm (629 mg/kg bw/day) LOAEL (reproductive) ≥ 10000 ppm (629 mg/kg bw/day) No evidence of sensitivity of the young
Developmental Toxicity Study in Rats Crl:WI(Han) Rats PMRA # 2377967	Maternal NOAEL = 1000 mg/kg bw/day Maternal LOAEL > 1000 mg/kg bw/day Developmental NOAEL = 300 mg/kg bw/day Developmental LOAEL = 1000 mg/kg bw/day; effects included ↑ increased incidences of litters containing fetuses with distended ureter or delayed skull ossification Evidence of sensitivity of the young
Developmental Toxicity Study in Rabbits Hsd:IfNZW Rabbits PMRA # 2377970	Maternal NOAEL = 1000 mg/kg bw/day Maternal LOAEL > 1000 mg/kg bw/day Developmental NOAEL = 1000 mg/kg bw/day Developmental LOAEL > 1000 mg/kg bw/day No evidence of sensitivity of the young
Bacterial Reverse Mutation Assay (Ames test) PMRA # 2377971	Negative in *S. typhimurium* strains (TA 98, TA100, TA1535, TA1537 and TA1538) and *E. coli* WP2uvrA in the presence and absence of metabolic activation.
In vitro Mammalian Cell Assay (forward gene mutation) PMRA#2377978	Negative in V79-HPRT cells

In vitro Mammalian Clastogenicity Assay (chromosomal aberration) PMRA#2377984	Negative in Chinese hamster lung cells (CHL/IU)
Micronucleus Assay PMRA #2377985	Negative in BDF_1[SPF] mice No mortality, clinical signs of toxicity and no differences in body weight compared to controls.
Acute neurotoxicity (gavage) Wistar Rat PMRA # 2377992	NOAEL = 1000 mg/kg bw in ♂/♀ LOAEL = 2000 mg/kg bw in ♂/♀; effects included ↓ overall locomotor activity (total and/or ambulatory counts) on study day 0 (0-30 min)
90-Day neurotoxicity study Wistar rat PMRA # 2377994	NOAEL = 338/1223 mg/kg bw/day in ♂/♀ LOAEL not determined in ♀ LOAEL = 1024 mg/kg bw/day in ♂; effects included ↓ bw and lower bwg, ↓ fc (♂) No evidence of neurotoxicity
28-Day Immunotoxicity (diet) Wistar rat PMRA # 2378005	NOAEL = 471 mg/kg bw/day in ♀ LOAEL = 1419 mg/kg bw/day in ♀; effects included ↑ spleen wt (♀)
Special study Ovary: Reporter Genes Assay (hERα and hAR assays) PMRA # 2378010	Neither S-2200TG nor its metabolites (5-COOH-S-2200, 4-OH-S-2200, 5-CH_2OH-S-2200 and 5-CA-S-2200-NHM) showed agonistic or antagonistic effects on hERα and hAR from HeLa cells derived from human uterine cervix carcinoma. Note:Test substances were assayed only once.
Ovary: Steroidogenesis Assay PMRA # 2378006	S-2200TG did not modulate testosterone or estradiol production under the conditions of this study up to 30 µM (viability ≥ 80%) in H295R cells.
Liver and thyroid changes (diet) Wistar Rat PMRA # 2378008	7-day treatment: **≥23/26 mg/kg bw/day in ♂/♀:** ↑ T4-UGT (♂) **≥116/131 mg/kg bw/day in ♂/♀:** ↑ CYP2B ; ↑ rel liver wt (♀) **≥379/420 mg/kg bw/day in ♂/♀:** ↓ fc, diffuse hepatocellular hypertrophy, ↑ DNA synthesis ; ↓ bw, ↓ bwg, ↑ rel liver wt (♂); ↑ thyroid wt , diffuse thyroid follicular cell hypertrophy (♀) **744/812 mg/kg bw/day in ♂/♀:** enlarged liver, bile duct brown pigment, peribiliary inflammation, ↓ T4 (♂) ; ↓ bw , ↓ bwg , ↑ abs liver wt, ↑ T4-UGT, ↑ TSH (♀) 14-day treatment: **796/952 mg/kg bw/day in ♂/♀:** ↓ bwg , ↑ liver wt, ↑ thyroid wt, diffuse hepatocellular hypertrophy (♂♀) with ↑ severity versus 7-day treatment (♂), ↓ T4, ↑ TSH ; ↑ DNA synthesis (♂); ↓ bw , diffuse thyroid follicular cell hypertrophy, ↓ T3 (♀) **7-day treatment + recovery:** bw and bwg recoveries, fc recovery, liver wt still significantly ↑ in ♂, recovery for thyroid wt, no remarkable pathology findings at necropsy, ↑ CYP4A, recovery for thyroid hormone levels except for T4 in ♂

Table 6 Toxicity Profile of Metabolites of Mandestrobin

Study Type/Animal/PMRA #	Study Results
Acute Oral Toxicity 2-CH2OH-S-2200 Wistar Rat PMRA # 2377935	$LD_{50♀}$ > 2000 mg/kg bw Low Toxicity
Bacterial Reverse Mutation Assay (Ames test) 2-CH2OH-S-2200 PMRA#2377976	Negative in *S. typhimurium* strains (TA 98, TA100, TA1535, TA1537 and TA1538) and *E. coli* WP2uvrA in the presence and absence of metabolic activation.
Acute Oral Toxicity 2-COOH-S-2200 Wistar Rat PMRA # 2377932	$LD_{50♀}$ > 2000 mg/kg bw Low Toxicity
Bacterial Reverse Mutation Assay (Ames test) 2-COOH-S-2200 PMRA#2377973	Negative in *S. typhimurium* strains (TA 98, TA100, TA1535, TA1537 and TA1538) and *E. coli* WP2uvrA in the presence and absence of metabolic activation.
In vitro Mammalian Clastogenicity Assay (chromosomal aberration) 2-COOH-S-2200 PMRA#2377983	Positive at 2200 µg/mL after 24 hours in absence of metabolic activation (relative cell growth 48.8%) in Chinese hamster lung cells (CHL/IU).
Micronucleus Assay 2-COOH-S-2200 PMRA #2377986	Negative in BDF_1[SPF] mice. No mortality, clinical signs of toxicity and no differences in body weight compared to controls.
Acute Oral Toxicity 4-OH-S-2200 Wistar Rat PMRA # 2377944	$LD_{50♀}$ > 2000 mg/kg bw Low Toxicity
Bacterial Reverse Mutation Assay (Ames test) 4-OH-S-2200 PMRA#2377977	Negative in *S. typhimurium* strains (TA 98, TA100, TA1535, TA1537 and TA1538) and *E. coli* WP2uvrA in presence and absence of metabolic activation.
Acute Oral Toxicity 5-COOH-S-2200 Wistar Rat PMRA # 2377933	300 mg/kg bw < $LD_{50♀}$ < 2000 mg/kg bw High Toxicity All the animals dosed at 2000 mg/kg bw died within 24 hours. 2000 mg/kg bw: the animals presented retention of a white fluid in the stomach, yellowish-white fluid content in the small intestine and foamy fluid in the trachea

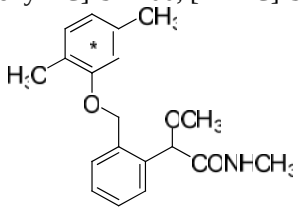
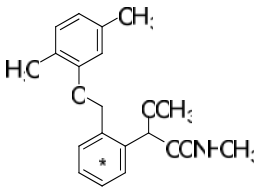
Bacterial Reverse Mutation Assay (Ames test) 5-COOH-S-2200 PMRA#2377975	Negative in *S. typhimurium* strains (TA 98, TA100, TA1535, TA1537 and TA1538) and *E. coli* WP2uvrA in presence or absence of metabolic activation.
In vitro Mammalian Cell Assay (forward gene mutation) 5-COOH-S-2200 PMRA#2377981	Negative in V79-HPRT cells in presence and absence of metabolic activation.
In vitro Mammalian Clastogenicity Assay (chromosomal aberration) 5-COOH-S-2200 PMRA#2377984	Negative in Chinese hamster lung cells (CHL/IU) in presence and absence of metabolic activation.
Acute Oral Toxicity De-Xy-S-2200 Wistar Rat PMRA # 2377931	$LD_{50♀}$ > 2000 mg/kg bw Low Toxicity
Bacterial Reverse Mutation Assay (Ames test) De-XY-S-2200 PMRA#2377972	Negative in *S. typhimurium* strains (TA 98, TA100, TA1535, TA1537 and TA1538) and *E. coli* WP2uvrA in presence and absence of metabolic activation.

Table 7 Toxicology Endpoints for Use in Health Risk Assessment for Mandestrobin

Exposure Scenario	Study	Point of Departure and Endpoint	CAF[1] or Target MOE
Acute dietary general population	An ARfD is not required		
Repeated dietary	Rat chronic toixicity/oncogenicity study	NOAEL= 27 mg/kg bw/day; effects included reduced body weight/body weight gains as well as liver and kidney effects	100
	ADI = 0.3 mg/kg bw/day		
Short-term dermal Intermediate-term dermal	Rat 28-day dermal toxicity study	NOAEL= 1000 mg/kg bw/day LOAEL was not determined due to absence of effects up to the limit dose.	100
Short-term inhalation[2] Intermediate-term inhalation[2]	Rat reproductive toxicity study	NOAEL= 56 mg/kg bw/day; effects included increased bile duct brown pigmentation and periductular inflammatory cell infiltration in F_1 parental generation.	100
Non-dietary oral ingestion (short-term)	Rat reproductive toxicity study	NOAEL= 56 mg/kg bw/day; effects included increased bile duct brown pigmentation and periductular inflammatory cell infiltration in F_1 parental generation.	100
Cancer	An increase in benign sex cord-stromal tumours in females in the rat oncogenicity study was considered equivocal based on the weight of evidence. The endpoints selected for the non-cancer risk assessment are protective of these equivocal findings.		

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

Table 8 Integrated Food Residue Chemistry Summary

NATURE OF THE RESIDUE IN LETTUCE			**PMRA # 2377840**	
Radiolabel Position	[Phenoxy-^{14}C]-S-2200; [Ph-^{14}C]-S-2200 		[Benzyl-^{14}C]-S-2200; [Bz-^{14}C]-S-2200 	
In all studies, the *R/S* ratio of S-2200 remained approximately 1:1, indicating no *R/S* isomerization.				
Test Variety	*Lactuca sativa* (Buttercrunch)			
Test Site	In individual pots in greenhouse			
Formulation	The test material was formulated as a 25% suspension concentrate (SC) with an approximate S-2200 R:S isomer ratio of 50:50			
Treatment/Rate	1 foliar application of 800 g a.i./ha at BBCH 43 followed by a 2nd application of 800 g a.i./ha at BBCH 48 for a total of 1600 g a.i./ha			
PHI (days)	Immature lettuce leaves: 5 days after the 1st application Mature lettuce leaves: 5 days after the 2nd application			
Analytical Method for Overall TRR **Identification & Characterization**	LSC and combustion HPLC and TLC co-chromatography			
Extraction Solvents	Acetonitrile (surface wash only); acetone/water (80:20; v/v); acetone/water/hydrochloric acid (80:20:1; v/v/v)			
Post-Extraction Solids (PES)	Enzymatic hydrolysis with Driselase (enzyme mixture of fungal carbohydrolases), mild acid hydrolysis (0.1M HCl, 40°C, overnight) and mild base hydrolysis (0.1M NaOH, 40°C, overnight)			
Storage Stability	Representative samples from both radiolabels were re-extracted and analysed to verify the stability of the analytes during freezer storage (5 months). Similar profiles were obtained, which indicated stability of [^{14}C]-S-2200 metabolites in lettuce samples.			
Matrices	**Total Rate (g a.i./ha)**	**PHI (days)**	**[Ph-^{14}C]-S-2200**	**[Bz-^{14}C]-S-2200**
			TRR (ppm, in S-2200 equivalents)	
Immature Lettuce Leaves	800	5 (after 1st appl.)	35.11	27.94
Mature Lettuce Leaves	1600	5 (after 2nd appl.)	43.14	41.59
Metabolites Identified	**Major Metabolites (>10% of the TRR)**			
Radiolabel Position	**[Ph-^{14}C]-S-2200**		**[Bz-^{14}C]-S-2200**	
Lettuce – Immature leaves	S-2200		S-2200	
Lettuce – Mature leaves	S-2200		S-2200	
Most of the radioactivity was recovered in the surface washes (78.5-88.4% of the TRR). The metabolites De-Xy-S2200, MCBX, and conjugates of 2-CH_2OH-S-2200, 4-OH-S-2200, 5-CH_2OH-S-2200 and 5-COOH-S-2200 were detected along with several other minor metabolites.				

NATURE OF THE RESIDUE IN RAPESEED		PMRA # 2377845
Radiolabel Position	**[Ph-^{14}C]-S-2200**	**[Bz-^{14}C]-S-2200**
Test Variety	*Brassica napus* L. (Phoenix Liberty Link)	
Test Site	In individual pots maintained under open field conditions (grown to maturity)	
Formulation	The test material was formulated as a 25% suspension concentrate (SC) with an approximate S-2200 R:S isomer ratio of 50:50	
Treatment/Rate	TRT # 1: 1 foliar application of 400 g a.i./ha at BBCH 55-61	TRT # 2: 1 foliar application of 400 g a.i./ha at BBCH 66-67, and a 2nd application 14-days after the 1st for a total of 800 g a.i./ha/season
PHI (days)	54 (seeds)	14 (forage); 40 (seeds)
Analytical Method for Overall TRR Identification & Characterization	LSC and combustion HPLC and TLC co-chromatography	
Extraction Solvents	Acetonitrile (forage surface wash); hexane (seed samples only); acetone/water (80:20; v/v); acetone/water/hydrochloric acid (80:20:1; v/v/v)	
Post-Extraction Solids (PES)	Sequential enzyme hydrolysis with amylase and protease followed by weak acid hydrolysis (1M HCl, 40°C, overnight), strong acid hydrolysis (6M HCl, 80°C, 4 hours), weak base hydrolysis (0.1M NaOH, 40°C, overnight) and strong base hydrolysis (6M NaOH, 80°C, overnight)	
Storage Stability	Representative samples from both radiolabels were re-extracted and analysed to verify the stability of the analytes during freezer storage (7-11 months). Similar profiles were obtained, which indicated stability of [^{14}C]-S-2200 metabolites in rapeseed samples.	

Matrices	**Total Rate (g a.i./ha)**	**PHI (days)/ Growth Stage**	**[Ph-^{14}C]-S-2200**	**[Bz-^{14}C]-S-2200**
			TRR (ppm, in S-2200 equivalents)	
Rapeseed – Seeds (TRT #1)	400	54 (BBCH 89)	0.05	0.11
Rapeseed – Seeds (TRT #2)	800	40 (BBCH 89)	0.47	0.64
Rapeseed – Forage (TRT #2)	800	14 (BBCH 55-61)	3.99	3.44

Metabolites Identified	**Major Metabolites (>10% of the TRR)**	
Radiolabel Position	**[Ph-^{14}C]-S-2200**	**[Bz-^{14}C]-S-2200**
Rapeseed (Seeds) – TRT #1	None	None
Rapeseed (Seeds) – TRT #2	S-2200, 4-OH-S-2200 (conj.)	S-2200, 4-OH-S-2200 (conj.)
Rapeseed (Forage) – TRT #2	S-2200, 2-CH_2OH-S-2200 (conj.), 4-OH-S-2200 (conj.)	S-2200, 2-CH_2OH-S-2200 (conj.), 4-OH-S-2200 (conj.)

For forage, the radioactivity in the surface rinse ranged from 34 to 37% of the TRR, and approximately 55 to 58% of the TRR was present in the extractable fractions. For seed, approximately 81 to 99% of the TRR was present in extractable fractions from each treatment group. Minor metabolites included free forms of 5-COOH-S-2200, and MCBX and a conjugate of 5-CH_2OH-S-2200.

NATURE OF THE RESIDUE IN WHEAT		PMRA # 2377842
Radiolabel Position	**[Ph-^{14}C]-S-2200**	**[Bz-^{14}C]-S-2200**
Test Variety	*Triticum L.* (Promontory)	
Test Site	In individual pots maintained under greenhouse conditions (grown to maturity)	
Formulation	The test material was formulated as a 25% suspension concentrate (SC) with an approximate S-2200 R:S isomer ratio of 50:50	
Treatment/Rate	A single foliar application of 300 g a.i./ha at BBCH 32 (104 days before final harvest)	

PHI (days)	7 (BBCH 37 Wheat Forage); 14 (BBCH 37 Wheat Hay); 104 (BBCH 92 Wheat Grain)
Analytical Method for Overall TRR Identification & Characterization	LSC and combustion HPLC and TLC co-chromatography
Extraction Solvents	Acetonitrile (surface wash only); acetone/water (80:20; v/v); acetone/water/hydrochloric acid (80:20:1; v/v/v)
Post-Extraction Solids (PES)	Sequential enzyme hydrolysis with Driselase, mild acid hydrolysis (0.1M HCl, 40°C overnight) and mild base hydrolysis (0.1M NaOH, 40°C overnight)
Storage Stability	Representative samples from both radiolabels were re-extracted and analysed to verify the stability of the analytes during freezer storage (8 months). Similar profiles were obtained, which indicated stability of [^{14}C]-S-2200 metabolites in wheat samples

Matrices	**Total Rate (g a.i./ha)**	**PHI (days)/ Growth Stage**	**[Ph-^{14}C]-S-2200**	**[Bz-^{14}C]-S-2200**
			TRR (ppm, in S-2200 equivalents)	
Wheat Forage	300	7 (BBCH 37)	11.14	10.44
Wheat hay	300	14 (BBCH 37)	6.21	9.04
Wheat grain	300	104 (BBCH 92)	0.01	0.09
Wheat straw	300	104 (BBCH 92)	1.85	2.49

Metabolites Identified	**Major Metabolites (>10% of the TRR)**	
Radiolabel Position	**[Ph-^{14}C]-S-2200**	**[Bz-^{14}C]-S-2200**
Wheat forage	S-2200, 2-CH_2OH-S-2200 (conj.)	S-2200
Wheat hay	S-2200, 2-CH_2OH-S-2200 (conj.), 4-OH-S-2200 (conj.)	S-2200, 2-CH_2OH-S-2200 (conj.)
Wheat straw	None	De-Xy-S-2200
Wheat grain	None	De-Xy-S-2200

The radioactivity in the surface rinse ranged from 19 – 41% of the TRR for the forage and hay samples and approximately 3% TRR in the straw samples from both treatment groups. Approximately 53 - 73% of the TRR was present in the extractable fraction of the forage, hay, straw and grain from both wheat treatment groups. MCBX, 2-CH_2OH-S-2200 (free), 4-OH-S-2200 (free), 5-CH_2OH-S-2200 (free and conjugated), and 5-COOH-S-2200 (free) were considered minor metabolites. S-2200 was not detected in the wheat grain from either treatment group but the TRR was very low in these samples. De-Xy-S-2200 accounted for 2 to 12% of the TRR (0.14 - 0.33 ppm) in the forage, hay and straw samples and accounted for 61% of the TRR (0.05 ppm) in the grain sample from the [Bz-^{14}C]-S-2200 treatment group.

