Proposed Registration Decision PRD2017-03

Polyoxin D zinc salt

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Overview

Proposed Registration Decision for Polyoxin D zinc salt

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 Polyoxin D Zinc Salt Technical and its associated end-use products: Polyoxin D Zinc Salt 5SC Fungicide, Polyoxin D Zinc Salt 11.3% WDG Fungicide, Polyoxin D Zinc Salt 11.3% WDG Domestic Fungicide, containing the technical grade active ingredient polyoxin D zinc salt, to suppress or control a broad range of diseases in various crops grown outdoors or under greenhouse conditions.

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 Polyoxin D Zinc Salt Technical and its associated end-use products.

What Does Health Canada Consider When Making a Registration Decision?

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

To reach its decisions, the PMRA applies modern, rigorous risk-assessment methods and policies. These methods consider the unique characteristics of sensitive subpopulations in humans (for example, children) as well as organisms in the environment. These methods and policies also consider the nature of the effects observed and the uncertainties when predicting the impact of pesticides. For more information on how the 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.

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

2 "Value" as defined by subsection 2(1) of the *Pest Control Products Act*: "…the product's actual or potential contribution to pest management, taking into account its conditions or proposed conditions of registration, and includes the product's (*a*) efficacy; (*b*) effect on host organisms in connection with which it is intended to be used; and (*c*) health, safety and environmental benefits and social and economic impact."

Before making a final registration decision on polyoxin D zinc salt, 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 polyoxin D zinc salt, which will include the decision, the reasons for it, a summary of comments received on the proposed final registration decision and the PMRA's response to these comments.

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

What Is Polyoxin D Zinc Salt?

Polyoxin D zinc salt is a new active ingredient for disease management in certain fruits, vegetable crops, turfgrass and ornamental plants. It has a non-lethal mode of action that stops the growth of sensitive causal pathogens by interfering with fungal pathogen cell wall growth. Its mode of action is highly specific.

Health Considerations

Can Approved Uses of Polyoxin D Zinc Salt Affect Human Health?

Polyoxin D Zinc Salt 5SC Fungicide, Polyoxin D Zinc Salt 11.3% WDG Fungicide, and Polyoxin D Zinc Salt 11.3% WDG Domestic Fungicide, containing polyoxin D zinc salt, are unlikely to affect your health when used according to label directions.

Potential exposure to polyoxin D zinc salt may occur through the diet 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.

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-containing products are used according to label directions.

In laboratory animals, polyoxin D zinc salt was of low acute toxicity by the oral, dermal and inhalation routes of exposure. It was minimally irritating to the eye and skin, and caused a mild allergic skin reaction. Consequently, the words "POTENTIAL SKIN SENSITIZER" are required on the label for the technical grade of the active ingredient.

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

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

The end-use products are of low acute toxicity by the oral, dermal, and inhalation routes, and are non-irritating or minimally irritating to the eyes and skin. Polyoxin D Zinc Salt 5SC Fungicide caused a mild allergic skin reaction, while the other end-use products did not. The label of Polyoxin D Zinc Salt 5SC Fungicide must include the words "POTENTIAL SKIN SENSITIZER" and the hazard statement, "Warning, contains the allergen soy" for the presence of soy in the end-use product.

Registrant-supplied short and long term (lifetime) animal toxicity tests, as well as information from the published scientific literature were assessed for the potential of polyoxin D zinc salt to cause target organ systemic toxicity, chronic toxicity, cancer, reproductive and developmental toxicity, immunotoxicity, and various other effects.

Polyoxin D zinc salt was of low toxicity in laboratory animals. It did not cause cancer in animals and did not damage genetic material. There was no damage to immune or reproductive systems and no birth defects in animals. There was no indication that the young were more sensitive than the adult animal. Health effects in animals given repeated high doses are reduced organ weights of liver and spleen.

The risk assessment protects against these effects by ensuring that the level of human exposure is well below the lowest dose at which these effects occur in animal studies.

Residues in Water and Food

Dietary risks from food and water are not of concern.

Dietary risk to humans is considered to be low based on the low toxicity of polyoxin D zinc salt and because residue levels on food commodities will be low.

It is anticipated that the consumption of food commodities that have been treated with polyoxin D zinc salt will not pose a health risk of concern to any segment of the population, including infants, children, adults and seniors.

Exposure to residues of polyoxin D zinc salt in drinking water through run-off or greenhouse effluent is also expected to be low because residues will degrade in soil. Based on the low toxicity profile of polyoxin D zinc salt, no risk due to exposure from drinking water is anticipated.

Risks in Residential and Other Non-Occupational Environments

Estimated risk for residential and other non-occupational exposure is not of concern.

Residential and bystander exposure to individuals coming in contact with polyoxin D zinc salt during application is not expected to result in unacceptable risk when Polyoxin D Zinc Salt 5SC Fungicide, Polyoxin D Zinc Salt 11.3% WDG Fungicide, and Polyoxin D Zinc Salt 11.3% WDG Domestic Fungicide are used according to label directions.

Occupational Risks From Handling Polyoxin D Zinc Salt 5SC Fungicide, Polyoxin D Zinc Salt 11.3% WDG Fungicide, and Polyoxin D Zinc Salt 11.3% WDG Domestic Fungicide

Occupational risks are not of concern when Polyoxin D Zinc Salt 5SC Fungicide, Polyoxin D Zinc Salt 11.3% WDG Fungicide, and Polyoxin D Zinc Salt 11.3% WDG Domestic Fungicide are used according to the label directions, which include protective measures.

An assessment conducted for individuals handling and applying Polyoxin D Zinc Salt 5SC Fungicide, Polyoxin D Zinc Salt 11.3% WDG Fungicide, and Polyoxin D Zinc Salt 11.3% WDG Domestic Fungicide indicated that the risk is not of concern when the product is used according to label directions.

Environmental Considerations

What Happens When Polyoxin D Zinc Salt Is Introduced Into the Environment?

Polyoxin D zinc salt is not expected to pose risks of concern to the environment when used according to label instructions.