Nature of the Residue in Soybeans and Corn (Radiotracer)		**PMRA # 2378156/2378157**
Test Variety	Soybean: Pioneer 93M42; Corn: TR3026RRxTR2040RRxTR1914	
Formulation	Formulated product as 3.2 FS: 1.20 MBq/mg applied	Formulated product as 3.2 FS: 1.21 MBq/mg applied
Treatment/Rate	[Ph-^{14}C]-S-2200 Soybean: Seed/9.33 g/100 kg Corn: 11.03 g/100 kg	[Bz-^{14}C]-S-2200 Soybean: Seed/10.72 g/100 kg Corn: 11.55 g/100 kg
Analytical Method for Overall TRR Identification & Characterization	LSC and combustion HPLC and TLC co-chromatography	
Radiolabel Position	**[Ph-^{14}C]-S-2200**	**[Bz-^{14}C]-S-2200**
Matrices	**TRR (ppm)**	**TRR (ppm)**
Soybean forage	0.027, 0.038	0.040, 0.061
Soybean hay	0.030, 0.027	0.045, 0.050
Soybean pod with seed	<0.005, <0.005	<0.005, <0.005
Soybean mature seed	<0.005, <0.005	<0.005, <0.005
Corn kernels plus cob	<0.005, <0.005	<0.005, <0.005
Corn forage	<0.005, <0.005	<0.005, <0.005
Corn stover	<0.005, <0.005	0.011, 0.005

Corn grain	<0.005, <0.005	<0.005, <0.005

The total radioactive residue in treated RAC was below the minimum quantification limit (MQL) of 0.005 ppm in all RACs, with the exception of soybean (forage and hay), and corn (stover). Samples of soybean forage and hay grown from seeds treated with [Ph-^{14}C]-S-2200 and [Bz-^{14}C]-S-2200, and corn stover from seeds treated with [Bz-^{14}C]-S-2200 were extracted with acetonitrile in order to further characterize the residues that were detected above 5 ppb. The parent S-2200 was detected in the soybean forage, soybean hay and corn stover (<7.9% of the TRR; ≤0.003 ppm). Trace amounts of 2-COOH-S-2200 and 5-COOH-S-2200 were also observed in the soybean forage and hay samples (<5.1% of the TRR; <0.002 ppm). The only major metabolite was De-Xy-S-2200, which was observed in soybean forage (12.3% of the TRR; 0.005 ppm) from the [Ph-^{14}C]-S-2200.

Confined Accumulation in Rotational Crops – Lettuce, wheat, carrot	**PMRA # 2377934**
Test Site	Each plot consisted of an above-ground plastic sheet-lined wooded container maintained under field condition
Formulation	The test material was formulated as a 25% suspension concentrate (SC) with an approximate S-2200 R:S isomer ratio of 50:50
Analytical Method for Overall TRR Identification & Characterization	LSC and combustion HPLC and TLC co-chromatography
Extraction Solvents	Acetone/water (80:20; v/v); acetone/water/hydrochloric acid (80:20:1; v/v/v)
Post-Extraction Solids (PES)	Sequential enzyme hydrolysis with Driselase or amylase, mild acid hydrolysis (0.1M HCl, 40°C overnight) and mild base hydrolysis (0.1M NaOH, 40°C overnight), strong acid hydrolysis (6M HCl, 80°C for 4 hours) and strong base hydrolysis (6M NaOH, 80°C for 4 hours)
Storage Stability	Samples were stored and analyzed within 3 months for carrots. Representative samples of lettuce (6 months) and wheat (9 months) from both radiolabels were re-extracted and analysed to verify the stability of the analytes during freezer storage. Similar profiles were obtained, which indicated stability of [^{14}C]-S-2200 metabolites in the tested samples.

Radiolabel Position	**[Ph-^{14}C]-S-2200 and [Bz-^{14}C]-S-2200**

Crop/Crop group/*Variety*	**Rate (g a.i./ha)**	**PBI (days)**	**Growth stage at harvest**	**Harvested RAC**
Lettuce/Leafy vegetable/*Salad Bowl*	1600	30, 120, 365	50% mature size	Immature heads
			Maturity	Mature heads
Wheat/Cereal grains/*Blanca Royale*	1600	30, 120, 365	6-8” to stem elongation	Forage (immature)
			Early flower to soft dough	Hay
			Maturity	Grain and straw
Carrot/Root vegetable/ *Danvers Half Long 126*	1600	30, 120, 365	Maturity	Tops (foliage) and roots

Rotational crop sample		**Overall TRR (ppm, in S-2200 equivalents)**					
		[Ph-^{14}C]-S-2200			**[Bz-^{14}C]-S-2200**		
		30 DAT	**120 DAT**	**365 DAT**	**30 DAT**	**120 DAT**	**365 DAT**
Wheat	Forage	2.73	0.14	0.10	2.54	0.31	0.26
	Hay	1.56	0.29	0.35	4.54	0.72	0.74
	Straw	1.32	0.34	0.31	0.82	0.59	0.38
	Grain	0.04	0.04	<0.01	0.12	0.20	<0.01
Lettuce	Immature	0.33	0.03	0.07	0.32	0.08	0.07
	Mature	0.08	0.02	0.02	0.22	0.05	0.02
Carrot	Mature roots	0.05	0.03	<0.01	0.04	0.04	<0.01
	Mature foliage	0.11	0.05	0.03	0.07	0.08	0.03

Metabolites Identified		Major Metabolites (>10% of the TRR)	
Matrices	**PBI (days)**	**[Ph-^{14}C]-S-2200**	**[Bz-^{14}C]-S-2200**
Immature Lettuce	30	5-CH_2OH-S-2200 (conj.), 4-OH-S-2200 (conj.)	5-CH_2OH-S-2200 (conj.), 4-OH-S-2200 (conj.)
	120	None	4-OH-S-2200 (conj.)
	365	S-2200, 4-OH-S-2200 (conj.), 5-CH_2OH-S-2200 (conj.)	S-2200, 4-OH-S-2200 (conj.)
Mature Lettuce	30	S-2200, 4-OH-S-2200 (conj.), 5-CH_2OH-S-2200 (conj.)	4-OH-S-2200 (conj.), 5-CH_2OH-S-2200 (conj.)
	120	None	None
	365	4-OH-S-2200 (conj.), 5-CH_2OH-S-2200 (conj.)	None
Wheat forage	30	2-CH_2OH-S-2200 (conj.), 4-OH-S-2200 (conj.), 5-CH_2OH-S-2200 (conj.)	5-CH_2OH-S-2200 (conj.), 4-OH-S-2200 (conj.)
	120	4-OH-S-2200 (conj.), 5-CH_2OH-S-2200 (conj.)	None
	365	5-CH_2OH-S-2200 (conj.)	None
Wheat hay	30	4-OH-S-2200 (conj.), 5-CH_2OH-S-2200 (conj.), 2-CH_2OH-S-2200	4-OH-S-2200 (conj.)
	120	4-OH-S-2200 (conj.), 5-CH_2OH-S-2200 (conj.)	None
	365	None	None
Wheat straw	30/120	None	None
	365	None	4-OH-S-2200 (conj.)
Wheat grain	30/120/365	Not Profiled[1]	Not Profiled[1]
Carrot tops	30	None	None
	120	None	S-2200
	365	None	5-CH_2OH-S-2200 (conj.)
Carrot roots	30	S-2200	S-2200
	120	S-2200 2-CH_2OH-S-2200	S-2200
	365	Not profiled[1]	Not profiled[1]

[1] Not profiled due to low total radioactive residues.

Approximately 50 - 90% of the TRR was present in the extractable fraction of the lettuce, wheat and carrot samples from both treatment groups. The results generated in this study demonstrated that there was moderate uptake of radioactive residues in rotational crops seeded in soil 30, 120, and 365 days after treatment with ^{14}C-S-2200, followed by extensive metabolism to polar metabolites and incorporation into the constituents of the plant. The metabolite De-Xy-S-2200, arising from cleavage of the ether linkage, was found at very low levels only in the benzyl-labelled 30 DAT immature and mature lettuce. Minor metabolites also included MCBX, 5-COOH-S-2200, and free and glycoside conjugates of 2-CH_2OH-S-2200, 4-OH-S-2200, and 5-CH_2OH-S-2200.

NATURE OF THE RESIDUE IN LAYING HEN	**PMRA # 2377838**

Two groups of ten laying hens were dosed orally with [Ph^{14}C]-S-2200 at 13.37 ppm and [Bz-^{14}C]-S-2200 at 13.15 ppm in the diet), via gelatin capsule, once daily for 14 days. Samples of excreta were collected daily. Samples of eggs were collected twice daily. The hens were euthanized 6 hours after administration of the final dose.

Formulated Test Substance	The approximate S-2200 *R:S* isomer ratio was 50:50.
Analytical Method for Overall TRR **Identification & Characterization**	LSC and combustion Radio-HPLC using co-chromatography; LC-MS/MS

Extraction Solvents	Eggs, fat, and muscle: Sequential extraction with hexane, ethyl acetate, acetonitrile and 1% formic acid in acetonitrile Liver and skin: Sequential extraction with hexane, ethyl acetate, acetrontrile, 1% formic acid in acetonitrile, water, 1M HCl, and 1M ammonia solution
Post-Extraction Solids (PES)	Liver: Sequential hydrolysis using protease digestion for 18 hours at 37°C, acid hydrolysis with 10M HCl, base hydrolysis with 10M NaOH under reflux
Storage Stability	Samples were stored and analyzed within 6 months.

Matrices	**[Ph-^{14}C]-S-2200**		**[Bz-^{14}C]-S-2200**	
	TRR (ppm)	**% of AD**	**TRR (ppm)**	**% of AD**
Excreta	-	83.37	-	98.36
Cage wash	-	1.33	0	0.99
Muscle (breast)	0.0127	0.007	0.025	0.014
Muscle (thigh)	0.0144	0.003	0.023	0.005
Fat (peritoneal)	0.033	0.003	0.032	0.005
Skin	0.0478	0.003	0.0543	0.003
Liver	0.295	0.055	0.299	0.063
Eggs (Day 2-14)	0.051-0.113	0.21	0.050-0.081	0.18

The majority of the administered dose was excreted, with 85% of the total dose of [Ph-^{14}C]-S-2200 and 99% of the total dose of [Bz-^{14}C]-S-2200 being recovered in the excreta and cage wash. The highest residues were detected in liver and eggs. Following administration of [Ph-^{14}C]-S-2200 to hens, total radioactive residues in eggs reached a maximum on day 11 (0.113 ppm). Similarly, following administration of [Bz-^{14}C]-S-2200 to hens, total radioactive residues in eggs reached a maximum on day 7 (0.081 ppm). The major residue from laying hen dosed with [Ph-^{14}C]-S-2200 and [Bz-^{14}C]-S-2200 was S-2200 in fat (33.9-49.5% of the TRR; 0.011-0.016 ppm), and eggs (33.1-51.2% of the TRR; 0.025-0.058 ppm). Another major residue from laying hen dosed with [Ph-^{14}C]-S-2200 was 4-OH-S-2200 in liver (13.6% of the TRR; 0.040 ppm). Only S-2200 was confirmed by LC-MS.

All other minor metabolites were only tentatively identified based on chromatographic retention times of metabolite standards. The metabolism of [^{14}C]-S-2200 was considered extensive as some tissues contained up to 21 peaks, including diffuse regions of interest. The unextractable radioactivity in liver, remaining after acid, alkaline, and enzymatic hydrolysis (PES), was presumed to be associated mostly with endogenous material, or more polar multi-components.

Metabolites identified	**Major Metabolites (>10% of the TRRs)**	
Radiolabel Position	**[Ph-^{14}C]-S-2200**	**[Bz-^{14}C]-S-2200**
Egg (Day 11)	S-2200	S-2200
Liver	4-OH-S-2200	None
Muscle	None	None
Skin	None	None
Fat	S-2200	S-2200

NATURE OF THE RESIDUE IN LACTATING GOAT	**PMRA # 2377836**

Two lactating goats were dosed orally with [Ph^{14}C]-S-2200 at 12.65 ppm and [Bz-^{14}C]-S-2200 at 14.33 ppm in the diet), via gelatin capsule, once daily for 7 days. Samples of excreta were collected once daily and milk was collected twice daily. The goats were euthanized 6 hours after administration of the final dose.

Formulated Test Substance	The approximate S-2200 *R:S* isomer ratio was 50:50.
Analytical Method for Overall TRR Identification & Characterization	LSC and combustion Radio-HPLC using co-chromatography; LC-MS/MS
Extraction Solvents	Fat, milk fat, muscle: Sequential extraction with hexane, ethyl acetate, acetonitrile and 1% formic acid in acetonitrile Liver and kidney: Sequential extraction with hexane, ethyl acetate, acetrontrile, 1% formic acid in acetonitrile, water, 1M HCl, and 1M ammonia solution

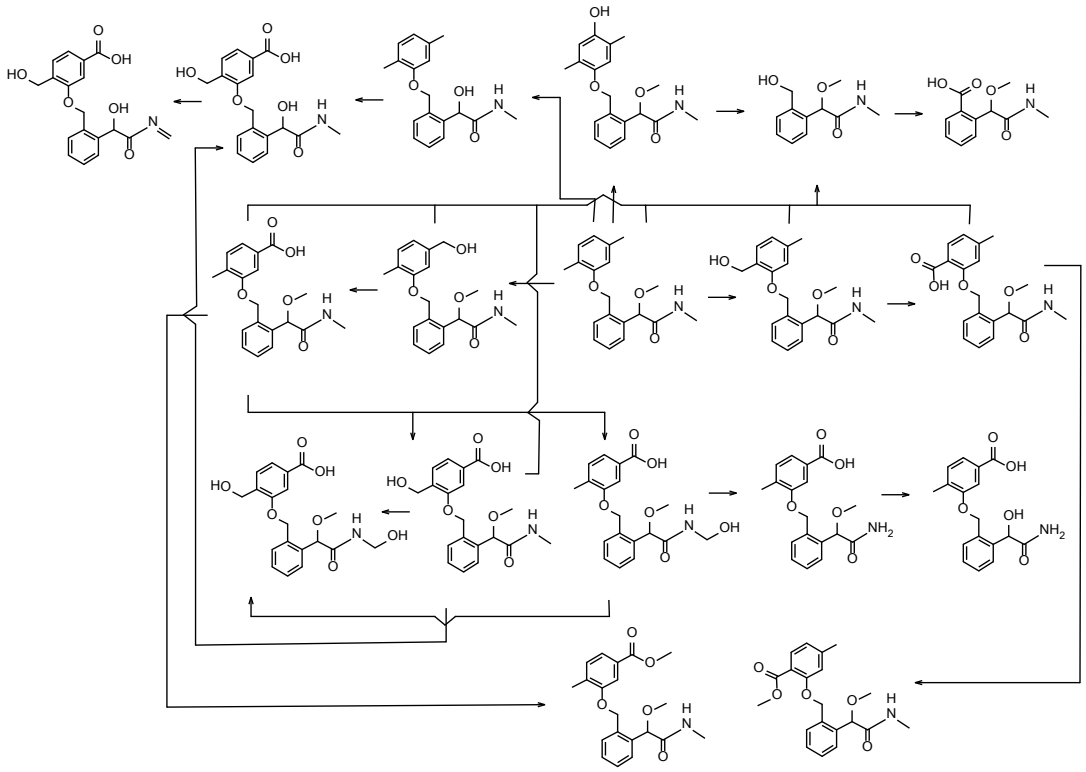
Post-Extraction Solids (PES)	Liver: Sequential hydrolysis using protease digestion for 18 hours at 37°C, acid hydrolysis with 10M HCl, base hydrolysis with 10M NaOH under reflux
Storage Stability	Samples were stored and analyzed within 6 months.

Matrices	**[Ph-^{14}C]-S-2200**		**[Bz-^{14}C]-S-2200**	
	TRR (ppm)	**% of AD**	**TRR (ppm)**	**% of AD**
Urine	-	35.22	-	39.73
Cage wash	-	1.19	-	0.68
Feces	-	42.49	-	38.07
Muscle (flank)	0.012	0.005	0.016	0.003
Muscle (loin)	0.008	0.001	0.014	0.001
Fat (omental)	0.012	0.006	0.028	0.002
Fat (renal)	0.013	0.008	0.034	0.004
Fat (subcutaneous)	0.010	0.001	0.033	<0.001
Kidney	0.170	0.022	0.412	0.031
Liver	0.319	0.225	0.613	0.289
Milk – fat fraction	0.008-0.033	0.002	0.006-0.035	0.005
Milk – aqueous fraction	0.004-0.010	0.024	0.006-0.018	0.073

S-2200 was extensively metabolised and the majority of the administered dose (79% of [Ph-^{14}C]-S-2200 and 78% of [Bz-^{14}C]-S-2200) was excreted in approximately equal proportions in the urine and faeces. Following administration of [Ph-^{14}C]-S-2200 to goats, total radioactive residues in the aqueous fraction of milk reached a maximum on day 6 (0.01 ppm), and on day 7 in the milk fat (0.033 ppm). Similarly, following administration of [Bz-^{14}C]-S-2200 to goats, total radioactive residues in the aqueous fraction of milk reached a maximum on day 3 (0.018 ppm) and on day 5 in the milk fat (0.035 ppm). Residues in the tissues, with the exception of the liver, were readily extractable with organic solvents or polar solvents most notably following administration of [Ph-^{14}C]-S-2200. The major residue from lactating goat dosed with [Ph-^{14}C]-S-2200 and [Bz-^{14}C]-S-2200 was S-2200 in fat (22.9-49.6% of the TRR; 0.006-0.007 ppm), muscle (18.2-23.0% of the TRR; 0.002-0.003 ppm), and milk fat fraction (32.7-35.3% of the TRR; 0.011-0.012 ppm); 4-OH-S-2200 (conj.) in kidney (13.3-14.9% of the TRR; 0.025-0.055 ppm); and 5-COOH-S-2200 in kidney (20.2-25.0% of the TRR; 0.043-0.083 ppm), and liver (10.6-19.3% of the TRR; 0.062-0.065 ppm). Other major residues from lactating goat dosed with [Bz-^{14}C]-S-2200 were 2-CH_2OH-S-2200 in muscle (10.1% of the TRR; 0.002 ppm), and 5-CA-S-2200-NHM in milk (14.7% of the TRR; 0.003 ppm). LC-MS was used to confirm the identity of S-2200 (milk fat, muscle and fat), 2-CH_2OH-S-2200 (muscle), 5-COOH-S-2200 (liver and kidney) and 4-OH-S-2200 glucuronide (kidney). All other minor metabolites were only tentatively identified based on chromatographic retention times of metabolite standards. The metabolism of [^{14}C]-S-2200 was considered extensive as some tissues contained up to 25 peaks, including diffuse regions of interest. The unextractable radioactivity in liver, remaining after acid, alkaline, and enzymatic hydrolysis (PES), was presumed to be associated mostly with endogenous material, or more polar multi-components.