Polyoxin D zinc salt will enter the environment when used as a fungicide on certain fruits and vegetable crops (field and greenhouse), turf and ornamentals. Polyoxin D, the organic component of Polyoxin D zinc salt, mixes readily with water. Polyoxin D can be broken down by soil microorganisms and it is not expected to build-up in the terrestrial environment. Polyoxin D zinc salt is not expected to move through the soil and enter groundwater. Polyoxin D can break down by reacting with water and also when exposed to sunlight, especially in clear shallow waters, and therefore is not expected to persist in aquatic habitats. Polyoxin D is not expected to accumulate in the tissues of organisms.

Polyoxin D zinc salt is not expected to pose risks of concern to honeybees and other beneficial insects, birds, small mammals, terrestrial and aquatic plants, fish, or aquatic invertebrates. If exposed to high enough concentrations, Polyoxin D zinc salt may pose a risk to amphibians. Spray buffer zones to protect sensitive aquatic habitats will be required. When used according to label directions, Polyoxin D zinc salt is not expected to pose a risk of concern to the environment.

Value Considerations

What Is the Value of Polyoxin D Zinc Salt 5SC, Polyoxin D Zinc Salt 11.3% WDG and Polyoxin D Zinc Salt 11.3% WDG Domestic Fungicide?

Registration of these products will provide Canadian growers with a new mode of action to manage important fungal diseases on various crops. These products will be applied in a broad range of uses including greenhouse and field crops, turfgrass, ornamental and domestic uses.

Polyoxin D Zinc Salt 5SC, containing polyoxin D zinc salt, has been demonstrated to be effective against certain economically important diseases in ginseng, potato, tomato, grape, strawberry, apple, pear, cucurbit vegetables (Crop Group 9), berries and small fruits (Crop Group 13) and greenhouse ornamental plants. Polyoxin D Zinc Salt 11.3% WDG and Polyoxin D Zinc Salt 11.3% WDG Domestic, also containing polyoxin D zinc salt, have been demonstrated to be effective against certain economically important diseases in turfgrass and outdoor-grown ornamental plants.

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 Polyoxin D Zinc Salt 5SC Fungicide, Polyoxin D Zinc Salt 11.3% WDG Fungicide, and Polyoxin D Zinc Salt 11.3% WDG Domestic Fungicide to address the potential risks identified in this assessment are as follows.

Key Risk-Reduction Measures

Human Health

The Polyoxin D Zinc Salt 5SC Fungicide label must include the hazard statement “Warning, contains the allergen soy.”

For Polyoxin D Zinc Salt 5SC Fungicide and Polyoxin D Zinc Salt 11.3% WDG Fungicide, personal protective equipment (PPE), including long-sleeved shirt, long pants, socks, shoes, and chemical-resistant gloves are required for individuals involved with mixing, loading, application, clean-up, and machine maintenance or repair. If early entry into treated areas that involve contact with treated plants, soil, water, etc. is necessary (that is, prior to treated surfaces drying), individuals are required to wear coveralls, socks shoes, and chemical-resistant gloves. The potential for spray drift to areas of human habitation or areas of human activity must be considered. A label statement regarding spread drift will be required.

Entry into areas treated with Polyoxin D Zinc Salt 11.3% WDG Domestic Fungicide is not permitted until the spray dries.

Environment

Polyoxin D zinc salt may pose a risk to amphibians. Spray buffer zones (1 metre default buffer zone) and precautionary label statements will be required.

Next Steps

Before making a final registration decision on polyoxin D zinc salt, 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 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

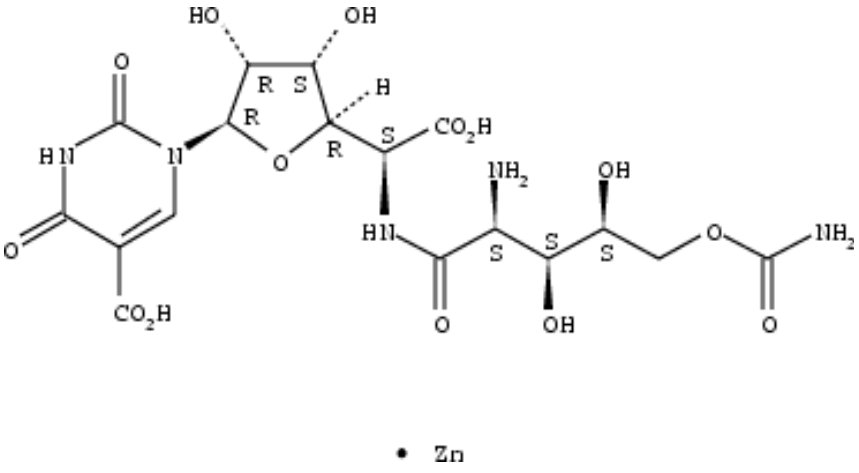
When the PMRA makes its registration decision, it will publish a Registration Decision on polyoxin D zinc salt (based on the Science Evaluation of this consultation document). In addition, the test data referenced in this consultation document will be available for public inspection, upon application,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

Science Evaluation

Polyoxin D Zinc Salt

1.0 The Active Ingredient, Its Properties and Uses

1.1 Identity of the Active Ingredient

Active substance	Polyoxin D zinc salt
Function	Fungicide
Chemical name	
1. International Union of Pure and Applied Chemistry (IUPAC)	Zinc 5-(2-amino-5-*O*-carbamoyl-2-deoxy-L-xylonamido)-1-(5-carboxy-1,2,3,4-tetrahydro-2,4-dioxopyrimidin-1-yl)-1,5-dideoxy-β-D-allofuranuronate
2. Chemical Abstracts Service (CAS)	Zinc 5-[[2-amino-5-*O*-(aminocarbonyl)-2-deoxy-L-xylonoyl]amino]-1-(5-carboxy-3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl)-1,5-dideoxy-β-D-allofuranuronate
CAS number	146659-78-1
Molecular formula	$C_{17}H_{23}N_5O_{14}Zn$
Molecular weight	586.8
Structural formula	
Purity of the active ingredient	23.8%