Metabolites identified	**Major Metabolites (>10% of the TRR)**	
Radiolabel Position	**[Ph-^{14}C]-S-2200**	**[Bz-^{14}C]-S-2200**
Milk – fat fraction	S-2200	S-2200
Milk – aqueous fraction	Not analysed	5-CA-S-2200-NHM
Liver	5-COOH-S-2200	5-COOH-S-2200
Kidney	5-COOH-S-2200, 4-OH-S-2200 (conj.)	5-COOH-S-2200, 4-OH-S-2200 (conj.)
Muscle	S-2200	S-2200, 2-CH_2OH-S-2200
Fat	S-2200	S-2200

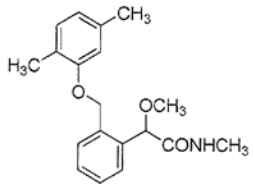
Proposed Metabolic Pathway of S-2200 in Primary Crops, Secondary Crops, Livestock and Rat

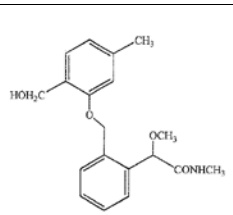
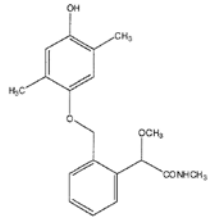
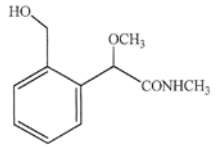
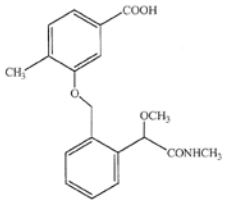


Major Metabolic Pathways in Primary Crops, Secondary Crops, and Livestock.

The major metabolic pathways included hydroxylation of the phenoxy ring to form 4-OH-S-2200 and subsequent formation of the glycoside conjugate, and oxidation of the methyl group attached to the phenoxy ring to form 2-CH_2OH-S-2200 and 5-CH_2OH-S-2200 and their corresponding glycoside conjugates (plants) and glucuronides (livestock). Minor metabolic pathways included the demethylation of the methoxy group of the side chain to form MCBX and cleavage of the ether linkage to form De-Xy-S-2200. In livestock, conjugates are glucuronides.

Chemical Structure and Codes of Mandestrobin (S-2200) and Major Metabolites Identified in Plant (Primary and Secondary) and Livestock Metabolism Studies

Code	Chemical Structure	Found In
S-2200		**Rat** **Livestock:** ruminant (muscle, fat, milk); poultry (fat, eggs) **Primary Crops:** wheat hay/forage; lettuce (mature and immature); rapeseed seed/forage **Secondary Crops:** lettuce (mature and immature); carrot (roots and foliage)

2-CH_2-OH-S-2200		**Rat** **Primary Crops:** wheat hay/forage **Secondary Crops:** carrot roots
4-OH-S-2200		**Rat** **Livestock:** poultry (liver)
De-Xy-S-2200		**Rat** **Primary Crops:** wheat grain/straw; soybean forage (seed treatment) **Secondary Crops:** lettuce (mature and immature); carrot (roots and foliage)
5-COOH-S-2200		**Rat** **Livestock:** ruminant (kidney, liver)
4-OH-S-2200 (Bound/ Conjugated/ glycosides)		**Rat** **Livestock:** ruminant (kidney) **Primary Crops:** rapeseed seed/forage **Secondary Crops:** wheat hay/forage/straw; lettuce (mature and immature)
2-CH_2-OH-S-2200 (conjugated/glycosides)		**Primary Crops:** wheat hay/forage; rapeseed forage **Secondary Crops:** wheat forage
5-CH_2-OH-S-2200 (conjugated/glycosides)		**Secondary Crops:** wheat hay/forage; lettuce (mature and immature); carrot foliage

Freezer Storage Stability		**PMRA # 2377901, 2377902**
Matrix	**Demonstrated storage interval at -18°C (months)**	**Actual storage interval (months)**
Storage stability studies		
Rapeseed (seed)	12 and on-going*	38
Rapeseed (oil)	12	10
Rapeseed (meal)	12	9
Lettuce	12	No associated residue trial
Barley (grain)	12	
Barley (straw)	12	

Concurrent storage stability studies		
Strawberries	5 and on-going*	19
Grapes	8 and on-going*	16
Grape (juice)	7	7
Grape (raisins)	5 and on-going*	9
Soybean (seed)	12	8.5
Corn forage	12	12
Corn K+CWHR	12	11
Corn grain	12	9
Corn stover	9	9

In addition, storage stability of incurred ^{14}C-S-2200 residues in rapeseed forage was investigated over a period of 4 years, and no significant decline of S-2200 was observed.
* Additional storage stability studies to be submitted by applicant at a later date.

CROP FIELD TRIALS

Residue trials were conducted throughout Canada and the United States using formulated products (S-2200 2.5 SC, S-2200 4 SC, and S-2200 3.2 FS Fungicide) containing mandestrobin on corn, grapes, soybeans, strawberries, and rapeseed. Adjuvants were added to each spray mixture. Only trial values that were conducted at GAP or within ±25% of GAP were included herein. Residues of S-2200 decline with increasing PHIs in strawberries and grapes. In the case of rapeseeds, the residues declined in one trial, whereas residues were less than LOQ in the other trial.

Crop Field Trials on Strawberries (Foliar)	**PMRA #s 2377911(CDN) and 2377917 (US)**

Number and Location of Field Trials

Region	**1**	**2**	**3**	**5**	**10**	**12**	**Total**
CDN Required*	1	0	0	3	0	1	**5**
US Required*	1	0	1	1	2	1	**6**
Submitted	1	1	1	3	3	1	**10**

*As per DIR98-02 and USEPA Residue Chemistry Test Guidelines (crop group reduction).

Use Pattern

Approved Use Pattern (GAP)	**Study Use Pattern**
Single foliar appl. rate: 210-420 g a.i./ha # of appl.: 4-5 appl. per year at 7-14 day intervals Maximum rate: 1680 g a.i./ha/season PHI: 0 day	**CDN trials:** Single foliar appl. rate: ~420 g a.i./ha + adjuvant # of appl.: 4 appl. per year Maximum rate: 1674-1734 g a.i./ha/season PHI: 0 day **US trials:** Single foliar appl. rate: ~420 g a.i./ha + adjuvant # of appl.: 4 appl. per year Maximum rate: 1675 – 1702 g a.i./ha/season PHI: 0 day Decline Trials: 0, 1, 3, 5 and 7 days

Total Rate (g a.i./ha)	**PHI (days)**	**S-2200 Residue Levels (ppm)**							
		n	**Min. #**	**Max. #**	**LAFT ***	**HAFT ***	**Median ***	**Mean ***	**SD ***
US trials									
1675-1702	0	8	0.33	2.12	0.45	2.05	0.84	0.97	0.52
Canadian trials									
1674-1734	0	2	0.6	1.07	0.62	0.995	0.81	0.81	0.27
Combined trials									
1674-1734	0	10	0.33	2.12	0.45	2.05	0.84	0.94	0.47

Values based on total number of samples; * Values based on per-trial averages; n = number of independent trials.

Crop Field Trials on Grapes (Foliar)					PMRA #s 2377913 (CDN) and 2377920 (US)
Number and Location of Field Trials					
Region	**1**	**5**	**10**	**11**	**Total**
CDN Required*	0	4	0	1	**5**
US Required*	2	0	5	2	**9**
Submitted	2	3	7	3	**15**
*As per DIR98-02 and USEPA Residue Chemistry Test Guidelines (crop group reduction).					

Approved Use Pattern (GAP)	Study Use Pattern
Single foliar appl. rate: 210-420 g a.i./ha # of appl.: 3-4 appl. per year at 10-14 day intervals Maximum seasonal rate: 1260 g a.i./ha PHI: 10 days	**CDN trials:** Single foliar appl. rate: ~420 g a.i./ha + adjuvant # of appl.: 3 appl. per year Maximum rate: 1249-1324 g a.i./ha/season PHI: 9-11 days
	US trials: Single foliar appl. rate: ~420 g a.i./ha + adjuvant # of appl.: 3 appl. per year Maximum rate: 1240-1295 g a.i./ha/season PHI: 10 days Decline Trials: 0, 3, 7, 10 and 14 days

Total Rate (g a.i./ha)	PHI (days)	S-2200 Residue Levels (ppm)							
		n	Min. #	Max. #	LAFT *	HAFT *	Median *	Mean *	SD *
US trials									
1240-1295	10	10	0.68	3.74	0.74	3.46	1.40	1.56	0.83
Canadian trials									
1249-1324	9-11	4	0.44	1.13	0.47	1.08	0.86	0.82	0.29
Combined trials									
1240-1324	9-11	14	0.44	3.74	0.47	3.46	1.19	1.37	0.79

Values based on total number of samples; * Values based on per-trial averages; n = number of independent trials;

Crop Field Trials on Rapeseed (Foliar)							PMRA #s 2377930 (CDN) and 2377926 (US)
Number and Location of Field Trials							
Region	**1**	**2**	**5**	**7**	**11**	**14**	**Total**
CDN Required*	1	0	1	0	0	14	**16**
US Required*	0	1	2	1	2	0	**6**
Submitted	0	0	4	2	3	14	**23**
*As per DIR98-02 and USEPA Residue Chemistry Test Guidelines (crop group reduction).							

Approved Use Pattern (GAP)	Study Use Pattern
# of appl.: 1 appl. per year Maximum foliar seasonal rate: 420 g a.i./ha PHI: 35 days	**CDN trials:** Maximum foliar rate: 406-442 g a.i./ha/season + adjuvant # of appl.: 3 appl. per year PHI: 31-44 days Decline Trial: 28, 33, 37 and 41 days
	US trials: Maximum foliar rate: 402-458 g a.i./ha/season + adjuvant # of appl.: 1 appl. per year PHI: 34-36 days Decline Trial: 26, 31, 36 and 41 days

Total Rate (g a.i./ha)	PHI (days)	S-2200 Residue Levels (ppm)							
		n	Min. #	Max. #	LAFT *	HAFT *	Median *	Mean *	SD *
US trials									
402-458	34-36	12	<0.02	0.13	<0.02	0.125	<0.02	0.03	0.04
Canadian trials									
406-442	31-44	8	<0.02	0.544	<0.02	0.508	0.03	0.09	0.15
Combined trials									
402-458	31-44	20	<0.02	0.544	<0.02	0.508	0.02	0.07	0.12

Values based on total number of samples; * Values based on per-trial averages; n = number of independent trials

Crop Field Trials on Field Corn (Seed Treatment) — **PMRA # 2378153**

Number and Location of Field Trials

Three (3) trials were conducted at exaggerated rates in Region 5 in NAFTA representative growing regions based on the results of the radiotracer study.

Approved Use Pattern (GAP)	Study Use Pattern
Maximum seasonal rate: 6 g a.i./100 kg seed	Maximum seasonal rate: 3 trials at 10 g a.i./100 kg seed and at 50 g a.i./100 kg seed; Samples were collected between 71-168 days after seed planting.

Crop Matrix	Total Rate (g a.i./ha)	PHI (days)	S-2200 Residue Levels (ppm)							
			n	Min. #	Max. #	LAFT *	HAFT *	Median *	Mean *	SD *
K+CWHR	11.6-13.7 (~50 g a.i./ 100 kg seed)	71-78	3	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	--
Forage		88-92	3	<0.02	<0.02	<0.02	<0.02	<0.02	<0.02	--
Grain		118-168	3	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	--
Stover		118-168	3	<0.02	<0.02	<0.02	<0.02	<0.02	<0.02	--

Residues from the 10 g a.i./100 kg seed application were not analyzed as residues from the 8-fold application rate were all <LOQ. # Values based on total number of samples; * Values based on per-trial averages; n = number of independent trials

Crop Field Trials on Soybeans (Seed Treatment) — **PMRA # 2378152**

Number and Location of Field Trials

Three (3) trials were conducted at exaggerated rates in Regions 4 (1 trial) and 5 (2 trials) in NAFTA representative growing regions based on the results of the radiotracer study.

Approved Use Pattern (GAP)	Study Use Pattern
Maximum seasonal rate: 10 g a.i./100 kg seed	Maximum seasonal rate: 3 trials at 10 g a.i./100 kg seed and at 50 g a.i./100 kg seed; Samples were collected between 116-136 days after seed planting.

Crop Matrix	Total Rate (g a.i./ha)	PHI (days)	S-2200 Residue Levels (ppm)							
			n	Min. #	Max. #	LAFT *	HAFT *	Median *	Mean *	SD *
Soybean seed	21.7-29.1 (~50 g a.i./100 kg seed)	116-136	3	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	--

Residues from the 10 g a.i./100 kg seed application were not analyzed as residues from the 5-fold application rate were all <LOQ. # Values based on total number of samples; * Values based on per-trial averages; n = number of independent trials

Residue Data in Field Accumulation – Spring, wheat, lettuce, garden beets — **PMRA # 2377938, 2377942**

Primary Crop	Study Use Pattern	Rotational Crop (PBIs)
Leaf Lettuce	1 trial in Region 10 (US) - 4 foliar applications of S-2200 on leaf lettuce for a total of 1696 g a.i./ha	Wheat, spinach, garden beets: (101 DAT/3.8 months) Sorghum, spinach, garden beets: (253 DAT/8.4 months) Wheat, spinach, garden beets: (356 DAT/11.8 months)

Commodity	Total Rate (g a.i./ha)	PBI (days)	S-2200 Residue Levels (ppm)							
			n	Min. #	Max. #	LAFT *	HAFT *	Median *	Mean *	SD *
Wheat (forage, hay, straw & grain)	1696	101 & 356	1	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	--
Spinach			1	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	--
Garden beets (roots and leaves)			1	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	--
Sorghum (forage, stover & grain)		253	1	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	--
Spinach			1	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	--
Garden beets (roots and leaves)			1	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	--

Primary Crop	Approved Use pattern (GAP)	Study Use Pattern	Rotational Crop (PBIs)
Rapeseed	Maximum foliar rate: 420 g a.i./ha/season (ground and air) Timing: 20-50% bloom # of appl.: 1 appl./year PHI: 35 days	1 trial in Region 7 (US) - 1 foliar application of S-2200 on rapeseed at 415 g a.i./ha (1-fold GAP)	Spring wheat (286 DAT/9.5 months) Garden beets, lettuce (304 DAT/10 months)

Commodity	Total Rate (g a.i./ha)	PBI (days)	S-2200 Residue Levels (ppm)							
			n	Min. #	Max. #	LAFT *	HAFT *	Median *	Mean *	SD *
Spring Wheat (forage, hay, straw, grain)	415	286 & 304	1	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	--
Lettuce			1	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	--
Garden beets (roots and leaves)			1	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	--

Values based on total number of samples; * Values based on per-trial averages; n = number of independent trials.

Based on the results of the field accumulation study, a plant-back interval of 4 months is recommended. Immediate plant-back for labelled-crops.

Processed Food and Feed - Grapes		PMRA# 2377920	
Test Site		One trial in NAFTA Growing Region 10	
Treatment		Broadcast foliar applications	
Rate		6298 g a.i./ha (5-fold GAP)	
End-use product/formulation		S-2200 4 SC	
PHI (days)		10	
Processed Commodities		**Average Residues (ppm)**	**Processing Factor**
Grape	**RAC**	11.6	--
	Juice	16.2	1.4
	Raisins	22.4	1.9

Processed Food and Feed - Rapeseed		PMRA# 2377926	
Test Site		One trial in NAFTA Growing Region 5	
Treatment		Broadcast foliar applications	
Rate		2095 g a.i./ha (5-fold GAP)	
End-use product/formulation		S-2200 4 SC	
PHI (days)		34	
Processed Commodity		**Average Residues (ppm)**	**Processing Factor**
Rapeseed	**RAC**	0.23	--
	Refined oil	0.02	0.09
	Meal	0.05	0.22

Residues in Livestock Studies	
Residues in livestock studies were not conducted as the only potential livestock feed items from the petitioned uses were rapeseed meal, corn (seed treatment), and rotational crops (sorghum, and wheat), and as such, there was no expectation of quantifiable residues in meat, milk or eggs. In the absence of livestock feeding studies, the metabolism studies (laying hen, lactating goat) can confirm that no finite residues of S-2200 are expected in meat, milk, and eggs.	
Dietary Burden and Anticipated Residues	**PMRA # 2523426**
Dietary burdens of 0.03 ppm (dairy cattle) and 0.008 ppm (poultry) were estimated based on potential livestock feeding items. The anticipated residues in poultry tissues and eggs were calculated to be less than 0.00004 ppm based on the residue-to-feed ratio from the laying hen metabolism study. The anticipated residues in livestock tissues and milk were calculated to be less than 0.00006 ppm based on the residue-to-feed ratio from the lactating goat metabolism study.	