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

Technical Product – Polyoxin D Zinc Salt Technical

Property	Result
Colour and physical state	Brown powder
Odour	Musty
Melting range	~170°C (decomposition)
Boiling point or range	Not applicable
Density	1.8392 g/cm^3
Vapour pressure at 20 °C	<1.33 × 10^5 mPa for Polyoxin D
Ultraviolet (UV)-visible spectrum	pH / λ_{max}(nm) / ε ($M^{-1}cm^{-1}$) neutral 270 18586 acidic 274 24251 basic 268.5 17726
Solubility in water at 20 °C	Polyoxin D solubility: 35.4 g/L, pH 3.5, 30°C (Very soluble) Polyoxin D zinc salt solubility: 1.0 g/100 mL
Solubility in organic solvents at 20 °C	Slightly soluble in methanol and octanol Polyoxin D solubility: Solvent / Solubility (g/L) Acetone 0.011 Methanol 0.175 Toluene <0.0011 Dichloromethane <0.0011
n-Octanol-water partition coefficient (K_{ow})	Log K_{ow} = -1.45 for Polyoxin D (The Pesticide Manual)
Dissociation constant (pK_a)	3.25, 4.16, 8.00, 9.56, 10.5 Polyoxin D: 2.66 (carboxyl), 3.69 (carboxyl), 7.89 (amino), 10.21 (uracil)
Stability (temperature, metal)	Stable to metals (zinc and iron); stable at subambient temperatures; not stable at elevated temperatures; not stable in sunlight.

End-Use Product – Polyoxin D Zinc Salt 5SC Fungicide

Property	Result
Colour	Not required for this product
Odour	Not required for this product
Physical state	Liquid
Formulation type	Suspension concentrate
Guarantee	5.0%
Container material and description	Polyethylene bottle and tote (1 L–1000 L)

Property	Result
Relative density	1.0535
pH of 1% dispersion in water	7.01
Oxidizing or reducing action	No oxidizing or reducing action
Storage stability	Stable for 1 year when stored at room temperature in commercial packaging material (polyethylene).
Corrosion characteristics	Product is non-corrosive to the packaging material
Explodability	Product is not potentially explosive

End-Use Products – Polyoxin D Zinc Salt 11.3% WDG Fungicide and Polyoxin D Zinc Salt 11.3% WDG Domestic Fungicide

Property	Result
Colour	Dusty sable brown
Odour	Earthy, claylike odour
Physical state	Solid
Formulation type	Water-dispersible granules
Guarantee	11.3%
Container material and description	Metallized polyester pouches 27 g – 15 kg (domestic product) 227 g – 15 kg (commercial product)
Density at 23.5 °C	0.561 g/mL (pour density) 0.576 g/mL (tap density)
pH of 1% dispersion in water	7.07
Oxidizing or reducing action	Reducing action: A significant temperature increase and evolution of bubbles were observed when the product was exposed to household bleach (oxidizing agent). The product was compatible with zinc powder (reducing agent), monoammonium phosphate (fire retardant) and water.
Storage stability	The product is stable for one year stored in metallized polyester pouches at ambient temperature. There is a slight decrease (0.6% absolute, 4.88% relative) in the Polyoxin D zinc salt content after one year.
Corrosion characteristics	The product is non-corrosive to the metallized polyester pouches.
Explodability	The product has no explosive properties.

1.3 Directions for Use

To control or suppress certain fungal diseases on outdoor and greenhouse fruits and vegetables and on greenhouse ornamentals, apply Polyoxin D Zinc Salt 5SC Fungicide as a preventative or, in some cases, a curative treatment in conjunction with good management practices. Low rates may be used preventatively before onset of symptoms or in periods of low disease pressure. Use higher rates and shorter intervals when disease pressure is high.

To control or suppress certain fungal diseases on turfgrass and outdoor-grown ornamentals, apply Polyoxin D Zinc Salt 11.3% WDG or Polyoxin D Zinc Salt 11.3% WDG Domestic as a preventative or a curative treatment at the rates specified, and in conjunction with good management practices.

1.4 Mode of Action

Polyoxin D zinc salt has a unique mode of action against several important fungal diseases in fruits, vegetable crops, turfgrass and ornamental plants. Polyoxin D zinc salt, designated as a Group 19 fungicide by the Fungicide Resistance Action Committee (FRAC), stops the growth of sensitive fungal pathogens by inhibiting an enzyme needed for pathogen cell wall growth.

2.0 Methods of Analysis

2.1 Methods for Analysis of the Active Ingredient

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

2.2 Method for Formulation Analysis

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

2.3 Methods for Residue Analysis

No methods are required to quantify residues of polyoxin D zinc salt due to its low toxicity (see Section 3.0 for additional details).

3.0 Impact on Human and Animal Health

3.1 Toxicology Summary

A detailed review of the toxicological database for polyoxin D zinc salt was conducted.

The database is complete, consisting of the full array of toxicity studies currently required for hazard assessment purposes. Many studies were carried out in accordance with currently accepted international testing protocols and Good Laboratory Practices (GLP) while some of the older studies were performed prior to the widespread use of GLP. In addition, use was made of other regulatory authority documentation to supplement the assessment. The scientific quality of the data is good and the database is considered adequate to define the majority of the toxic effects that may result from exposure to polyoxin D zinc salt.

In a metabolism study, radiolabelled polyoxin D was rapidly and nearly completely eliminated within 48 hours. Urine and feces accounted for 2.0–2.7% and 91.8–94.1% of the dose, respectively, by 96 hours postdosing – that is, more than 90% of the dose was excreted in feces. The excretion by expired air was slight, and the most of the absorbed radioactivity was excreted in urine. After 96 hours following dosing, radioactivity in the carcass was 0.1% or less of the

administered dose indicating low residual activity in the body. Based on the excretion rates for urine and expired air, the estimated absorption rate was 2.0–2.8%. Absorbed polyoxin D was not widely distributed in the tissues. Except for the small intestine and large intestine, residues in plasma and all tissues were determined to be no greater than 0.1% of the administered dose at 1 hour after dosing. The parent compound and four metabolites were detected in urine, feces, plasma, liver and kidney. The major metabolite (except in the liver) was polyoxin C acid accounting for 40–90% of the radioactivity in each sample, while the major metabolite in liver was uracil-5 carboxylic acid accounting for 54–80% of the radioactivity. Two unknown metabolites were detected only in feces, which were considered to be degradates produced by the gastrointestinal tract. Polyoxin D was detected only in urine and feces. The major metabolic pathway in the rat was cleavage of the peptide bond in polyoxin D to produce polyoxin C acid followed by degradation to uracil-5-carboxylic acid. Absorption, distribution, metabolism and elimination showed no dose dependent or sex dependent differences.