Table 9 Food Residue Chemistry Overview of Metabolism Studies and Risk Assessment

Plant Studies	
Residue Definition for Enforcement **Residue Definition for Risk Assessment** Primary crops (wheat, lettuce, rapeseed) Rotational crops (wheat, sorghum, lettuce, spinach, beets)	Parent (S-2200)
Metabolic Profile in Diverse Crops	Plant metabolism studies have been conducted covering the crop categories of cereals, oilseeds and leafy vegetables (except *brassica*). A confined rotational crop study has also investigated the metabolism of residues taken up by wheat, lettuce and carrot. The route of metabolism of S-2200 has been shown to be similar, with the extent of metabolism being greater in commodities harvested at longer pre-harvest intervals. In the primary crop metabolism studies, measurement of the ratio of *R*- and *S*-isomers of S-2200 showed that there was no epimerization of S-2200 at the 2-position of the acetamide moiety.
Animal Studies	
Animals	**Ruminant and Poultry**
Residue Definition for Enforcement	**Not being proposed**

Residue Definition for Risk Assessment	In the absence of a livestock feeding study and an enforcement method for animal matrices, and considering that there is no expectation of measurable residues in meat, milk and eggs, based on the anticipated residues, (calculated from the metabolism studies), a residue definition for animal matrices is not being proposed. However, this will be reassessed in the event that there is an expansion of use to a livestock feed item, that contributes significantly to the dietary burden, and livestock feeding studies and enforcement methods are submitted to the Agency.
Metabolic Profile in Animals (goat, hen)	Mandestrobin is extensively metabolized in livestock. Metabolism studies in laying hens and lactating goats showed that the metabolic pathways in livestock were similar to that found in the rat.
Fat Soluble Residue	Yes

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 **ADI = 0.3 mg/kg bw/day** **Estimated chronic drinking water concentration = 225 µg/L**	**All infants < 1 year**	2.1	7.7
	Children 1–2 years	7.1	9.2
	Children 3 to 5 years	4.2	5.9
	Children 6–12 years	1.7	3.0
	Youth 13–19 years	0.7	1.8
	Adults 20–49 years	0.8	2.3
	Adults 50+ years	1.0	2.5
	Females 13-49 years	0.9	2.4
	Total population	1.3	2.8

Table 10 Fate and Behaviour in the Environment

Property	Test substance	Value[1]	Transformation products	Comments	Reference
Abiotic transformation					
Hydrolysis at 50°C	[Benzyl-^{14}C]-S-2200 *R*-isomer, [Benzyl-^{14}C]-S-2200 *S*-isomer	pH 4: stable pH 7: stable pH 9: stable	none	Not a route of transformation in the environment	2377861 2377863
Phototransformation on soil	[Benzyl-^{14}C]-S-2200 *R*-isomer, [Benzyl-^{14}C]-S-2200 *S*-isomer and [Phenoxy-^{14}C]-S-	DT_{50} (irradiated) = 52.3-63.8 d; DT_{90} (irradiated) = 173.7-211.8 d; DT_{50} (dark) = 71.7-82.9	Major: UR* Minor: DX-CA-S-2200; De-Xy-S-2200; 2-COOH-S-2200; 5-	Not a route of transformation in the environment; no	2377867 2377864

Property	Test substance	Value[1]	Transformation products	Comments	Reference
	2200 *R*-isomer	d; DT_{90} (dark) = 238.1-275.4 d (SFO)	COOH-S-2200; MCBX; S-2200-OR; CO_2	isomerization occurred	
Phototransformation in water 25±1°C	[Benzyl-^{14}C]-S-2200 and [Phenoxy-^{14}C]-S-2200 *R*-isomer (combined labels)	<u>S-2200 *R*-isomer</u> DT_{50}=4.39 d; DT_{90}=14.6 d (SFO) (combined labels) Dark: none <u>S-2200-OR</u> DT_{50}=9.25 d; DT_{90}=30.7 d (SFO)	<u>Minor (Benzyl label only</u>: De-Xy-S-2200; CO_2 <u>Major:</u> S-2200-OR; S-2200-ORC; 2200-PR and CO_2. (CO_2 for phenoxy label, only)	Non-persistent Phototransformation is expected to be an important route of dissipation	2377871
	[Benzyl-^{14}C]-S-2200 *S*-isomer	Irradiated: <u>S-2200 *S*-isomer</u> DT_{50}=4.59 d; DT_{90}=15.3 d (SFO) Dark: none <u>S-2200-OR</u> DT_{50}= 8.23 d; DT_{90}=27.3 d (SFO)	<u>Major:</u> S-2200-OR; S-2200-ORC; De-Xy-S-2200 <u>Minor</u>: S-2200-PR; CO_2	Non-persistent Phototransformation is expected to be an important route of dissipation	2377869
Phototransformation in air	Mandestrobin	Mandestrobin is not expected to be volatile under field conditions based on vapour pressure and Henry's law constant.			
Biotransformation					
Biotransformation in aerobic soil	[Benzyl-^{14}C]-S-2200 *R*-isomer,	<u>California Sand</u> DT_{50}: 295 d; DT_{90}: 980 d (SFO)	<u>Major</u>: 5-COOH-S-2200; CO_2; UR <u>Minor</u>: DX-CA-S-2200; 2-COOH-S-2200; 2-$CONH_2$-S-2200; 5-$CONH_2$-S-2200; MCBX; De-Xy-S-2200	Biotransformation in aerobic soil is a main route of dissipation for mandestrobin	2377894
		<u>Mississippi Silt loam</u> DT_{50}: 393 d; DT_{90}: 1867 d (DFOP) Slow $t_{1/2}$ = 635 d	<u>Major</u>: CO_2; UR <u>Minor</u>: DX-CA-S-2200; 2-COOH-S-2200; 5-COOH-S-2200; 2-$CONH_2$-S-2200; 5-$CONH_2$-S-2200; MCBX; De-Xy-S-2200	Mandestrobin is moderately persistent to persistent	
		<u>North Dakota Sandy loam</u> DT_{50}: 334 d; DT_{90}: 6785 d (IORE) $t_{R\ IORE}$ = 2040 d	<u>Major</u>: 5-COOH-S-2200; CO_2 <u>Minor</u>: DX-CA-S-2200; 2-COOH-S-2200; 2-$CONH_2$-S-2200; 5-$CONH_2$-S-2200; MCBX; De-Xy-S-2200		
	[Benzyl-^{14}C]-S-2200 *R*-isomer	<u>Sandy loam (Speyer 5M)</u> DT_{50}: 66.5 d;	<u>Major</u>: 5-COOH-S-2200; CO_2; UR	Mandestrobin is moderately persistent to	2377881

Property	Test substance	Value[1]	Transformation products	Comments	Reference
		DT_{90}: 221 d (SFO)	Minor: DX-CA-S-2200; MCBX; 2-COOH-S-2200; 2,5-DMP	persistent	
		Loamy sand (Speyer 2.2) DT_{50}: 238 d; DT_{90}: 920 d (DFOP) Slow $t_{1/2}$ = 294 d	Major: none Minor: 5-COOH-S-2200; 2-COOH-S-2200; MCBX; DX-CA-S-2200;CO_2		
		Clay loam (SK920191) DT_{50}: 43.3 d; DT_{90}: 205 d (DFOP) Slow $t_{1/2}$ = 70 d	Major: 5-COOH-S-2200; CO_2; UR Minor: 2-COOH-S-2200; MCBX; De-Xy-S-2200;DX-CA-S-2200		
		Silt loam (Chelmorton) DT_{50}: 96.5 d; DT_{90}: 631 d (DFOP) Slow $t_{1/2}$ = 230 d	Major: CO_2; UR Minor: 5-COOH-S-2200; 2-COOH-S-2200; MCBX; DX-CA-S-2200		
	[Benzyl-^{14}C]-S-2200 *R*-isomer	Loam (Aschard) DT_{50}: 43.9 d; DT_{90}: 213 d (DFOP) Slow $t_{1/2}$ = 77.4 d	Major: 5-COOH-S-2200; CO_2; UR Minor: 2-COOH-S-2200; MCBX; De-Xy-S-2200;DX-CA-S-220	Slightly persistent	2377886
		Silty clay loam (Monteil) DT_{50}: 37.5 d; DT_{90}: 152 d (IORE) $t_{R\ IORE}$ = 45.8 d			
	[Benzyl-^{14}C]- and [Phenoxy-^{14}C]- S-2200 *R*-isomer	Loam (New Jersey) DT_{50}: 110 d; DT_{90}: 930 d (DFOP) Slow $t_{1/2}$ = 397 d (combined labels)	Major: DX-CA-S-2200; 5-COOH-S-2200; 2-$CONH_2$-S-2200; 5-$CONH_2$-S-2200; CO_2; UR Minor: 2-COOH-S-2200; MCBX; De-Xy-S-2200	Mandestrobin is moderately persistent	2377890
	[Benzyl-^{14}C]-S-2200 *S*-isomer	Loam (New Jersey) DT_{50}: 118 d; DT_{90}: 1494 d (IORE) $t_{R\ IORE}$ = 450 d	Major: DX-CA-S-2200; 2-$CONH_2$-S-2200; 5-$CONH_2$-S-2200; CO_2; UR Minor: 2-COOH-S-2200; 5-COOH-S-2200; MCBX; De-Xy-S-2200		

Property	Test substance	Value[1]	Transformation products	Comments	Reference
	[Benzyl-^{14}C]-S-2200 *S*-isomer	Sandy loam (Speyer 5M) DT_{50}: 85.4 d; DT_{90}: 284 d (SFO)	Major: 5-COOH-S-2200; CO_2; UR Minor: 2-COOH-S-2200; MCBX; De-Xy-S-2200;DX-CA-S-220	Mandestrobin is moderately persistent to persistent	2377883
		Loamy sand (Speyer 2.2) DT_{50}: 22305 d; DT_{90}: 6599792944837 d (IORE) $t_{R\ IORE}$ = 1.99e+12 d	Major: none Minor: 5-COOH-S-2200; 2-COOH-S-2200; MCBX; DX-CA-S-2200; CO_2		
		Clay loam (SK920191) DT_{50}: 90.2 d; DT_{90}: 367 d (DFOP) Slow $t_{1/2}$ = 119 d	Major: 5-COOH-S-2200; CO_2; UR Minor: 2-COOH-S-2200; MCBX		
		Silt loam (Chelmorton)) DT_{50}: 124 d; DT_{90}: 730 d (DFOP) Slow $t_{1/2}$ = 261 d	Major: CO_2; UR Minor: 5-COOH-S-2200; 2-COOH-S-2200; MCBX ;DX-CA-S-2200		
	[Benzyl-^{14}C]-S-2200 *S*-isomer	Loam (Aschard) DT_{50}: 72.2 d; DT_{90}: 266 d (DFOP) Slow $t_{1/2}$ = 83.3 d	Major: 5-COOH-S-2200; CO_2; UR Minor: 2-COOH-S-2200; MCBX; De-Xy-S-2200; DX-CA-S-2200	Moderately persistent	2377888
		Silty clay loam (Monteil) DT_{50}: 56.5 d; DT_{90}: 269 d (IORE) $t_{R\ IORE}$ = 81 d	Major: CO_2; UR Minor: 5-COOH-S-2200; 2-COOH-S-2200; MCBX; De-Xy-S-2200; DX-CA-S-2200		
	[Benzyl-^{14}C]5-COOH-S-2200	Silt loam (SK104691) DT_{50}: 20.3 d; DT_{90}: 89.7 d (IORE) $t_{R\ IORE}$ = 27 d	Major: CO_2; UR Minor: DX-CA-S-2200	Slightly to moderately persistent	2377879
		Clay loam (SK920191) DT_{50}: 24.6 d; DT_{90}: 165 d (IORE) $t_{R\ IORE}$ = 49.8 d	Major: CO_2; UR Minor: none		
		Sandy loam (Speyer 5M) DT_{50}: 39.1 d; DT_{90}: 161 d (IORE) $t_{R\ IORE}$ = 48.5 d	Major: CO_2; UR Minor: none		

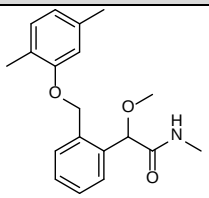
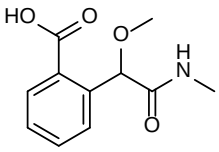
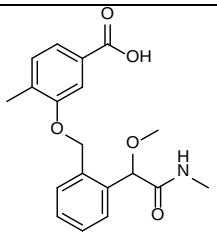
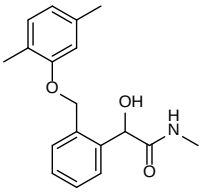
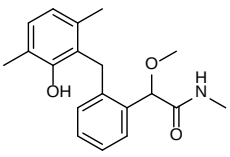
Property	Test substance	Value[1]	Transformation products	Comments	Reference
	[Benzyl-^{14}C]2-COOH-S-2200	Silt loam (SK104691) DT_{50}: 18.1 d; DT_{90}: 60 d (SFO) Clay loam (SK920191) DT_{50}: 19.7 d; DT_{90}: 73 d (IORE) $t_{R\ IORE}$ = 22 d Sandy loam (Speyer 5M) DT_{50}: 27.2 d; DT_{90}: 76.9 d (IORE) $t_{R\ IORE}$ = 23.2 d	Major: CO_2; UR Minor: DX-CA-S-2200 Major: CO_2; UR Minor: DX-CA-S-2200 Major: CO_2; UR Minor: DX-CA-S-2200 De-Xy-S-2200	Slightly to moderately persistent	2377877
Biotransformation in anaerobic soil	[Benzyl-^{14}C]- and [Phenoxy-^{14}C]- S-2200 *R*-isomer [Benzyl-^{14}C] S-2200 *R*-isomer	Water: loam soil system (New Jersey) DT_{50}: 3801 d; DT_{90}: 12625 d (SFO) (combined labels) DT_{50}: 1795 d; DT_{90}: 5963 d (SFO)	Major: UR (New Jersey) Minor: DX-CA-S-2200; 2-COOH-S-2200; 5-COOH-S-2200; De-Xy-S-2200; MCBX; CO_2	Not a route of dissipation for mandestrobin	2377897
	[Benzyl-^{14}C] S-2200 (1:1, *R:S* isomer ratio)	Water: loamy sand soil system (California) DT_{50}: 12,772 d; DT_{90}: 42426 d (SFO) Water: sandy loam soil system (North Dakota) DT_{50}: 861 d; DT_{90}: 2860 d (SFO) Water: silt loam soil system (Mississippi) DT_{50}: 1,723 d; DT_{90}: 5722 d (SFO)	Major: none (California); Unknown A (North Dakota and Mississippi) Minor: 5-COOH-S-2200; 2-COOH-S-2200; DX-CA-S-2200; MCBX; De-Xy-S-2200; CO_2	Not a route of dissipation for mandestrobin	2377900
Biotransformation in aerobic water-sediment systems (20±2°C)	[Benzyl-^{14}C]-S-2200 *R*-isomer; [Phenoxy-^{14}C]-S-2200 *R*-isomer (combined labels)	Lake water:silt loam sediment DT_{50}=322 d DT_{90}= 1069 d (SFO) Lake water:loamy sand sediment DT_{50}: 781 d; DT_{90}: 2803 d (DFOP) Slow $t_{1/2}$ = 870	Major: 5-COOH-S-2200 Minor: 2-COOH-S-2200, MCBX; CO_2 Major: none Minor: 5-COOH-S-2200; 2-COOH-S-2200, MCBX; CO_2	Partition: 77.9% (at 62 d) and 74.1% in sediment at end of study Partition: 67.8% in sediment at end of study Mandestrobin is persistent	2377903
	[Benzyl-^{14}C]-S-2200 *S*-isomer	Calwich Abbey Lake water: silt loam sediment DT_{50}=161 d DT_{90}= 535 d (SFO) Swiss Lake water:	Major: MCBX; UR* Minor: 5-COOH-S-2200; CO_2 Major: none	Partition: 69.6% (at 29 d) and 58.2% in sediment at end of study	2377905

Property	Test substance	Value[1]	Transformation products	Comments	Reference
		loamy sand sediment DT_{50}: 733 d; DT_{90}: 2435 d (SFO)	Minor: 5-COOH-S-2200; 2-COOH-S-2200, MCBX; CO_2	Partition: 64.0% in sediment at end of study Mandestrobin is moderately persistent to persistent	
Biotransformation in anaerobic water-sediment (25°C)	Benzyl-^{14}C]-S-2200 *R*-isomer + [Phenoxy-^{14}C]-S-2200 *R*-isomer (combined) [Benzyl-^{14}C]-S-2200 *S*-isomer	Water:clay sediment Bosket Lake DT_{50}: 2,917 d; DT_{90}: 9691 d (SFO) (combined label)	***R*-isomer** Major: UR Minor: MCBX; 5-COOH-S-2200; 2,5-DMP; 2-COOH-S-2200; DX-CA-S-2200; De-Xy-S-2200; CO_2	Partition: 87.09 % in sediment at end of study	2377907
		DT_{50}: 458 d; DT_{90}: 1523 d (SFO)	***S*-isomer** Major: MCBX Minor: 5-COOH-S-2200; 2-COOH-S-2200; DX-CA-S-2200; De-Xy-S-2200; DPMBA; CO_2	Partition: 68.47% (at 120 d) and 50.77 % in sediment at end of study	
		Water:sand sediment Golden Lake DT_{50}: 8,822 d; DT_{90}: 29307 d (SFO) (combined label) DT_{50}: 859 d; DT_{90}: 2854 d (SFO)	***R*-isomer** Major: none Minor: MCBX; 5-COOH-S-2200; 2,5-DMP; 2-COOH-S-2200; De-Xy-S-2200; CO_2	Partition: 88.39 % in sediment at end of study	
			***S*-isomer** Major: MCBX Minor: 5-COOH-S-2200; 2-COOH-S-2200; DPMBA; CO_2	Partition: 69.58 % in sediment at end of study Mandestrobin is persistent	
Mobility					
Adsorption / desorption in soil (5+2 soils)	[Benzyl-^{14}C] S-2200 (1:1, *R:S* isomer ratio)	K_F = 2.05-18.2 (L/kg-soil)$^{-1/n}$ K_{FOC} = 287-1104 (L/kg-OC)$^{-1/n}$ 1/n = 0.882-0.962		Low to moderately mobile	2377910 2377919
(3 + 3 soils)	[Benzyl-^{14}C]-2-COOH-S-2200	K_F = 0.27-2.94 (L/kg-soil)$^{-1/n}$ K_{FOC} = 6-226 (L/kg-OC)$^{-1/n}$ 1/n = 0.850-0.922		Moderate to very high mobility	2377912 2377915
(3 + 3 soils)	[Benzyl-^{14}C]-5-COOH-S-2200;	K_F = 1.26-8.89 (L/kg-soil)$^{-1/n}$ K_{FOC} = 29-684 (L/kg-OC)$^{-1/n}$ 1/n = 0.853-1.038		Low to very high mobility	2377914 2377916
Adsoption (HPLC)	S-2200	K_{OC} = 1780		Mobilty: Low	2377918