In the rat, polyoxin D zinc salt was of low acute toxicity via the oral, dermal and inhalation routes of exposure, and it was minimally irritating to the eyes and skin of rabbits. Polyoxin D zinc salt was weakly sensitizing to the skin in guinea pigs.

Polyoxin D zinc salt was of low toxicity in a 90-day oral toxicity study in the rat. There were no mortalities. In the high dose group (20000 ppm only), there were treatment-related effects, such as lower bodyweights and a decrease in food efficiency in males throughout the treatment period with statistically significant decreases in body weight at weeks 7-13. Decrease in absolute weights of the liver and spleen in both sexes, and a decreased relative weight of the liver (male only) were observed. In the other dose groups, there were no treatment-related effects in either sex.

A waiver request for the requirement of a 90-day and/or 12-month oral toxicity study in dog was accepted as the 12-month dog study is a conditional requirement and the short-term oral toxicity study in rats (90-day) showed no subchronic oral toxicity concerns for polyoxin D zinc salt. Also, polyoxin D zinc salt has a nontoxic mode of action, acts exclusively against fungi, and it has a low mammalian toxicity profile.

In a developmental toxicity study in rats, there were no mortalities, and no clinical signs or treatment-related adverse effects on bodyweight gain or litter parameters. The only treatment-related effect was in the high dose group (1000 mg/kg/day), where females (20/24) had thickening of the limiting ridge in the stomach compared to controls (0/23). There were no treatment-related effects observed on any parameters assessing embryofetal development at any doses.

In a developmental toxicity study in rabbits, there were no treatment-related effects in maternal rabbits at any dose except for decreased food intake and slight decrease of body weight at 800 mg/kg /day. There were no adverse treatment-related effects on litter parameters and embryofetal development parameters at any doses.

In a two-generation reproductive study in rats, treatment with polyoxin D zinc salt at doses up to 1% of diet did not produce any adverse effects on reproductive capacity of the F0, F1 and F2 generations or survival over all generations. Also, there were no treatment-related adverse effects

on embryofetal development from selected animals of the F1 and F2 generations. The postnatal growth of delivered pups was normal without any observable abnormalities. A transient reduction of bodyweight for pups from the first generation was not considered to be treatment-related.

Although polyoxin D zinc salt was clastogenic in two chromosomal aberrations tests, negative results in bacterial mutagenicity studies and a negative result in an in vivo micronucleus study indicate that polyoxin D zinc salt is not genotoxic. There was no evidence of carcinogenicity in rats or mice in chronic toxicity/oncogenicity studies.

Waiver requests submitted for requirements for neurotoxicity and developmental neurotoxicity testing were accepted based on the low mammalian toxicity of polyoxin D zinc salt and its nontoxic mode of action, as well as the lack of neurological effects in other studies, and the lack of structural similarity to other substances that may cause delayed neurotoxicity.

In an immunotoxicity study in mice, polyoxin D zinc salt did not demonstrate any immunotoxicological potential.

In acute toxicity testing, the end-use product Polyoxin D Zinc Salt 5SC Fungicide was of low acute toxicity via the oral, dermal, and inhalation routes of exposure. It was non-irritating to the eyes and minimally irritating to skin, and was a mild skin sensitizer in the Buehler test. Polyoxin D Zinc Salt 5SC Fungicide contains the allergen soy; therefore, the label must include a hazard statement for soy's allergenicity.

The other end-use products Polyoxin D Zinc WDG (commercial and domestic) were of low acute toxicity by the oral, dermal, and inhalation routes, and were minimally irritating to the eyes and skin, and were not skin sensitizers.

Incident Reports

Polyoxin D zinc salt is a new active ingredient pending registration for use in Canada. Hence, there were no incidents involving this active ingredient in the PMRA database as of 9 August 2016.

3.2 Occupational and Residential Risk Assessment

3.2.1 Dermal Absorption

Dermal absorption of Polyoxin D Zinc Salt 5SC Fungicide, Polyoxin D Zinc Salt 11.3% WDG Fungicide, or Polyoxin D Zinc Salt 11.3% WDG Domestic Fungicide is not expected to be of concern due to its moderate water solubility, high molecular weight, and the low toxicity via the dermal route.

3.2.2 Use Description

Polyoxin D Zinc Salt 5SC Fungicide, is proposed for use as a fungicide on field and greenhouse grown crops. Polyoxin D Zinc Salt 11.3% WDG Fungicide and Polyoxin D Zinc Salt 11.3% WDG Domestic Fungicide are proposed for use on turf and outdoor ornamentals.

Application of Polyoxin D Zinc Salt 5SC Fungicide is by airblast or groundboom sprayer for orchards or field crops, and by hydraulic reel sprayer in the greenhouse. Polyoxin D Zinc Salt 11.3% WDG Fungicide is to be applied by groundboom sprayer and hydraulic reel sprayer on turf, and by hydraulic reel sprayer on ornamentals grown outdoors. Typical methods of applying Polyoxin D Zinc Salt 11.3% WDG Domestic Fungicide include a manually-pressurized handwand, hose-end sprayer, backpack, or sprinkler can.

Applications of Polyoxin D Zinc Salt 5SC Fungicide, Polyoxin D Zinc Salt 11.3% WDG Fungicide, and Polyoxin D Zinc Salt 11.3% WDG Domestic Fungicide should ensure thorough coverage of the foliage, but with minimal run-off.

The proposed rate of application ranges from 0.28 to 1.00 kg of Polyoxin D Zinc Salt 5SC Fungicide per hectare and may be applied up to 3 times in a growing season on ginseng and on ornamental plants. The remaining crops are limited to ≤ 150 g a.i./ha/season. Workers will handle 0.06–0.81 kg a.i./day. Worker re-entry without personal protective equipment (PPE) is not permitted until sprays have dried.