Property	Test substance	Value[1]	Transformation products	Comments	Reference
	2-COOH-S-2200 5-COOH-S-2200 2-$CONH_2$-S-2200 5-$CONH_2$-S-2200 Dx-CA-S-2200	K_{OC} < 18 K_{OC} = 19 K_{OC} = 122 K_{OC} = 172 K_{OC} < 18		Very high Very high High Moderate Very high	
4-years lysimeter study (2 lysimeters)	[Benzyl-^{14}C]-S-2200 25SC	Silty sand soil: 0.26% and 0.43% AR recovered in leachate	De-Xy-S-2200; DX-CA-S-2200; 2-COOH-S-2200; 5-COOH-S-2200; MCBX	Low leaching / mobility potential	2377921
Volatilization	Not required based on the low vapour pressure (3.36×10^{-8} Pa at 20ºC) and Henry's law constant (6.5×10^{-12} atm m^3/mol).				
Field studies					
Saskatchewan Bare soil	S-2200 4SC	Loam: DT_{50} 1.04 d; DT_{90}: 367 d (DFOP) Slow $t_{1/2}$ = 163 d	Minor: DX-CA-S-2200; 2-COOH S-2200 5-COOH S-2200	No residues beyond 30 cm soil depth Mandestrobin is non-persistent in soil	2377953
North Dakota Bare ground	S-2200 4SC	Loam: DT_{50}: 4.89 d; DT_{90}: 2015 d (IORE) $t_{R\ IORE}$ = 606 d or 142 (excluding outlier at 303 d)	Minor: DX-CA-S-2200; 2-COOH S-2200 5-COOH S-2200	No residues beyond 15 cm soil depth. Mandestrobin is non-persistent in soil	2377968
Ontario, Canada Bare ground	S-2200 4SC	Sandy loam: DT_{50}= 83.9 d; DT_{90}: 486 d (DFOP) Slow $t_{1/2}$ = 173 d	Minor: DX-CA-S-2200; 2-COOH S-2200 5-COOH S-2200	No residues beyond 15 cm soil depth soil Mandestrobin is moderately persistent in soil	2495782
Field dissipation Established Turfgrass in Ontario, Canada	S-2200 4SC	Turf/Thatch: DT_{50}: 8.43 d; DT_{90}: 28 d (SFO) Sandy loam soil: DT_{50}:43.3 d; DT_{90}: 380 d (IORE) $t_{R\ IORE}$ = 114 d	Minor: DeXy- S-2200; Minor: 2-COOH S-2200 5-COOH S-2200	No residues beyond 30 cm soil depth. Mandestrobin is non-persistent to slightly persistent	2377963
Bioconcentration/bioaccumulation					
Bioconcentration and Metabolism with Bluegill Sunfish (*Lepomis macrochirus*)	[Benzyl-^{14}C]S-2200	Whole body steady state Bioconcentration factor = 25-26 Kinetics for S-2200 was not calculated	Transformation products formed by hydroxylation then conjugated with sulfate and glucuronic acid	depuration half-life for the total radioactive residues ~2 days	2378049

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

Table 11 Major Transformation Products Formed in the Environment

Code	Chemical name	Chemical structure	Study	max %AR (day)	%AR at Study End (study length)	References
PARENT						
S-2200	(*RS*)-2-methoxy-*N*-methyl-2-[α-(2,5- xylyloxy)-*o*-tolyl]acetamide					
MAJOR (>10%) TRANSFORMATION PRODUCTS						
DX-CA-S-2200	(*RS*)-2-(*N*-methylcarbamoyl-methoxymethyl) benzoic acid		Aerobic soil	**11.8** (131)	8.4 (362)	2377890
			Anaerobic soil	6.2 (266)	6 (363)	2377897
			Soil photolysis	6.7 (17)	6.3 (30)	2377864
			Aqueous photolysis	-	-	-
			Hydrolysis	-	-	-
			Aerobic aquatic	-	-	-
			Anaerobic aquatic	0.37 (120)	0.16 (357)	2377907
			Field studies	3.3 (59)	0 (420)	2377953
5-COOH-S-2200	(*RS*)-3-{2-[1-methoxy-1-(*N*-methylcarbamoyl) methyl]benzyloxy}-4-methylbenzoic acid		Aerobic soil	**18** (59)	12.6 (120)	2377881
			Anaerobic soil	8.4 (63)	7.9 (363)	2377897
			Soil photolysis	-	-	-
			Aqueous photolysis	-	-	-
			Hydrolysis	-	-	-
			Aerobic aquatic	**11.9** (62)	2 (101)	2377903
			Anaerobic aquatic	1.34 (240)	0 (365)	2377907
			Field studies	6.8 (28)	0 (656)	2377963
MCBX	(*RS*)-2-hydroxy-*N*-methyl-2-[α-(2,5- xylyloxy)-*o*-tolyl]acetamide		Aerobic soil	2.8 (15)	0.7 (364)	2377894
			Anaerobic soil	7.5 (314)	7.5 (314)	2377890
			Soil photolysis	0.9 (17)	0.6 (30)	2377864
			Aqueous photolysis	-	-	-
			Hydrolysis	-	-	-
			Aerobic aquatic	**18.1** (102)	18.1 (102)	2377905
			Anaerobic aquatic	32.04 (357)	32.04 (357)	2377907
			Field studies	-	-	-
S-2200-OR	(*RS*)-2-[2-(2-hydroxy-3,6-dimethylbenzyl) phenyl]-2-methoxy-*N*-methylacetamide		Aerobic soil	-	-	-
			Anaerobic soil	-	-	-
			Soil photolysis	1.8 (30)	1.8 (30)	2377864
			Aqueous photolysis	**24.5** (7)	8.5 (30)	2377871
			Hydrolysis	-	-	-
			Aerobic aquatic	-	-	-
			Anaerobic aquatic	-	-	-
			Field studies	-	-	-
S-2200-	(*RS*)-*N*,1,4-		Aerobic soil	-	-	-

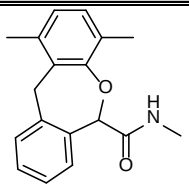
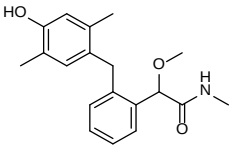
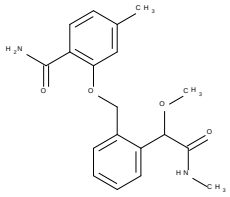
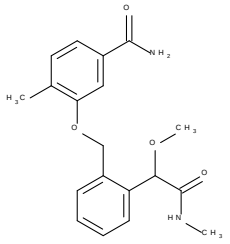
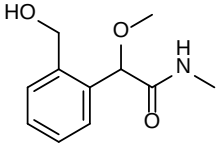
Code	Chemical name	Chemical structure	Study	max %AR (day)	%AR at Study End (study length)	References
ORC	trimethyl-6,11-dihydrodibenzo [b,e]oxepine-6-carboxamide		Anaerobic soil	-	-	-
			Soil photolysis	-	-	-
			Aqueous photolysis	**19.8** (14)	12.8 (30)	2377871
			Hydrolysis	-	-	-
			Aerobic aquatic	-	-	-
			Anaerobic aquatic	-	-	-
			Field studies			
S-2200-PR	(*RS*)-2-[2-(4-hydroxy-2,5-dimethylbenzyl) phenyl]-2-methoxy-*N*-methylacetamide		Aerobic soil	-	-	-
			Anaerobic soil	-	-	-
			Soil photolysis	-	-	-
			Aqueous photolysis	**10.2** (4)	1.7 (30)	2377871
			Hydrolysis	-	-	-
			Aerobic aquatic	-	-	-
			Anaerobic aquatic	-	-	-
			Field studies	-	-	-
2-CONH2-S-2200	2-({2-[1-methoxy-2-(methylamino)-2-oxoethyl]benzyl }oxy)-4-methylbenzamide		Aerobic soil	**14.1** (362)	14.1 (362)	2377890
			Anaerobic soil	-	-	-
			Soil photolysis	-	-	-
			Aqueous photolysis	-	-	-
			Hydrolysis	-	-	-
			Aerobic aquatic	-	-	-
			Anaerobic aquatic	-	-	-
			Field studies			
5-$CONH_2$-S-2200	3-({2-[1-methoxy-2-(methylamino)-2-oxoethyl]benzyl }oxy)-4-methylbenzamide		Aerobic soil	**13.7** (362)	13.7 (362)	2377890
			Anaerobic soil	-	-	-
			Soil photolysis	-	-	-
			Aqueous photolysis	-	-	-
			Hydrolysis	-	-	-
			Aerobic aquatic	-	-	-
			Anaerobic aquatic	-	-	-
			Field studies	-	-	-
De-Xy-S-2200	(*RS*)-2-(2-hydroxymethylphenyl)-2-methoxy- *N*-methylacetamide		Aerobic soil	3 (0)	0 (362)	2377890
			Anaerobic soil	3.6 (48)	0 (363)	2377897
			Soil photolysis	3.3 (30)	3.3 (30)	237864
			Aqueous photolysis	**9.6** (30)	9.6 (30)	2377869
			Hydrolysis	-	-	-
			Aerobic aquatic	-	-	-
			Anaerobic aquatic	3.73 (7)	0.58 (357)	2377907
			Field studies	-	-	-

Table 12 Toxicity of Mandestrobin and Transformation Products to Non-Target Terrestrial Species

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[1]	Reference
Invertebrates					
Earthworm, *Eisenia fetida*	14-d Acute	S-2200 TG	LC_{50}= 168 mg a.i./kg soil dw	n/a	2378014
		2-COOH-S-2200	14-d LC_{50}>1000 mg /kg soil dw (highest concentration tested)	n/a	2378015
		5-COOH-S-2200	LC_{50}>1000 mg /kg soil dw (highest concentration tested)	n/a	2378016
	56-d Chronic	S-2200 TG	NOEC = 7.5 mg a.i./kg soil dw	n/a	2378021
Honeybee , *Apis mellifera*	Acute oral	S-2200 TG	LD_{50} >110.71 µg a.i./bee (highest dose tested)	Practically non-toxic	2378017
	Acute contact	S-2200 TG	LD_{50} >100 µg a.i./bee (highest dose tested)	Practically non-toxic	2378017
Honeybee, *Apis mellifera* Larva	Acute	S-2200 TG	LD_{50} >100 µg a.i./larva (highest dose tested)	n/a	2378018
Predatory mite, *Typhlodromus pyri Scheuten*	7-d Contact, Glass plates	S-2200 25SC	LR_{50} > 1000 g a.i./ha ER_{50} (reproduction) > 1000 g a.i./ha (highest rate tested)	n/a	2378019
Parasitoid, *Aphidius rhopalosiphi*	48h-Contact, Glass plates	S-2200 25SC	48-h LR_{50} > 1000 g a.i./ha (highest rate tested) 48 h-ER_{50} (reproduction) = 757.2 g a.i./ha	n/a	2378020
Birds					
Bobwhite quail, *Colinus virginianus*	Acute Oral	S-2200 TG	14-d LD_{50} >2250 mg a.i./kg bw (highest concentration tested)	Practically non-toxic	2378050
Canary, *Serinus canaria*		S-2200 TG	14-d LD_{50} >1000 mg a.i./kg bw	non-toxic at the highest dose with no regurgitation	2378051
Bobwhite quail, *Colinus virginianus*	5-d Dietary	S-2200 TG	8-d LC_{50} >5620 mg a.i./kg diet (>1136 mg a.i./kg bw/day) (highest concentration tested)	Practically non-toxic	2378052
Mallard duck, *Anas platyrhynchos*		S-2200 TG	8-d LC_{50} >5620 a.i./kg diet (>2460 mg a.i./kg bw/day) (highest concentration tested)	Practically non-toxic	2378053
Bobwhite quail *Colinus virginianus*	21-w Reproduction	S-2200 TG	21-w NOEC = 1000 mg a.i./kg diet (91.1 mg a.i./kg bw/day)	n/a	2378055

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[1]	Reference
Mallard duck, *Anas platyrhynchos*	20-w Reproduction	S-2200 TG	20-w NOEC = 1000 mg a.i./kg diet (129.1 mg a.i./kg bw/day)	n/a	2378057
Mammals					
Rat	Acute	S-2200 TG	LD_{50} >2000 mg a.i./kg bw (highest concentration tested)	Practically non-toxic	2377929
	2-generation reproduction	S-2200 TG	NOAEL (offspring) = 3000 ppm (166/195 mg/kg bw/d ♂/♀)	n/a	2377964 2525908
Vascular plants					
Four monocots: onion, ryegrass, wheat and corn.	Seedling Emergence	S-2200 4 SC	EC_{25} >560 g a.i./ha NOEC = 560 g a.i./ha (highest rate tested)	n/a	2378070
Six dicots: sugarbeet, oilseed rape, cabbage, soybean, lettuce and tomato.	Vegetative Vigor	S-2200 4 SC	EC_{25} >560 g a.i./ha NOEC = 560 g a.i./ha (highest rate tested)	n/a	2378071

[1] Atkins *et al*. (1981) for bees and USEPA classification for others, where applicable; n/a, not applicable

Table 13 Screening Level and Refined Risk Assessment of Mandestrobin for Non-Target Species, Other than Birds and Mammals

Organism	Exposure	Endpoint Value	EEC	RQ	Level of Concern
Invertebrates					
Earthworm	Acute	LC_{50}/2: 84 mg a.i./kg soil	0.844 mg a.i./kg soil	0.01	Not exceeded
Bee	Contact	LD_{50}: > 100 µg a.e./bee	0. 472 kg a.i/ha × 2.4 µg a.i./bee per kg/ha = 1.13 µg a.i./bee	< 0.01	Not exceeded
	Oral	LD_{50}: > 110.71 µg a.i./bee	0. 472 kg a.i./ha × 29 µg a.i./bee per kg/ha = 13.7 µg a.i./bee	< 0.1	Not exceeded
	Larva acute	LD_{50}: > 100 µg a.i./larva	0. 472 kg a.i./ha × 29 µg a.i./bee per kg/ha = 13.7 µg a.i./larva	<0.1	Not exceeded
Predatory arthropod, *Typhlodromus pyri*	Contact, glass plate	LR_{50}: > 1000 g a.i./ha	In-field: 472 g a.i./ha Cumulative rate of 744.4 g a.i./ha	In-field: < 0.7	Not exceeded
Parasitoid arthropod, *Aphidius rhopalosiphi*	Contact, glass plate	LR_{50}: > 1000 g a.i./ha			

Organism	Exposure	Endpoint Value	EEC	RQ	Level of Concern
Vascular plants					
Vascular plant	Seedling emergence; Vegetative vigour	ER_{25}: >560 g a.i./ha	In-field: 472 g a.i./ha Cumulative rate of 744.4 g a.i./ha	In-field: <1.3	Exceeded[1]
			Off-field (aerial appl., 17% drift): 80.24 g a.i./ha; cumulative rate of 126.55 g a.i./ha	Off-field (aerial): <0.2	Not exceeded

[1]The cumulative rate (744.4 g a.i/ha) based on foliar dissipation was used and ER_{25} was >560 g a.i./ha as the maximum seasonal rate was not tested in studies.