The proposed rate of application for Polyoxin D Zinc Salt 11.3% WDG Fungicide is 2.7 kg/ha for turf and 0.150 to 0.584 kg/1000 L for ornamentals grown outdoors. The end-use product may be applied up to 3 times in a growing season (7 to 14 or 21 days between applications). For turf application, workers will handle 4.94 to 9.88 kg a.i./day and 0.033 to 0.40 kg a.i./day for ornamental use.

The proposed rate of application of Polyoxin D Zinc Salt 11.3% WDG Domestic Fungicide is 2.7 kg/ha for turf and 0.150–0.584 kg/1000 L for ornamentals. Polyoxin D Zinc Salt 11.3% WDG Domestic Fungicide may be applied up to 3 times in a growing season (7 to 14 days or 21 days between applications). Residential users will typically handle 0.00032–0.0027 kg a.i./day when treating ornamentals and 0.003–0.061 kg a.i./day when applying the end-use product on turf.

3.2.3 Mixer, Loader, and Applicator Exposure and Risk

Occupational exposure to Polyoxin D Zinc Salt 5SC Fungicide and Polyoxin D Zinc Salt 11.3% WDG Fungicide is characterized as short-term and intermediate in duration and is primarily by the dermal route, but incidental inhalation, oral, and ocular exposure is also possible while mixing, loading, and applying the product, as well as during clean-up and equipment maintenance.

Residential user exposure to Polyoxin D Zinc Salt 11.3% WDG Domestic Fungicide is short-term in duration and is primarily by the dermal route, but incidental inhalation, oral, and ocular exposure is also possible while mixing, loading, and applying the product, as well as during clean-up.

The risk due to occupational exposure of Polyoxin D Zinc Salt 5SC Fungicide and Polyoxin D Zinc Salt 11.3% WDG Fungicide from mixing, loading, applying, clean-up, and maintenance of machinery for workers is considered to be acceptable when used according to the label, which includes wearing long-sleeved shirt and long pants, chemical-resistant gloves, shoes, and socks.

Early entry (that is, prior to the treated area having dried), will require individuals to wear coveralls, chemical-resistant gloves, shoes, and socks. The risk due to residential user exposure of Polyoxin D Zinc Salt 11.3% WDG Domestic Fungicide from mixing, loading, applying, and clean-up is considered to be acceptable when used according to the label.

3.2.4 Postapplication Exposure and Risk

There is a potential for exposure to workers re-entering areas treated with Polyoxin D Zinc Salt 5SC Fungicide and Polyoxin D Zinc Salt 11.3% WDG Fungicide. Given the nature of the postapplication activities typically performed, dermal contact is possible. While the degree of exposure will be related to the time of re-entry and the duration of the activities, the potential risk due to exposure resulting from postapplication work is not a concern when used according to label directions. A restricted entry interval is not required, but workers entering freshly treated areas will be required to wear PPE (that is, coveralls, chemical-resistant gloves, shoes, and socks) until sprays have completely dried.

The potential risk due to postapplication exposure to Polyoxin D Zinc Salt 11.3% WDG Domestic Fungicide is not a concern if users avoid contact with treated areas until the sprays have dried completely.

3.2.5 Residential and Bystander Exposure and Risk

Because both of the commercial end-use products, Polyoxin D Zinc Salt 5SC Fungicide and Polyoxin D Zinc Salt 11.3% WDG Fungicide, are proposed for outdoor use, there is a potential for bystander exposure. Standard mitigative label statements to minimize the potential for bystander exposure are required.

Bystander exposure resulting from the residential use of Polyoxin D Zinc Salt 11.3% WDG Domestic Fungicide is not a concern.

3.3 Food Residue Exposure Assessment

3.3.1 Food

Polyoxin D zinc salt has a low mammalian toxicity profile. The compound had low oral toxicity in acute and short-term tests and there were no specific toxicological endpoints identified. Toxicokinetics in the rat have demonstrated that polyoxin D zinc salt is readily excreted almost without being absorbed. Residue levels on crops are expected to be low based on the residue data from metabolism studies, application rates which are low and the expected degradation of residues in the field. For these reasons, no adverse effects are anticipated from the presence of residues on food commodities and feed.

Therefore, it is not anticipated that dietary exposure to residues of polyoxin D zinc salt on food commodities and feed will result in health risks of concern in the general population and potentially sensitive subpopulations, including infants and children.

3.3.2 Drinking Water

Although the end-use products will not be applied near or directly to water, some drinking water exposure may be possible through run-off from treated areas, or from greenhouse effluent.

In soil, polyoxin D zinc salt will degrade rapidly and the EP labels instructs users not to contaminate irrigation or drinking water supplies or aquatic habitats through equipment cleaning or waste disposal. Users are also prohibited from allowing effluent or runoff from greenhouse facilities containing this active ingredient to enter lakes, streams, ponds or other waters. Furthermore, municipal treatment of drinking water is expected to prevent contamination of drinking water with residues.

In addition, toxicity of polyoxin D zinc salt is low. Consequently, exposure from drinking water is not expected to pose a health risk of concern.

3.3.3 Acute and Chronic Dietary Risks for Sensitive Subpopulations

Calculations of acute reference doses and acceptable daily intakes are not required for polyoxin D zinc salt. Based on all the available information and hazard data, the PMRA concludes that polyoxin D zinc salt is of low toxicity. Thus there are no threshold effects of concern. As a result, there is no need to apply uncertainty factors to account for intra- and interspecies variability, safety factors or margins of exposure. Further factoring of consumption patterns among infants and children, special susceptibility in these subpopulations to the effects of polyoxin D zinc salt, including neurological effects from pre- or post-natal exposures, and cumulative effects on infants and children of polyoxin D zinc salt and other registered products containing polyoxin D zinc salt, does not apply to this active ingredient. As a result, the PMRA has not used a margin of exposure (safety) approach to assess the risks of polyoxin D zinc salt to human health.

3.3.4 Aggregate Exposure and Risk

Based on all the relevant information in the PMRA files, there is reasonable certainty that no harm will result from aggregate exposure of residues of polyoxin D zinc salt to the general Canadian population, including infants and children, when the end-use products are used as labelled. This includes all anticipated dietary (food and drinking water) exposures and all other non-occupational exposures (dermal and inhalation) for which there is reliable information.

3.3.5 Maximum Residue Limits (MRLs)

As part of the assessment process prior to the registration of a pesticide, Health Canada must determine whether the consumption of the maximum amount of residues, that are expected to remain on food products when a pesticide is used according to label directions, will not be a concern to human health. This maximum amount of residues expected is then legally established as a maximum residue limit (MRL) under the *Pest Control Products Act* for the purposes of the adulteration provision of the *Food and Drugs Act*. Health Canada sets science-based MRLs to ensure the food Canadians eat is safe.

Polyoxin D zinc salt is of low toxicity by the oral route and toxicokinetic studies indicate that polyoxin D zinc salt is poorly absorbed and is readily excreted predominantly unchanged from the gastrointestinal tract. Plant metabolism studies indicate that residues in the edible portion of crops are low and actual residues on field-grown crops are expected to be even lower since polyoxin D zinc salt will degrade rapidly in the field. Food handling practices (that is, washing) will also further reduce residue levels on crops and processed commodities. Furthermore, application rates are low and the use pattern of polyoxin D zinc salt is unlikely to change due to the fungicide resistance management recommendations on products containing polyoxin D zinc salt as the active ingredient which strictly limit the number of applications per season. Consequently, an MRL for food commodities and feed treated with polyoxin D zinc salt will not be specified.

3.4 Antimicrobial Resistance Assessment

The mechanism of action associated with polyoxin D is competitive inhibition against the substrate for chitin synthase to disrupt the synthesis of chitin, a key component of fungal cell walls. Neither the polyoxin group of anti-fungal compounds nor nikkomycins, which are similar in both structure and activity to polyoxins, are registered in Canada or in the United States as human or veterinary drugs. Polyoxin D is ineffective against bacteria at practical use levels while the level of inhibition against fungi varied from highly effective to ineffective. The potential use of polyoxin antifungal compounds as drugs is also limited by their low permeability, hydrolytic lability and varying susceptibilities of fungal species.

While cross-resistance was observed between polyoxins and dipeptide antibiotics, these observations are expected since both compounds enter cells using the same transport system. There are, however, no reports on the use of dipeptide antibiotics for treatment of fungal diseases in humans or animals.

Current antibiotics for the treatment of systemic mycoses do not target chitin synthesis. Also, the transport systems that mediate polyoxin absorption are not involved in the uptake of these compounds or in the development of fungal resistance to these compounds. Therefore, cross-resistance with polyoxin D is unlikely.

Although the proposed use scenarios present the potential development of antimicrobial resistance through occupational, dietary and environmental exposure to either polyoxin D or resistant fungi, there is no health risk of concern as polyoxins are not a clinically important class of antimicrobial drugs and resistance to polyoxin D is not likely to cause cross-resistance with clinically important antimicrobial drugs.

4.0 Impact on the Environment

4.1 Fate and Behaviour in the Environment

Polyoxin D, the organic acid component of polyoxin D zinc salt, is produced via a fermentation process using the soil microbe, *Streptomyces cacaoi* var. *asoensis*, that was isolated from a soil sample collected in Japan. The use of polyoxin D zinc salt on terrestrial food and non-food crops, outdoor ornamentals and turf may result in the entry of this pesticide active ingredient to the

environment through spray drift or overland runoff. Polyoxin D is stable to hydrolysis under acidic conditions, while it is hydrolysed under neutral and alkaline conditions. Sterile natural water undergoes rapid photolysis with a half-life of 0.4 days under continuous irradiation. In the presence of buffered sterile water and sunlight, under neutral conditions (pH 7), polyoxin D is phototransformed with a half-life of 2.3 days under continuous irradiation. In soil, polyoxin D is slightly persistent with a half-life of 15.9 days. Polyoxin D was predicted to volatilize from water or moist soil surfaces by Henry's law constant. There were, however, no volatile organic compounds detected in laboratory studies so polyoxin D is not expected to enter the atmosphere. Various transformation products were produced (see Appendix I, Table 5). Of these, carbon dioxide was a major transformation product in aerobic soil (54.0% AR). Other volatile organic compounds were not detected.

Although the information required to assess mobility in soil was not complete, based on its slight persistence in soil and propensity to bind to soil particles, polyoxin D zinc salt is not expected to move to groundwater in significant quantities. Its potential for bioconcentration in aquatic organisms is also estimated to be low, based on a negative log K_{ow} value. Environmental parameters are summarized in Appendix I, Table 4.

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 exposure concentrations (EECs) are concentrations of pesticide in various environmental media, such as food, water, soil and air. The EECs are estimated using standard models which take into consideration the application rate(s), chemical properties and environmental fate properties, including the dissipation of the pesticide between applications. Ecotoxicology information includes acute and chronic toxicity data for various organisms or groups of organisms from both terrestrial and aquatic habitats including invertebrates, vertebrates, and plants. Toxicity endpoints used in risk assessments may be adjusted to account for potential differences in species sensitivity as well as varying protection goals (that is, 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). If the screening level risk quotient is below the level of concern, the risk is considered negligible and no further risk characterization is necessary. If the screening level risk quotient is equal to or greater than the level of concern, then a refined risk assessment is performed to further characterize the risk. A refined assessment takes into consideration more realistic exposure scenarios (such as drift to non-target habitats) and might consider different toxicity endpoints.

Refinements 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 summary of terrestrial toxicity data is presented in Appendix I, Table 6. The accompanying risk assessment is presented in Appendix I, Tables 7-8.

Bees (pollinators): Foraging bees could be exposed directly to spray droplets containing polyoxin D zinc salt during application or to polyoxin D zinc salt residues found on the surface of leaves (contact exposure). Laboratory tests showed that polyoxin D zinc salt technical was relatively non-toxic to adult bees on an acute contact basis and the LOC was not exceeded.

Foraging bees could also be exposed to polyoxin D zinc salt through the ingestion of pollen and nectar contaminated from direct spray (oral exposure). Laboratory tests showed that polyoxin D zinc salt technical was relatively non-toxic to adult bees on an acute oral basis and the LOC was not exceeded.