Table 14 Screening Level Risk Assessment of Foliar Application of Mandestrobin for Birds and Mammals

	Toxicity (mg a.i./kg bw/d)	Feeding Guild (food item)	EDE* (mg a.i./kg bw)	RQ	Level of Concern
Small Bird (0.02 kg)					
Acute	>100.00	Insectivore	60.59	<0.6	Not exceeded
Reproduction	91.10	Insectivore	60.59	0.7	Not exceeded
Medium Sized Bird (0.1 kg)					
Acute	>100.00	Insectivore	47.28	<0.5	Not exceeded
Reproduction	91.10	Insectivore	47.28	0.5	Not exceeded
Large Sized Bird (1 kg)					
Acute	>100.00	Herbivore (short grass)	30.54	<0.3	Not exceeded
Reproduction	91.10	Herbivore (short grass)	30.54	0.3	Not exceeded
Small Mammal (0.015 kg)					
Acute	>200.00	Insectivore	34.85	<0.2	Not exceeded
Reproduction	166	Insectivore	34.85	0.2	Not exceeded
Medium Sized Mammal (0.035 kg)					
Acute	>200.00	Herbivore (short grass)	67.59	<0.3	Not exceeded
Reproduction	166	Herbivore (short grass)	67.59	0.4	Not exceeded
Large Sized Mammal (1 kg)					
Acute	>200.00	Herbivore (short grass)	36.12	<0.2	Not exceeded
Reproduction	166	Herbivore (short grass)	36.12	0.2	Not exceeded

*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 (bw in g)$^{0.850}$
All birds Equation (body weight >200 g): FIR (g dry weight/day) = 0.648 (bw in g) 0.651
For mammals, the "all mammals" equation was used: FIR (g dry weight/day) = 0.235 (bw in g)$^{0.822}$
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 15 Screening Level Assessment of Seed Treatment with Mandestrobin for Birds and Mammals

	Study Endpoint (mg a.i./kg bw/day/UF)	EDE* (mg a.i./kg bw/day)	RQ	Level of concern
Small bird (0.02 kg				
Acute	100.00	25.394	0.3	Not exceeded
Reproduction	91.10	25.394	0.3	Not exceeded
Medium bird (0.10 kg)				
Acute	100.00	19.947	0.2	Not exceeded
Reproduction	91.10	19.947	0.2	Not exceeded
Large bird (1.00 kg)				
Acute	100.00	5.815	0.1	Not exceeded
Reproduction	91.10	5.815	0.1	Not exceeded
Small mammals (0.015 kg)				
Acute	200.00	14.512	0.1	Not exceeded
Reproduction	166	14.512	0.3	Not exceeded
Medium mammals (0.035 kg)				
Acute	200.00	12.480	0.1	Not exceeded
Reproduction	166	12.480	0.2	Not exceeded
Large mammals (1.00 kg)				
Acute	200.00	6.872	0.03	Not exceeded
Reproduction	166	6.872	0.1	Not exceeded

*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 200g, the "all birds" equation was used:
Passerine Equation (body weight <or = 200 g): FIR (g dry weight/day) = 0.398 (bw in g)$^{0.850}$
All birds Equation (body weight >200 g): FIR (g dry weight/day) = 0.648 (bw in g) 0.651
For mammals, the "all mammals" equation was used: FIR (g dry weight/day) = 0.235 (bw in g)$^{0.822}$
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 16 Toxicity of Mandestrobin, S-2200-*R*-Isomer, S-2200-*S*-Isomer and Transformation Products to Non-Target Aquatic Species

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[1]	Reference
Freshwater species					
Water flea, *Daphnia magna*	48-h Acute	S-2200 TG	EC_{50} = 1.2 mg a.i./L	Moderately toxic	2378022
		S-2200 (*R*-Isomer)	EC_{50} = 0.92 mg/L	Highly toxic	2378026
		S-2200 (*S*-Isomer)	EC_{50} > 14 mg/L	Slightly toxic at the highest concentration tested	2378027
		2-COOH-S-2200	EC_{50} > 100 mg/L	Practically non-toxic at the highest concentration tested	2378023
		5-COOH-S-2200	EC_{50} > 100 mg/L	Practically non-toxic at the highest	2378024

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[1]	Reference
				concentration tested	
		S-2200 -OR	EC_{50} > 14 mg	Slightly toxic at the highest concentration tested	2378028
		S-2200 -ORC	EC_{50} > 2.5 mg/L	Moderately toxic up to the limit of solubility of the test	2378025
	21-d Chronic	S-2200 TG	NOEC = 0.56 mg a.i./L	n/a	2378029
Sediment dwelling invertebrate, *Chironomus dilutus*	65-d Chronic	S-2200 TG	NOEC = 3.0 mg a.i./kg dw sediment, 4.93 mg a.i./L porewater	n/a	2378036
Sediment dwelling invertebrate, *Chironomus riparius*	28-d Chronic	S-2200 TG	NOEC = 8.1 mg a.i./L	n/a	2378033
Amphipod, *Hyalella azteca*	42-d Life cycle	S-2200 TG	NOEC = 5.0 mg a.i./kg dw sediment and 6.38 mg a.i./L in pore water	n/a	2378035
Rainbow trout, *Oncorhynchus mykiss*	96-h Acute	S-2200 TG	LC_{50} = 0.93 mg a.i./L	Highly toxic	2378037
		S-2200 (*R*-Isomer)	LC_{50} = 0.84 mg/L	Highly toxic	2378038
		S-2200 (*S*-Isomer)	LC_{50} >12 mg/L (highest concentration tested)	Slightly toxic	2378039
		2-COOH-S-2200	LC_{50} >89 mg/L (highest concentration tested)	Slightly toxic	2378040
		5-COOH-S-2200	LC_{50} >100 mg/L (highest concentration tested)	Practically non toxic	2378041
		S-2200 -OR	LC_{50} >9.0 mg/L (highest concentration tested)	Moderately toxic	2378042
		S-2200 -ORC	LC_{50} >1.4 mg/L (highest concentration with on precipitate)	Moderately toxic	2378043
Bluegill sunfish, *Lepomis macrochirus*)	96-h Acute	S-2200 TG	LC_{50} = 2.4 mg a.i./L	Moderately toxic	2378044
Fathead minnow, *Pimephales promelas*	96-h Acute	S-2200 TG	LC_{50} = 1.0 mg a.i./L	Highly toxic	2378045
Fathead minnow, (*Pimephales promelas*)	28-d Chronic	S-2200 TG	NOEC = 0.15 mg a.i./L (28 days post-hatch)	n/a	2378047
Green algae, *Pseudokirchneriella subcapitata*	96-h Acute	S-2200 TG	EC_{50} = 0.39 mg a.i./L (inhibition)	n/a	2378060
	72-h Acute	S-2200 (*R*-Isomer)	E_bC_{50} = 0.38 mg/L	n/a	2378067

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[1]	Reference
		S-2200 (*S*-Isomer)	E_bC_{50} >12 mg/L (highest concentration tested)	n/a	2378068
		2-COOH-S-2200	E_bC_{50} =58 mg/L	n/a	2378061
		5-COOH-S-2200	E_bC_{50} >54 mg/L (highest concentration tested)	n/a	2378062
		S-2200 -OR	E_bC_{50} >9.9 mg/L (highest concentration tested)	n/a	2378063
		S-2200 -ORC	E_bC_{50} >5.0 mg/L (highest concentration tested)	n/a	2378059
Blue-green algae, *Anabaena flos-aquae*	96-h Acute	S-2200 TG	EC_{50} = 0.065 mg a.i./L (yield) NOEC = 0.023 mg a.i./L (algistatic)	n/a	2378065
Diatom, *Navicula pelliculosa*	96-h Acute	S-2200 TG	EC_{50} = 1.7 mg a.i./L NOEC = 1.1 mg a.i./L	n/a	2378066
Monocot vascular plant, duckweed, *Lemna gibba*	7-d Dissolved	S-2200 TG	EC_{50} > 2.3 mg a.i./L NOEC = 0.32 mg a.i./L (Frond number)	n/a	2378072
Marine/estuarine species					
Crustacean, mysid shrimp, *Americamysis bahia*	96-h Acute	S-2200 TG	LC_{50} = 0.43 mg a.i./L	Highly toxic	2378031
	36-d Chronic	S-2200 TG	NOEC = 0.049 mg a.i./L	n/a	2378032
Sediment-dwelling amphipod, *Leptocheirus plumulosus*	28-d Chronic	S-2200 TG	NOEC = 10.3 mg a.i./kg dw sediment, 1.56 mg a.i./L porewater	n/a	2378034
Mollusk, Eastern oyster, *Crassostrea virginica*	96-h Acute	S-2200 TG	EC_{50} = 2.0 mg a.i./L	Moderately toxic	2378030
Sheepshead minnow, *Cyprinodon variegatus*	96-h Acute	S-2200 TG	LC_{50} >2.2 mg a.i./L	Moderately toxic	2378046
	28-d Chronic	S-2200 TG	NOEC = 0.64 mg a.i./L (28 days post-hatch)	n/a	2378048
Marine diatom, *Skeletonema costatum*	96-h Acute	S-2200 TG	EC_{50} = 0.5 mg a.i./L NOEC = 0.18 mg a.i./L (yield)	n/a	2378069

[1] USEPA classification, where applicable; n/a, not applicable

Table 17 Screening Level Risk Assessment of Mandestrobin to Aquatic Organisms

Organism		Exposure	Endpoint Value (mg a.i./L)	EEC (mg a.i./L)	RQ	Level of Concern
Freshwater species						
Invertebrates (*Daphnia magna*)		Acute	EC_{50}/2: 0. 6	0.24	0.4	Not exceeded
		Chronic	NOEC: 0.56	0.24	0.4	Not exceeded
Sediment Invertebrate *(Chironomus riparius/ dilutes)*		Chronic	NOEC: 4.93 (porewater)	0.057*	0.01	Not exceeded
Fish	*Oncorhynchus mykiss*	Acute	LC_{50}/10: 0.093	0.24	3.0	Exceeded
	Pimephales promelas	Chronic	NOEC: 0.15	0.24	1.9	Exceeded
Amphibians (fish end-points)		Acute,	LC_{50}/10: 0.093	1.26	13.5	Exceeded
		Chronic	NOEC: 0.15	1.26	8.4	Exceeded
Algae (*Anabaena flosaquae*)		Acute	EC_{50}/2: 0.0325	0.24	7.4	Exceeded
Vascular plants (monocot, *Lemna gibba*)		Dissolved	EC_{50}/2: 1.15	0.24	0.2	Not exceeded
Marine species						
Crustacean (*Americamysis bahia*)		Acute	LC_{50}/2: 0.215	0.24	1.1	Exceeded
		Chronic	NOEC: 0.049	0.24	4.9	Exceeded
Mollusk (*Crassostrea virginica*)		Acute	EC_{50}/2: 1	0.24	0.2	Not exceeded
Fish (*Cyprinodon variegatus)*		Acute	LC_{50}/10: > 0.22	0.24	<1.1	Exceeded
		Early-life stage	NOEC: 0.64	0.24	0.4	Not exceeded
Algae (*Skeletonema costatum*)		Acute	EC_{50}/2: 0.25	0.24	0.96	Not exceeded
Sediment Invertebrate (*Leptocheirus plumulosus*)		Chronic	NOEC: 1.56 (porewater)	0.057*	0.04	Not Exceeded
* peak EEC in sediment pore water from aquatic ecoscenario modelling						

Table 18 Screening Level Risk Assessment of Mandestrobin Isomers and Transformation Products for Terrestrial and Aquatic Organisms

Organism (exposure)	Compounds	Endpoint Value (mg/L)	EEC (mg/L)	RQ	Level of Concern
Earthworms *Eisenia foetida* (acute)	2-COOH-S-2200	LC_{50}/2:>500*	0.92*	< 0.1	Not exceeded
	5-COOH-S-2200	LC_{50}/2:>500*	0.92*	< 0.1	Not exceeded
Invertebrates *Daphnia magna* (acute)	S-2200 *R*-isomer	LC_{50}/2: 0.46	0.24	0.5	Not exceeded
	S-2200 *S*-isomer	LC_{50}/2:> 7	0.24	<0.1	Not exceeded
	2-COOH-S-2200	LC_{50}/2: >50	0.26	<0.1	Not exceeded
	5-COOH-S-2200	LC_{50}/2: >50	0.26	<0.1	Not exceeded
	S-2200-OR	LC_{50}/2: >7	0.24	<0.1	Not exceeded
	S-2200-ORC	LC_{50}/2: >1.25	0.20	<0.2	Not exceeded
Fish *Oncorhynchus mykiss* (acute)	S-2200 *R*-isomer	LC_{50}/10: 0.084	0.24	2.9	Exceeded
	S-2200 *S*-isomer	LC_{50}/10: > 1.2	0.24	<0.2	Not exceeded
	2-COOH-S-2200	LC_{50}/10: > 8.9	0.26	<0.1	Not exceeded
	5-COOH-S-2200	LC_{50}/10: > 10	0.26	<0.1	Not exceeded
	S-2200-OR	LC_{50}/10: > 0.9	0.24	<0.1	Not exceeded
	S-2200-ORC	LC_{50}/10: > 0.14	0.20	<1.4	Exceeded

Organism (exposure)	Compounds	Endpoint Value (mg/L)	EEC (mg/L)	RQ	Level of Concern
Algae *Pseudokirchneriella subcapitata* (acute)	S-2200 *R*-isomer	EC_{50}/2: 0.19	0.24	1.3	Exceeded
	S-2200 *S*-isomer	EC_{50}/2: >6	0.24	<0.1	Not exceeded
	2-COOH-S-2200	EC_{50}/2: 29	0.26	0.1	Not exceeded
	5-COOH-S-2200	EC_{50}/2: >27	0.26	<0.1	Not exceeded
	S-2200-OR	EC_{50}/2: >4.95	0.24	<0.1	Not exceeded
	S-2200-ORC	EC_{50}/2: >2.5	0.20	<0.1	Not exceeded
*mg/kg dw soil					

Table 19 Refined Risk Assessment of Potential Risk from Drift of Mandestrobin, S-2200 R-isomer and the Transformation Product S-2200-ORC to Aquatic Organisms

Organism	Exposure	Endpoint value	Refined EEC	RQ	Level of Concern
Mandestrobin					
Fish *Oncorhynchus mykiss*	Acute	LC_{50}/10: 0.093 mg a.i./L	Aerial appl. (17% drift): 0.0401 mg a.i./L	0.4	Not exceeded
Fish *Pimephales promelas*	Chronic	NOEC: 0.15 mg a.i./L	Aerial appl. (17% drift): 0.0401 mg a.i./L	0.3	Not exceeded
Amphibians (fish end-points)	Acute,	LC_{50}/10: 0.093 mg a.i./L	Aerial appl. (17% drift): 0.214 mg a.i./L	2.3	Exceeded
			Ground appl. (3% drift): 0.038 mg a.i./L	0.4	Not exceeded
	Chronic	NOEC: 0.15 mg a.i./L	Aerial appl. (17% drift): 0.214 mg a.i./L	1.4	Exceeded
			Ground appl. (3% drift): 0.038 mg a.i./L	0.3	Not exceeded
Algae *Anabaena flos-aquae*	Acute	EC_{50}/2: 0.0325 mg a.i./L	Aerial appl. (17% drift): 0.0401 mg a.i./L	1.2	Exceeded
			Ground appl. (3% drift): 0.007 mg a.i./L	0.2	Not exceeded
Crustacean Mysid shrimp *Americamysis bahia*	Acute	LC_{50}/2: 0.215 mg a.i./L	Aerial appl. (17% drift): 0.0401 mg a.i./L	0.2	Not exceeded
	Chronic	NOEC: 0.049 mg a.i./L	Aerial appl. (17% drift): 0.0401 mg a.i./L	0.8	Not exceeded
Fish *Pimephales promelas*	Acute	LC_{50}/10: > 0.133 mg a.i./L	Aerial appl. (17% drift): 0.0401 mg a.i./L	<0.3	Not exceeded
S-2200 *R*-isomer					
Fish *Oncorhynchus mykiss*	acute	LC_{50}/10: 0.084 mg/L	Aerial appl. (17% drift): 0.0401 mg/L	0.5	Not exceeded
Algae *Pseudokirchneriella subcapitata*	Acute	EC_{50}/2: 0.19 mg/L	Aerial appl. (17% drift): 0.0401 mg/L	0.2	Not exceeded
S-2200-ORC					
Fish *Oncorhynchus mykiss*	Acute	LC_{50}/10: > 0.14 mg/L	Aerial appl. (17% drift): 0.034 mg/L	<0.2	Not exceeded

Table 20 Risk Quotients for Aquatic Organisms Determined for Runoff of Mandestrobin, S-2200-*R*-Isomer and S-2200-ORC in Water Bodies

Organism	Exposure	Endpoint value (mg/L)	Refined EEC (mg/L)	RQ	Level of Concern
Mandestrobin					
Oncorhynchus mykiss	Acute	LC_{50}/10: 0.093	0.0821	0.9	Not exceeded
Pimephales promelas	Chronic	NOEC: 0.15	0.0821	0.5	Not exceeded
Amphibians	Acute	LC_{50}/10: 0.093	0.223	2.4	Exceeded
	Chronic	NOEC: 0.15	0.223	1.5	Exceeded
Anabaena flosaquae	Acute	EC_{50}/2: 0.0325	0.0821	2.5	Exceeded
Americamysis bahia	Acute	LC_{50}/2: 0.215	0.0821	0.4	Not exceeded
	Chronic	NOEC: 0.049	0.0821	1.7	Exceeded
Cyprinodon variegatus	Acute	LC_{50}/10: > 0.22	0.0821	<0.4	Not exceeded
***S-2200 R*-isomer**					
Oncorhynchus mykiss	Acute	LC_{50}/10: 0.084	0.0821	0.98	Not exceeded
Pseudokirchneriella subcapitata	Acute	EC_{50}/2: 0.19	0.0821	0.4	Not exceeded
S-2200-ORC					
Oncorhynchus mykiss	Acute	LC_{50}/10: > 0.14	0.0821	<0.6	Not exceeded

Table 21 Toxic Substances Management Policy Considerations-Comparison to TSMP Track 1 Criteria

TSMP Track 1 Criteria	TSMP Track 1 Criterion value		Mandestrobin Endpoints
Toxic or toxic equivalent as defined by the *Canadian Environmental Protection Act*[1]	Yes		Yes
Predominantly anthropogenic[2]	Yes		Yes
Persistence[3]:	Soil	Half-life ≥ 182 days	Laboratory studies: DT_{50} of 37.5 to 22,305 days in aerobic soil and 5 to 35 years in anaerobic soil Field studies: DT_{50} of 114 - 173 days
	Water	Half-life ≥ 182 days	DT_{50} of 161 to 781 days in aquatic aerobic system and 458 days to 24 years in anaerobic aquatic systems.
	Sediment	Half-life ≥ 365 days	Total system DT_{50} values range from 161 to 8822 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 (3.36×10^{-8} Pa at 20°C) and Henry's law constant (6.5×10^{-12} atm m^3/mol at 20°C).

Bioaccumulation[4]	Log $K_{OW} \geq 5$	3.51 at 25°C; Criteria not met
	bioconcentration factor ≥ 5000	25-26
	bioaccumulation factor ≥ 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 criteria may be refined if required (in other words, all other TSMP criteria are met).
[2]The policy considers a substance "predominantly anthropogenic" if, based on expert judgement, its concentration in the environment medium is largely due to human activity, rather than to natural sources or releases.
[3] If the pesticide and/or the transformation product(s) meet one persistence criterion identified for one media (soil, water, sediment or air) than the criterion for persistence is considered to be met.
[4]Field data (for example, bioaccumulation factors) are preferred over laboratory data (for example, bioconcentration factors) which, in turn, are preferred over chemical properties (for example, log K_{OW}).

Table 22 Fungicide Resistance Action Committee modes of action groups of currently registered alternative products (as of June 2015)

Crop	Disease	Fungicide Resistance Action Committee Mode of Action groups of registered alternatives
Foliar applied products		
Canola and crop subgroup 20A	White mold/sclerotinia rot	2; 3; 7; 7+11; 9+12; 11; 44; NC* (*Coniothyrium minitans* strain CON/M/91-08)
Grape and crop subgroup 13-07F	Botrytis bunch rot / gray mold	2; 7; 7+11; 7+9; 9; 9+12; 17; 44; P5: NC* (*Aureobasidium pullulans* DSM 14940 and DSM 14941; BLAD polypeptide)
	Powdery mildew	3; 7; 7+9; 7+11; 11; 13; 29+M2; 44; 46; M2; M4; P5; U8; NC* (mineral oil; potassium bicarbonate; *Streptomyces lydicus* strain WYEC 108; Garlic powder; BLAD polypeptide)
Strawberry and crop subgroup 13-07G	Botrytis gray mold	1; 2; 7; 7+11; 9; 9+12; 17; 44 M2; M3; M5; P5; NC* (*Trichoderma harzianum* Rifai strain KRL-AG2; BLAD polypeptide; *Streptomyces lydicus* strain WYEC 108)
Turfgrass	Dollar Spot	1; 2; 3; 3+11; 3+ M5; 7; 11; 44; M5; NC* (mineral oil; *Trichoderma harzianum* Rifai strain KRL-AG2; *T. harzianum* Rifai strain T-22)
	Brown Patch	1; 23; 3+11; 3+M; 7; 11; 12; 14; 44; M5 ; NC* (mineral oil; hydrogen peroxide)
	Fairy Ring	3+11; 7+11; 11
	Rust	11
	Take-all Patch	3; 11
Seed treatment products		
Corn	*Rhizoctonia solani* seed rot	3; 3+4+7; 7; 7+11; 11
	Fusarium seed rot	3; 3+4; 3+4+7; 4+11; 7; 7+11; 11
Legume vegetables and crop group 6	Rhizoctonia solani seed rot	1+4+12; 3+4+7; 4+11; 4+11+12; 4+12; 7; 7+11; 7+M3;11; 44
	Fusarium seed rot	1+4+12; 3; 3+4; 3+4+7; 4+11; 4+11+12; 4+12; 7; 7+11; 7+M3; 11; 44
	Phomopsis seed rot	3; 3+4+7; 3+7; 4+12; 4+11; 4+11+12; 7+11; 7+M3; 11
Canola and crop subgroup 20A	*Rhizoctonia solani* seed rot	3; 3+4+12; 3+4+7+12; 3+7; 4+7+11; 7; 7+11; 7+M3; 11
	Fusarium seed rot	3; 3+4; 3+7; 3+4+12; 3+4+7+12; 4+7+11; 7; 7+11; 11;44

*NC: not classified

Table 23 List of Supported Uses

S-2200 4 SC Fungicide; S-2200 4 SC AG Fungicide; S-2200 4 VPP Fungicide (foliar-applied products)

Supported claim	Conclusion and comment from value assessment
Control of white mold/sclerotinia rot (*Sclerotinia sclerotiorum*) on canola (crop subgroup 20A) with one foliar application of 439 – 877 mL/ha applied when the crop is at 20-50% bloom.	Supported as proposed
Control of botrytis bunch rot / gray mold (*Botrytis cinerea*) on grape (crop subgroup 13-07F) with three to four foliar applications of 439 - 877 mL/ha (seasonal max. 2631 mL/ha) prior to infection during early bloom, bunch pre-closure and veraison up to 10 days before harvest with an interval of 10 days for sequential applications.	Supported as proposed
Suppression of powdery mildew (*Uncinula necator*) on grape (crop subgroup 13-07F) with three to four foliar applications of 439 - 877 mL/ha (seasonal max. 2631 mL/ha) prior to infection at bud break with 10 to 14 intervals.	Supported as proposed; claim limited to susceptible crops only (grape and Amur grape)
Control of botrytis gray mold (*Botrytis cinerea*) on strawberry (crop subgroup 13-07G) with four to five foliar applications of 439 – 877 mL/ha (seasonal max. 3508 mL/ha) starting at 10% bloom, or prior to infection up to 0 days before harvest with reapplication intervals of 7 to 14 day.	Supported as proposed
Control of dollar spot (*Sclerotinia homoeocarpa*) on turfgrass with applications of 540-986 mL/ha (seasonal max. 3944 mL/ha) with 14 to 28 day intervals starting when conditions favor disease development.	Supported as proposed
Control of brown Patch (*Rhizoctonia solani*) on turfgrass with applications of 986 mL/ha (seasonal max. 3944 mL/ha) with 14 day intervals starting when conditions favor disease development or when the disease first appears.	Supported as proposed
Control of fairy ring (various basidiomycetes) on turfgrass with applications of 986 mL/ha (seasonal max. 3944 mL/ha) with 14 day intervals starting when conditions favor disease development or when the disease first appears.	Supported with the claim specified to *Agaricus campestris* rather than "various basidiomycetes" as the causal pathogen
Suppression of rust diseases (*Puccinia* spp.) on turfgrass with applications of 986 mL/ha (seasonal max. 3944 mL/ha) with 14 day intervals starting when conditions favor disease development or when the disease first appears.	Supported with the claim specified to 'Rust (*Puccinia graminis*)' rather than the general claim against 'Rust diseases *Puccinia* spp.'
Control of take-all patch (*Gaeumannomyces graminis*) on turfgrass with applications of 986 mL/ha (seasonal max. 3944 mL/ha) with 14 day intervals starting when conditions favor disease development or when the disease first appears.	Supported as proposed

S-2200 3.2 FS Fungicide (seed treatment product)

Supported claim	Conclusion and comment from value assessment
Control of seed decay caused by *Rhizoctonia solani* in on corn (field corn, sweet corn, and popcorn) with one application seed of 15.6 mL/ 100 kg seed.	Supported as proposed
Control of seed decay caused by *Fusarium* spp. in on corn (field corn, sweet corn, and popcorn) with one application seed of 15.6 mL/ 100 kg seed.	Supported as proposed
Control of seed decay caused by *Rhizoctonia solani* in legume vegetables (crop group 6) with one seed application of 26 mL/ 100 kg seed.	Supported as proposed

Control of seed decay caused by *Fusarium* spp. in legume vegetables (crop group 6) with one seed application of 26 mL/ 100 kg seed.	Supported as proposed
Suppression of seed decay caused by *Phomopsis* spp. in legume vegetables (crop group 6) with one seed application of 26 mL/ 100 kg seed.	The causal pathogen for the claim is specified to *Phomopsis longicolla*.
Control of seed decay caused by *Rhizoctonia solani* in canola (crop subgroup 20A) with one seed application of 26 mL/100 kg seed.	Supported as proposed
Control of seed decay caused by *Fusarium* spp. in canola (crop subgroup 20A) with one seed application of 26 mL/100 kg seed.	Supported as proposed

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

Mandestrobin is a new active ingredient which is concurrently being registered in Canada and the United States. The MRLs proposed for mandestrobin in Canada are the same as corresponding tolerances to be promulgated in the United States.

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

Currently, there are no Codex MRLs[9] listed for mandestrobin in or on any commodity on the Codex Alimentarius Pesticide Residues in Food website.

{Table 1 compares the MRLs proposed for mandestrobin in Canada with corresponding American tolerances and Codex MRLs[10]. American tolerances are listed in the Electronic Code of Federal Regulations, 40 CFR Part 180, by pesticide. A listing of established Codex MRLs is available on the Codex Alimentarius Pesticide Residues in Food website, by pesticide or commodity}.

Table 1 Comparison of Canadian MRLs, American Tolerances and Codex MRLs

Food Commodity	Canadian MRL (ppm)	American Tolerance (ppm)	Codex MRL (ppm)
Raisins	7.0	7.0	Not established
Small fruit vine climbing (Crop Subgroup 13-07F, except fuzzy kiwifruit)	5.0	5.0	Not established
Low growing berry (Crop Subgroup 13-07G, except cranberry)	3.0	3.0	Not established
Rapeseed (Crop Subgroup 20A)	0.5	0.5	Not established
Legume vegetables (Crop Group 6, except cowpea and field pea), corn (field, popcorn, sweet)	0.02	0.02	Not established

MRLs may vary from one country to another for a number of reasons, including differences in pesticide use patterns and the locations of the field crop trials used to generate residue chemistry data. For animal commodities, differences in MRLs can be due to different livestock feed items and practices.

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

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

References

A. List of Studies/Information Submitted by Registrant

1.0 Chemistry

PMRA Document Number	Reference
2377784	2012, S-2200 Technical: Product Identity and Composition, Description of Materials Used to Produce the Product, Description of Production Process and Discussion of Formation of Impurities, DACO: 2.11.1, 2.11.2, 2.11.3, 2.11.4
2377785	2012, S-2200 Technical: Product Identity and Composition, Description of Materials Used to Produce the Product, Description of Production Process and Discussion of Formation of Impurities, DACO: 2.11.1, 2.11.2, 2.11.3, 2.11.4 CBI
2377786	2013, S-2200 Fungicide Technical: Product Identity and Composition; Certified Limits; Enforcement Analytical Method, DACO: 2.12.1, 2.13.1, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9
2377787	2013, S-2200 Fungicide Technical: Product Identity and Composition; Certified Limits; Enforcement Analytical Method, DACO: 2.12.1, 2.13.1, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9 CBI
2377788	2012, Preliminary Analysis and Enforcement Analytical Method of S-2200 Technical Grade for Confirmation of Its Racemic Composition, DACO: 2.13.1
2377789	2012, Preliminary Analysis and Enforcement Analytical Method of S-2200 Technical Grade for Confirmation of Its Racemic Composition, DACO: 2.13.1 CBI
2377790	2012, Enforcement Analytical Methods of S-2200 Technical Grade, DACO: 2.13.1
2377791	2012, Enforcement Analytical Methods of S-2200 Technical Grade, DACO: 2.13.1 CBI
2377792	2013, Analytical Method for the Determination of the Contents of S-2200 on Dry and Wet Weight Basis, DACO: 2.13.1
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2377797	2010, Product Chemistry Testing for S-2167 PAI, DACO: 2.14.1, 2.14.12, 2.14.2, 2.14.3, 2.14.4, 2.14.5, 2.14.6
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2377799	2009, Determination of the Water Solubility of S-2200 PAI, DACO: 2.14.7, 8.2.1
2377800	2009, Determination of the Water Solubility of S-2167 PAI, DACO: 2.14.7, 8.2.1
2377801	2009, Determination of the Water Solubility of S-2354 PAI, DACO: 2.14.7, 8.2.1
2377802	2011, S-2200 PAI - Determination of the Solvent Solubility, DACO: 2.14.8
2377803	2011, S-2167 PAI - Determination of the Solvent Solubility, DACO: 2.14.8
2377804	2011, S-2167 PAI - Determination of the Solvent Solubility, DACO: 2.14.8
2377805	2013, S-2200TG: Determination of the Solvent Solubility, DACO: 2.14.8
2377807	2013, S-2200 Dissociation Constant Waiver Request, DACO: 2.14.10
2377808	2011, S-2200 PAI - Determination of Vapour Pressure, DACO: 2.14.9, 8.2.1
2377810	2011, S-2167 PAI - Determination of Vapour Pressure, DACO: 2.14.9, 8.2.1
2377811	2010, Determination of the Partition Coefficient (n-Octanol/Water) -- S-2167 PAI, DACO: 2.14.11, 8.2.1
2377812	2010, Determination of the Partition Coefficient (n-Octanol/Water) -- S-2200 PAI, DACO: 2.14.11, 8.2.1
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2377814	2013, Storage Stability and Corrosion Characteristics of S-2200 Technical Grade, DACO: 2.14.14 ,2.16
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2377822	2010, Determination of the Impact Explodability of S-2200 TGAI, DACO: 2.16
2377824	2011, Determination of the Thermal Explodability of S-2200 TGAI, DACO: 2.16

2377826	2012, Analytical Determination of Active Ingredient and Impurities in S-2200 Technical Grade, DACO: 2.16
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2377832	2012, Confirmation of Identification of Ingredients in S-2200 Technical Grade, DACO: 2.16 CBI
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2377871	2010, [14C]S-2167 (S-2200 R-isomer): Photodegradation and Quantum Yield in Sterile, Aqueous Solution, DACO: 8.2.3.3.2
2377875	2013, S-2200 - Stability in Air, DACO: 8.6
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2378123	2013, S-2200 3.2 FS Fungicide: Product Identity, Composition, and Analysis, DACO: 3.2.1, 3.2.2, 3.2.3, 3.3.1, 3.4.1, 3.4.2
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2378125	2013, Physical and Chemical Properties of S-2200 3.2 FS Fungicide, VC-1929, 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, 3.5.6, 3.5.7, 3.5.8, 3.5.9

2.0 Human and Animal Health

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2377931	2011, Acute Oral Toxicity Study of De-Xy-S-2200 in Rats, DACO: 4.2.1
2377932	2012, Acute Oral Toxicity Study of 2-COOH-S-2200 in Rats, DACO: 4.2.1
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2377935	2012, Acute Oral Toxicity Study of 2-CH2OH-S-2200 in Rats, DACO: 4.2.1
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2377940	2010, Primary Skin Irritation Test of S-2200 TG in Rabbits, DACO: 4.2.5
2377941	2010, Skin Sensitization Test of S-2200 TG in Guinea Pigs (Maximization Test), DACO: 4.2.6
2377943	2009, S-2200: 14 Day Dietary Administration Range-Finding Study in the Mouse, DACO: 4.3.1
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2377956	2009, S-2200: 4 Week Dietary Study in the Dog, DACO: 4.3.3
2377957	2011, A 28-Day Repeated Dose Dermal Toxicity Study of S-2200 Technical Grade in Rats, DACO: 4.3.5
2377959	2013, Waiver Request: S-2200 Fungicide Technical Subchronic (28-Day) Rat Inhalation Study, DACO: 4.3.6

2377960	2012, S-2200 Technical Grade: 78 Week Oral (Dietary) Administration Carcinogenicity Study in the Mouse, DACO: 4.4.3
2377961	2012, S-2200 Technical Grade: 104 Week Oral (Dietary) Administration Combined Toxicity/Carcinogenicity Study in the Rat, DACO: 4.4.4
2377962	2010, Dose Range-Finding Study for Two-Generation Reproduction Study of S-2200 TG in Rats, DACO: 4.5.1
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2377965	2009, S-2200 TG: Oral (Gavage) Range-Finding Study of Prenatal Development in the Rat, DACO: 4.5.2
2377967	2012, S-2200 TG: Oral (Gavage) Prenatal Development Toxicity Study in the Rat, DACO: 4.5.2
2377969	2009, S-2200 TG: Oral (Gavage) Range-Finding Study of Prenatal Development in the Rabbit, DACO: 4.5.3
2377970	2012, S-2200 TG: Oral (Gavage) Prenatal Development Toxicity Study in the Rabbit, DACO: 4.5.3
2377971	2010, Reverse Mutation Test of S-2200 TG in Bacterial Systems, DACO: 4.5.4
2377972	2011, Reverse Mutation Test of De-XY-S-2200 in Bacterial Systems, DACO: 4.5.4
2377973	2012, Reverse Mutation Test of 2-COOH-S-2200 in Bacterial Systems, DACO: 4.5.4
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2377976	2012, Reverse Mutation Test of 2-CH2OH-S-2200 in Bacterial Systems, DACO: 4.5.4
2377977	2012, Reverse Mutation Test of 4-OH-S-2200 in Bacterial Systems, DACO: 4.5.4
2377978	2010, Gene Mutation Assay in Chinese Hamster V79 Cells *In vitro* (V79 / HPRT) with S-2200 TG, DACO: 4.5.5
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2377984	2012, *In vitro* Chromosomal Aberration Test on 5-COOH-S-2200 in Chinese Hamster Lung Cells (CHL/IU), DACO: 4.5.6
2377985	2010, Micronucleus Test on S-2200 TG in CD-1 Mice, DACO: 4.5.7
2377986	2012, Micronucleus Assay of 2-COOH-S-2200 in Mice, DACO: 4.5.7
2377987	2011, Metabolism of S-2200 R-isomer (S-2167) and S-2200 S-isomer (S2354) in Rats, DACO: 4.5.9
2377989	2012, [14C]S-2200: Absorption, Distribution, Metabolism and Excretion Following Repeat Oral Administration to the Rat, DACO: 4.5.9

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2377991	2011, An Oral (Gavage) Dose Range-Finding Acute Neurotoxicity Study of S-2200 TG in Wistar Rats, DACO: 4.5.12
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2378131	2012, S-2200 3.2 FS: Local Lymph Node Assay (LLNA) in Mice, DACO: 4.6.6
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2377874	2013, Occupational and Residential Exposure and Risk Assessments for S-2200 4 SC Fungicide on Canola (Crop Subgroup 20A), Grapes (Crop Subgroup 13-07F), Strawberries (Crop Subgroup 13-07G), and Turf, DACO: 5.1
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2377878	2013, Pesticide Handlers Exposure Database Assessment in Support of Spray Applications of S-2200 4 SC Fungicide to Canola, Grapes, Strawberries, and Turfgrass, DACO: 5.3
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2378135	2013, Use Description and Exposure Scenarios for Canola, Corn, and Soybean Seed Treatment with S-2200 3.2 FS Fungicide, DACO: 5.2
2378136	2013, Mixer/Loader/Applicator Passive Dosimetry Study in Support of Commercial Seed Treatment of Canola, Corn, and Soybean with S-2200 3.2 FS Fungicide, DACO: 5.4
2378137	2013, Mixer/Loader/Applicator Passive Dosimetry Study in Support of On-Farm Seed Treatment of Soybean with S-2200 3.2 FS Fungicide, DACO: 5.4
2378138	2013, Postapplication: Seed Planter Passive Dosimetry Study in Support of Planting Canola, Corn, and Soybean Treated with S-2200 3.2 FS Fungicide, DACO: 5.6
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2378157	2013, Characterization of Radioactive Residues of [Benzyl-14C]S-2200 and [Phenoxy-14C]S-2200 in Corn and Soybean Samples from Study VP-37088, DACO 7.8
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2377913	2013, S-2200: Magnitude of the Residue on Grapes Grown in Canada, DACO 7.4.1, 7.3
2377920	2013, S-2200: Magnitude of the Residue on Grapes, DACO 7.4.1, 7.3, 7.4.5
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2378152	2013, Magnitude of the Residue of S-2200 in Soybeans Following Seed Treatment at an Exaggerated Rate, DACO 7.4.1
2377926	2013, S-2200: Magnitude of the Residue on Canola Grown in the United States, DACO 7.4.1, 7.3, 7.4.5
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3.0 Environment