Other terrestrial invertebrates: Studies with earthworms and other terrestrial invertebrates indicated polyoxin D zinc salt is relatively non-toxic to these organisms (14-day LC_{50} >1000 mg a.i/kg dw of soil and LC_{50} > 2100 mg/L, highest rate tested, respectively).

Birds and mammals: At the highest dose tested, oral exposure to polyoxin D zinc salt caused no mortality or adverse effects in the mallard duck (*Anas platyrhynchos*) on an acute oral and dietary basis. Polyoxin D zinc salt was shown to be practically non-toxic to rats on an acute oral basis. The screening level RQs for birds and mammals did not exceed the LOC.

Non-target terrestrial plants: A waiver for the requirement to provide vascular plant data was submitted and accepted based on the low toxicity of polyoxin D zinc salt to algae, its mode of action specific to inhibition of chitin synthesis, and a long history of use where phytotoxicity has not been observed.

4.2.2 Risks to Aquatic Organisms

A summary of aquatic toxicity data is presented in Appendix I, Table 6. The accompanying risk assessment is presented in Appendix I, Table 9.

Freshwater invertebrates: Polyoxin D zinc salt technical was moderately toxic to *Daphnia magna.* The screening level risk quotients for freshwater invertebrates from acute exposure to polyoxin D zinc salt did not exceed the LOC.

Freshwater fish: Polyoxin D zinc salt technical was demonstrated to be practically non-toxic to carp (*Cyprinus carpio),* but was of moderate toxicity to rainbow trout (*Oncorhynchus mykiss*). The risk quotients for rainbow trout from acute exposure to polyoxin D zinc salt did not exceed the LOC.

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 quotient for acute exposure of amphibians to polyoxin D zinc salt marginally exceeded the LOC (RQ=1.2). Spray buffer zones (1 m default buffer zone) are required to protect sensitive aquatic habitats from spray drift.

Freshwater algae and aquatic vascular plants: Toxicity values, E_bC_{50} of 6.47 mg a.i./L (biomass) and E_rC_{50}: 7.19 mg a.i./L (growth rate) were reported for polyoxin D zinc salt technical for a green algal species (*Selenastrum capricornutum).* The screening level RQ for acute exposure of green algae to polyoxin D zinc salt did not exceed the LOC. A waiver for aquatic vascular plant data was accepted based on the low toxicity of polyoxin D zinc salt to algae, its mode of action specific to inhibition of chitin synthesis, and a long history of use where phytotoxicity has not been observed.

4.2.3 Incident Reports

There were no incidents involving this active ingredient in the PMRA database as of 9 August 2016. A review of American incidents in the EIIS database (1992 to 2015) was also conducted. There were no environment incidents involving polyoxin D zinc salts in the database.

5.0 Value

5.1 Consideration of Benefits

Polyoxin D zinc salt has been used internationally, and for decades as fungicidal products. It is a new active ingredient for disease management in Canada. Polyoxin D zinc salt has a highly specific mode of action. To date, no reports of resitance to polyoxin D or polyoxin D zinc salt have been reported, based on commercial use.

Currently, there are various products (both conventional and non-conventional) registered in Canada for the uses proposed on the product labels of Polyoxin D Zinc Salt 5SC and Polyoxin D Zinc Salt 11.3% WDG (Commercial or Domestic); Appendix I, Tables 10 and 11. The registration of these polyoxin D zinc salt containing products provide Canadian growers with a new mode of action to manage several important fungal diseases on the crops specified on these products' labels, and are applicable to greenhouse and field crops, turfgrass, ornamental and domestic uses.

5.1.1 Acceptable Efficacy Claims

5.2 Effectiveness Against Pests

Efficacy data from thirty-two trials and reports from the published literature were submitted to support twelve use claims for Polyoxin D Zinc Salt 5SC in ginseng, potato, tomato, grape, strawberry, apple, pear, greenhouse ornamentals and two crop groups including cucurbit vegetables (Crop Group 9) and berries and small fruits (Crop Group 13). Both the trial data and

published literature demonstrated the value of Polyoxin D Zinc Salt 5SC in suppressing or controlling the proposed diseases when applied as preventative applications; however, the efficacy of a curative application was only confirmed for the use against powdery mildew on cucurbit vegetables. Based on the value information for these specific uses, the use claims were either supported as proposed or with modifications.

Efficacy data from thirty trials and scientific rationales were submitted to support ten use claims for Polyoxin D Zinc Salt 11.3% WDG and Polyoxin D Zinc Salt 11.3% WDG Domestic on turfgrass and outdoor-grown ornamentals. The results of the trial data coupled with the scientific rationales demonstrated the value of Polyoxin D Zinc Salt 11.3% WDG in suppressing or controlling the crop diseases listed on the proposed labels. Based on the value information provided, the use claims were supported.

5.3 Non-Safety Adverse Effects

There were no adverse effects to any of the crops evaluated in trials conducted at proposed rates for all polyoxin D zinc salt formulations tested. No phytotoxicity or crop injury was reported.

5.4 Supported Uses

Use claims for Polyoxin D Zinc Salt 5SC and Polyoxin D Zinc Salt 11.3% WDG (Commercial or Domestic) fungicides for control or suppression of various fungal diseases on fruits, vegetables, ornamentals (greenhouse and outdoor) and turfgrass were supported according to the use directions provided, or modified based on the outcome of the value assessment. Details of the supported uses are provided in Appendix I, Table 12.

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, that is, 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, polyoxin D zinc salt 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:

- Polyoxin D zinc salt does not meet all Track 1 criteria and it is not expected to form any transformation products that are Track 1 substances. Polyoxin D zinc salt is not expected to persist or bioaccumulate in the environment.

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

6.2 Formulants and Contaminants of Health or Environmental Concern

During the review process, contaminants in the technical and formulants and contaminants in the end-use products are compared against the *List of Pest control Product Formulants and Contaminants of Health or Environmental Concern* maintained in the *Canada Gazette*.[6] The list is used as described in the PMRA Notice of Intent NOI2005-01[7] and is based on existing policies and regulations including DIR99-03 and DIR2006-02,[8] and takes into consideration the Ozone-depleting Substance Regulations, 1998, of the *Canadian Environmental Protection Act* (substances designated under the Montreal Protocol). The PMRA has reached the following conclusions:

- Technical grade polyoxin D zinc salt and the end-use products: Polyoxin D Zinc Salt 5SC, Polyoxin D Zinc Salt 11.3% WDG and Polyoxin D Zinc Salt 11.3% WDG Domestic Fungicides, 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 polyoxin D zinc salt is adequate to define the majority of toxic effects that may result from exposure.