PMRA Document Number	Reference
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2377864	2010, [^{14}C]S-2354 (S-2200 *S*-isomer): Photodegradation on a Soil Surface, DACO: 8.2.3.3.1
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2377894	2013, S-2200: Degradation Under Aerobic Conditions in Soil - Rate Studies, DACO: 8.2.3.4.2
2377897	2013, S-2200: Anaerobic Soil Metabolism Study, DACO: 8.2.3.4.4
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2377964	2012, Two-Generation Reproduction Toxicity Study of S-2200 TG in Rats, DACO: 4.5.1
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2378025	2012, S-2200-ORC: Acute Toxicity to Water Fleas, (*Daphnia magna*) Under Static Conditions, Following OECD Guideline # 202 and The Official Journal of the European Communities L 142/456 Method C.2, DACO: 9.3.2
2378026	2012, S-2167 (*R*-Isomer of S-2200) - Acute Toxicity to Water Fleas, (*Daphnia magna*) Under Static Conditions, Following OECD Guideline #202 and The Official Journal of the European Communities L 142/456, Method C.2, DACO: 9.3.2

2378027	2012, S-2354 (*S*-Isomer of S-2200) Acute Toxicity to Water Fleas, (*Daphnia magna*) Under Static Conditions, Following OECD Guideline #202 and The Official Journal of the European Communities L 142/456, Method C.2, DACO: 9.3.2
2378028	2012, S-2200-OR - Acute Toxicity to Water Fleas, (*Daphnia magna*) Under Static Conditions, Following OECD Guideline #202 and The Official Journal of the European Communities L 142/456, Method C.2, DACO: 9.3.2
2378029	2010, S-2200 Technical Grade - Full Life Cycle Toxicity Test with Water Fleas (*Daphnia magna*) Under Static Renewal Conditions, Following OPPTS Draft Guideline 850.1300, OECD Guideline #211, The Official Journal of the European Communities L225, Method C.20 JMAFF 12 NohSan, No. 8147 *Daphnia spp*. Reproduction Toxicity Studies (2-7-2-3) and JMAFF 13 SeiSan No. 3986, DACO: 9.3.3
2378030	2012, S-2200: A 96-Hour Shell Deposition Test with the Eastern Oyster (*Crassostrea virginica*), DACO: 9.4.2
2378031	2012, S-2200: A 96-Hour Flow-Through Acute Toxicity Test with the Saltwater Mysid (*Americamysis bahia*), DACO: 9.4.2
2378032	2012, S-2200: A Flow-Through Life-Cycle Toxicity Test with the Saltwater Mysid (*Americamysis bahia*), DACO: 9.4.5
2378033	2012, S-2200 - Toxicity Test with Sediment-Dwelling Midges (*Chironomus riparius*) Under Static Conditions, Following OECD Guideline 219, DACO: 9.4.5
2378034	2013, S-2200: A Life Cycle Toxicity Test with the Marine Amphipod (*Leptocheirus plumulosus*) Using Spiked Sediment, DACO: 9.4.5
2378035	2013, S-2200: A Life Cycle Toxicity Test with the Freshwater Amphipod (*Hyalella azteca*) Using Spiked Sediment, DACO: 9.3.4
2378036	2013, S-2200: A Life Cycle Toxicity Test with *Chironomus dilutus* Using Spiked Sediment, DACO: 9.4.5
2378037	2009, S-2200 Technical Grade - Acute Toxicity to Rainbow Trout (*Oncorhynchus mykiss*) Under Static Conditions, Following OECD Guideline #203, EC Guideline L383A, Method C.1 and OPPTS Draft Guideline 850.1075, DACO: 9.5.2.1
2378038	2009, S-2167 (R-Isomer of S-2200) - Acute Toxicity to Rainbow Trout (*Oncorhynchus mykiss*) Under Static Conditions, Following OECD Guideline #203, EC Guideline L383A, Method C.1 and OPPTS Draft Guideline 850.1075, DACO: 9.5.2.1
2378039	2009, S-2354 (S-Isomer of S-2200) - Acute Toxicity to Rainbow Trout (*Oncorhynchus mykiss*) Under Static Conditions, Following OECD Guideline #203, EC Guideline L383A, Method C.1 and OPPTS Draft Guideline 850.1075, DACO: 9.5.2.1
2378040	2012, 2-COOH-S-2200: Acute Toxicity to Rainbow Trout (*Oncorhynchus mykiss*) Under Static Conditions, Following OECD Guideline # 203 and The Official Journal of the European Communities L 142/446 Method C.1, DACO: 9.5.2.1

2378041	2012, 5-COOH-S-2200: Acute Toxicity to Rainbow Trout (*Oncorhynchus mykiss*) Under Static Conditions, Following OECD Guideline # 203 and The Official Journal of the European Communities L 142/446 Method C.1, DACO: 9.5.2.1
2378042	2012, S-2200-OR: Acute Toxicity to Rainbow Trout (*Oncorhynchus mykiss*) Under Static Conditions, Following OECD Guideline # 203 and The Official Journal of the European Communities L 142/446 Method C.1, DACO: 9.5.2.1
2378043	2012, S-2200-ORC: Acute Toxicity to Rainbow Trout (*Oncorhynchus mykiss*) Under Static Conditions, Following OECD Guideline # 203 and The Official Journal of the European Communities L 142/446 Method C.1, DACO: 9.5.2.1
2378044	2009, S-2200 Technical Grade - Acute Toxicity to Bluegill Sunfish (*Lepomis macrochirus*) Under Static Conditions, Following OECD Guideline #203, EC Guideline L383A, Method C.1 and OPPTS Draft Guideline 850.1075, DACO: 9.5.2.2
2378045	2009, S-2200 Technical Grade - Acute Toxicity to Fathead Minnow (*Pimephales promelas*) Under Static Conditions, Following OECD Guideline #203, EC Guideline L383A, Method C.1 and OPPTS Draft Guideline 850.1075, DACO: 9.5.2.2
2378046	2012, S-2200: A 96-Hour Flow-Through Acute Toxicity Test with the Sheepshead Minnow (*Cyprinodon variegatus*), DACO: 9.5.2.4
2378047	2010, S-2200 Technical Grade - Early Life-Stage Toxicity Test with Fathead Minnow, *Pimephales promelas*, Following OECD Guideline #210 and OPPTS Draft Guideline 850.1400, DACO: 9.5.3.1
2378048	2012, S-2200: An Early Life-Stage Toxicity Test with the Sheepshead Minnow (*Cyprinodon variegatus*), DACO: 9.5.3.1
2378049	2010, Flow-Through Bioconcentration and Metabolism Study of [^{14}C]S-2200 with Bluegill Sunfish (*Lepomis macrochirus*), DACO: 9.5.6
2378050	2009, S-2200 TG: An Acute Oral Toxicity Study with the Northern Bobwhite, DACO: 9.6.2.1
2378051	2011, S-2200: An Acute Oral Toxicity Study with the Canary (*Serinus canaria*), DACO: 9.6.2.3
2378052	2009, S-2200 TG: A Dietary LC_{50} Study With the Northern Bobwhite, DACO: 9.6.2.4
2378053	2009, S-2200 TG: A Dietary LC_{50} Study With the Mallard, DACO: 9.6.2.5
2378054	2010, S-2200: A Pilot Reproduction Study with the Northern Bobwhite, DACO: 9.6.3.1
2378055	2011, S-2200: A Reproduction Study with the Northern Bobwhite, DACO: 9.6.3.1
2378056	2010, S-2200: A Pilot Reproduction Study with the Mallard, DACO: 9.6.3.2
2378057	2011, S-2200: A Reproduction Study with the Mallard, DACO: 9.6.3.2
2378059	2012, S-2200-ORC: 72-Hour Toxicity Test with the Freshwater Green Alga, *Pseudokirchneriella subcapitata*, DACO: 9.8.2

2378060	2010, S-2200 Technical Grade - 96-Hour Toxicity Test with the Freshwater Green Alga, *Pseudokirchneriella subcapitata*, Following OPPTS Draft Guideline 850.5400, DACO: 9.8.2
2378061	2012, 2-COOH-S-2200: 72-Hour Toxicity Test with the Freshwater Green Alga, *Pseudokirchneriella subcapitata*, Following The Official Journal of the European Communities L383A, Method C.3, JMAFF 12 Nohsan, No. 8147 Alga, Growth Inhibition Test 2-7-7 and JMAFF 13 Seisan No. 3986, DACO: 9.8.2
2378062	2012, 5-COOH-S-2200: 72-Hour Toxicity Test with the Freshwater Green Alga, *Pseudokirchneriella subcapitata*, Following The Official Journal of the European Communities L383A, Method C.3, JMAFF 12 Nohsan, No. 8147 Alga, Growth Inhibition Test 2-7-7 and JMAFF 13 Seisan No. 3986, DACO: 9.8.2
2378063	2012, S-2200-OR: 72-Hour Toxicity Test with the Freshwater Green Alga, *Pseudokirchneriella subcapitata*, Following The Official Journal of the European Communities L383A, Method C.3, JMAFF 12 Nohsan, No. 8147 Alga, Growth Inhibition Test 2-7-7 and JMAFF 13 Seisan No. 3986, DACO: 9.8.2
2378065	2012, S-2200: A 96-Hour Toxicity Test with the Freshwater Alga (*Anabaena flos-aquae*), DACO: 9.8.2
2378066	2012, S-2200: A 96-Hour Toxicity Test with the Freshwater Diatom (*Navicula pelliculosa*), DACO: 9.8.2
2378067	2013, S-2167 (R-Isomer of S-2200) - 72-Hour Toxicity Test with the Freshwater Green Alga, *Pseudokirchneriella subcapitata*, Following the Official Journal of the European Communities L383A, Method C.3, DACO: 9.8.2
2378068	2013, S-2354 (*S*-Isomer of S-2200) - 72-Hour Acute Toxicity Test with Freshwater Green Alga, *Pseudokirchneriella subcapitata*, Following the Official Journal of the European Communities L383A, Method C.3, DACO: 9.8.2
2378069	2012, S-2200: A 96-Hour Toxicity Test with the Marine Diatom (*Skeletonema costatum*), DACO: 9.8.3
2378070	2012, S-2200: A Toxicity Test to Determine the Effects of the Test Substance on Seedling Emergence of Ten Species of Plants, DACO: 9.8.4
2378071	2012, S-2200: A Toxicity Test to Determine the Effects of the Test Substance on Vegetative Vigor of Ten Species of Plants, DACO: 9.8.4
2378072	2012, S-2200: A 7-Day Static-Renewal Toxicity Test with Duckweed (*Lemna gibba* G3), DACO: 9.8.5
2378073	2009, Analytical Method Verification for the Determination of S-2200 TG in Avian Diet, DACO: 9.9
2378074	2012, Method Verification for the Determination of S-2200 on Drift Cards Used to Confirm Application During Non-Target Plant Tests, DACO: 9.9
2378075	2011, Effects of S-2200 TG on the Activity of the Soil Microflora, DACO: 9.9
2420267	2012, Analytical Method Verification for the Determination of S-2200 in Freshwater and Saltwater, DACO: 8.2.2.3

2420268	2012, Analytical Method Verification for the Determination of S-2200 in Freshwater and Saltwater, DACO: 8.2.2.3
2420269	2013, Analytical Method Verification for the Determination of S-2200 in Sediment , DACO: 8.2.2.2
2420270	2013, S-2200 Technical Grade - 72-Hour Acute Toxicity of Honey Bee Larvae, *Apis mellifera* L., during an In Vitro Exposure , DACO: 9.2.4.2
2420271	2013, S-2200: A Life Cycle Toxicity Test with the Freshwater Amphipod (*Hyalella azteca*) Using Spiked Sediment, DACO: 9.3.4
2420273	2013, S-2200: A Life Cycle Toxicity Test with the Freshwater Amphipod (*Hyalella azteca*) Using Spiked Sediment, DACO: 9.3.4
2420275	2013, S-2200: A Life Cycle Toxicity Test with the Freshwater Amphipod (*Hyalella azteca*) Using Spiked Sediment , DACO: 9.3.4
2420276	2013, S-2200: A Life Cycle Toxicity Test with the Freshwater Amphipod (*Hyalella azteca*) Using Spiked Sediment , DACO: 9.3.4
2420277	2013, S-2200: A Life Cycle Toxicity Test with the Freshwater Amphipod (*Hyalella azteca*) Using Spiked Sediment, DACO: 9.3.4
2420278	2013, S-2200: A Life Cycle Toxicity Test with the Freshwater Amphipod (*Hyalella azteca*) Using Spiked Sediment , DACO: 9.3.4
2420279	2012, S-2200: A 96-Hour Shell Deposition Test with the Eastern Oyster (*Crassostrea virginica*), DACO: 9.4.2
2420280	2012, S-2200: A 96-Hour Flow-Through Acute Toxicity Test with the Saltwater Mysid (*Americamysis bahia*), DACO: 9.4.2
2420281	2013, S-2200: A Life Cycle Toxicity Test with the Marine Amphipod (*Leptocheirus plumulosus*) Using Spiked Sediment, DACO: 9.4.5
2420283	2013, S-2200: A Life Cycle Toxicity Test with the Marine Amphipod (*Leptocheirus plumulosus*) Using Spiked Sediment, DACO: 9.4.5
2420284	2012, S-2200: A Flow-Through Life-Cycle Toxicity Test with the Saltwater Mysid (*Americamysis bahia*), DACO: 9.4.5
2420285	2013, S-2200: A Life Cycle Toxicity Test with *Chironomus dilutus* Using Spiked Sediment, DACO: 9.4.5
2420286	2013, S-2200: A Life Cycle Toxicity Test with *Chironomus dilutus* Using Spiked Sediment, DACO: 9.4.5
2420287	2012, S-2200: A 96-Hour Flow-Through Acute Toxicity Test with the Sheepshead Minnow (*Cyprinodon variegatus*), DACO: 9.5.2.4
2420288	2012, S-2200: An Early Life-Stage Toxicity Test with the Sheepshead Minnow (*Cyprinodon variegatus*), DACO: 9.5.3.1
2420289	2012, S-2200: A 96 Hour Toxicity Test with the Freshwater Alga (*Anabaena flos-aquae*), DACO: 9.8.2
2420290	2012, S-2200: A 96 Hour Toxicity Test with the Freshwater Diatom (*Navicula pelliculosa*), DACO: 9.8.2
2420291	2012, S-2200: A 96 Hour Toxicity Test with the Marine Diatom (*Skeletonema costatum*), DACO: 9.8.3
2420292	2012, S-2200: A Toxicity Test to Determine the Effects of the Test Substance on Seedling Emergence of Ten Species of Plants, DACO: 9.8.4

2420293	2012, S-2200: A Toxicity Test to Determine the Effects of the Test Substance on Vegetative Vigor of Ten Species of Plants, DACO: 9.8.4
2420294	2012, S-2200: A 7-Day Static-Renewal Toxicity Test with Duckweed (*Lemna gibba* G3), DACO: 9.8.5
2420295	2012, Method Verification For the Determination of S-2200 on Drift Cards Used to Confirm Application During Non-Target Plant Tests, DACO: 9.9

4.0 Value

PMRA Document Number	Reference
2377846	2013. Appendix 1 - Trial Reports for "S-2200 Fungicide: Annex IIA Tier II Summary, Efficacy Data and Information on S-2200 4 SC Fungicide, Containing Mandestrobin, for Use on Canola, Grape, Strawberry and Turfgrass". DACO 10.1, 10.2.1, 10.2.2, 10.2.3.1, 10.2.3.3, 10.3.1, 10.3.2, 10.4, 10.5, 10.5.1, 10.5.2, 10.5.3, 10.5.4
2377844	2013. S-2200 Fungicide: Annex IIA Tier II Summary, Efficacy Data and Information on S-2200 4 SC Fungicide, Containing Mandestrobin, for Use on Canola, Grape, Strawberry and Turfgrass. DACO 10.1, 10.2.1, 10.2.2, 10.2.3.1, 10.2.3.3, 10.3.1, 10.3.2, 10.4, 10.5, 10.5.1, 10.5.2, 10.5.3, 10.5.4, M12.7
2378119	2013. S-2200 Fungicide: Annex IIA Tier II Summary, Efficacy Data and Information on S-2200 3.2 FS Fungicide, a Seed Protectant Containing Mandestrobin, for Control of Seed and Seedling Diseases of Canola, Corn and Soybeans. DACO 10.1, 10.2.1, 10.2.2, 10.2.3.1, 10.2.3.2, 10.2.3.3, 10.3, 10.3.2, 10.3.3, 10.4, 10.5, 10.5.1, 10.5.2, 10.5.3, 10.5.4, M12.7
2378120	2013. Appendix 1: Trials Reports for "S-2200 Fungicide: Annex IIA Tier II Summary, Efficacy Data and Information on S-2200 3.2 FS Fungicide, a Seed Protectant Containing Mandestrobin, for Control of Seed and Seedling Diseases of Canola, Corn and Soybeans". DACO 10.1, 10.2.1, 10.2.2, 10.2.3.1, 10.2.3.2, 10.2.3.3, 10.3, 10.3.3, 10.4, 10.5, 10.5.1, 10.5.2, 10.5.3, 10.5.4, M12.7

B. Additional Information Considered

i) Published Information

1.0 Human and Animal Health

PMRA Document Number	Reference
2409268	U.S. EPA. 2012b. Standard Operating Procedures for Residential Pesticide Exposure Assessment. DACO 12.5.5
2528612	Clapp, M.J.L, Wade, J.D. and D.M. Samules. 1982. Control of Nephrocalcinosis by Manipulating the Calcium:Phosphorus Ratio in Commercial Rodent Diets, Laboratory Animals, 16:130-132. DACO: 4.8

2528613	Cockell, K.A. and B. Belonje. 2004. Nephrocalcinosis Caused by Dietary Calcium:Phosphorus Imbalance in Female Rats Develops Rapidly and Is Irreversible, The Journal of Nutrition, 134:637-640. DACO: 4.8
2528614	Frazier, K.S., Seely, J.C., Hard, G.C., Betton, G., Burnett, R., Nakatsuji, S., Nishikawa, A., Durchfeld-Meyer, B. and A. Bube. 2012. Proliferative and Nonproliferative Lesions of the Rat and Mouse Urinary System, Toxicologic Pathology, 40: 14S-86S. DACO: 4.8
2528616	Ritskes-Hoitinga, J., Lemmens, A.G., Danse, L.H.J.C. and A.C. Beynen. 1989. Phosphorus-Induced Nephrocalcinosis and Kidney Function in Female Rats, The Journal of Nutrition, 119:1423-1431. DACO: 4.8
2528615	Woo, D.C. and R.M. Hoar. 1972, “Apparent Hydronephrosis” as a Normal Aspect of Renal Development in Late Gestation of Rats: The Effect of Methyl Salicylate, Teratology, 6:191-196. DACO: 4.8