Toxicokinetic parameters indicate that polyoxin D zinc salt is poorly absorbed with over 90% being excreted unchanged directly in the feces. Polyoxin D zinc salt was of low toxicity in laboratory animals even at limit doses. Decrease in absolute weights of liver and spleen were observed for the high dose in a 90-day oral toxicity study in rats. In reproductive and prenatal developmental studies, polyoxin D zinc salt did not adversely affect reproductive capacity or survival over all generations, or embryofetal development. There was no evidence of immunotoxicity or carcinogenicity in rodents. Polyoxin D zinc salt was determined to be non-mutagenic and non-clastogenic in an in vitro micronucleus test. There were no toxicology end points identified. The end-use products are of low acute toxicity by the oral, dermal, and inhalation routes, and are non-irritating or minimally irritating to the eyes and skin. Polyoxin D Zinc Salt 5SC Fungicide is a potential skin sensitizer, while the other end-use products are not.

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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.*

The risk assessment protects against the toxic effects noted above by ensuring that the level of human exposure is well below the lowest dose at which these effects occurred in animal tests.

Polyoxin D zinc salt has a low mammalian toxicity profile and residue levels on food commodities and feed items, and in drinking water are expected to be low. Dietary exposure is not expected to result in a health risk of concern when the product is used according to label instructions. PMRA did not specify an MRL for polyoxin D zinc salt.

With respect to the development of antimicrobial resistance, there is no health risk of concern because polyoxins are not used as antimicrobial drugs and any resistance to polyoxin D that may develop is not likely to cause cross-resistance with clinically important antimicrobial drugs.

7.2 Environmental Risk

Polyoxin D zinc salt is not expected to persist in the environment. Based on the available laboratory studies, no risks of concern were identified to non-target terrestrial or aquatic organisms, except for amphibians where the level of concern was only marginally exceeded. To mitigate potential risks to amphibians, a no-spray buffer zone of 1 m will be required to protect sensitive aquatic habitats from spray drift. Label statements to inform users of potential risks to the environment are also required.

7.3 Value

Polyoxin D zinc salt, the active ingredient of Polyoxin D Zinc Salt 5SC and Polyoxin D Zinc Salt 11.3% WDG (Commercial or Domestic), has been demonstrated to be effective against several important fungal diseases in ginseng, potato, tomato, grape, strawberry, apple, pear, ornamentals (greenhouse and out-door), turfgrass and two crop groups including cucurbit vegetables (Crop Group 9) and berries and small fruits (Crop Group 13). These products can be used as a preventative treatment or in some cases a curative treatment of plant diseases in conjunction with good management practices. The registration of these products provides Canadian growers with a new mode of action to manage some important fungal diseases on the crops and plants specified on these products' labels.

Based on the value information provided, the registration of Polyoxin D Zinc Salt 5SC and Polyoxin D Zinc Salt 11.3% WDG (Commercial or Domestic) to suppress or control fungal diseases in labeled crops is supported.

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 Polyoxin D Zinc Salt Technical and its end-use products: Polyoxin D Zinc Salt 5SC Fungicide, Polyoxin D Zinc Salt 11.3% WDG Fungicide, and Polyoxin D Zinc Salt 11.3% WDG Domestic Fungicide, containing the technical grade active ingredient polyoxin D zinc salt, to suppress or control a broad range of diseases in various crops grown outdoors or under greenhouse conditions.

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

♀	female
♂	male
a.i.	active ingredient
AR	applied radioactivity
AUC0-t	area under the plasma concentration-time curve calculated to the last measured concentration (AUC(0-t))
bw	body weight
CAS	Chemical Abstracts Service
CHL	Chinese hamster lung
cm	centimetre(s)
°C	degrees Celsius
Cmax	maximum serum concentration
d	day(s)
dw	dry weight
EC_{50}	effective concentration on 50% of the population
EDE	estimated daily exposure
EEC	estimated environmental concentration
F0	parental generation
F1	first generation
F2	second generation
FIR	food ingestion rate
FRAC	Fungicide Resistance Action Committee
g	gram(s)
GLP	good laboratory practices
h	hour(s)
ha	hectare(s)
ICR	Institute for Cancer Research
IUPAC	International Union of Pure and Applied Chemistry
kg	kilogram(s)
K_{ow}	n–octanol-water partition coefficient
L	litre(s)
LC_{50}	lethal concentration on 50% of the population
LD_{50}	lethal dose on 50% of the population
LOAEL	lowest observed adverse effect level
m	metre(s)
MAS	maximum average score for 24, 48 and 72 hours
µg	microgram(s)
mg	milligram(s)
MIS	maximum irritation score
mL	millilitre(s)
MRL	maximum residue limit
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
NOEL	no observed effect level

p*K*a	dissociation constant
PMRA	Pest Management Regulatory Agency
PPE	personal protective equipment
ppm	parts per million
SC	suspension concentrate
sRBC	sheep red blood cell
TGAI	technical grade active ingredient
TSMP	Toxic Substances Management Policy
USEPA	United States Environmental Protection Agency
UV	ultraviolet
WDG	water dispersible granule

Appendix I Tables and Figures

Table 1 Toxicity Profile of Technical Polyoxin D Zinc Salt

Study Type/Animal/PMRA #	Study Results
Acute Toxicity	
Acute oral toxicity / Rat, Sprague-Dawley PMRA# 2457310	LD_{50} ♂ > 15000 mg/kg LD_{50} ♀ between 10000 to 15000 mg/kg Low toxicity
Acute dermal toxicity / Rat, Sprague-Dawley PMRA# 2457316	LD_{50} ♂ & ♀ > 2000 mg/kg bw Low toxicity
Acute inhalation toxicity / Rat, Wistar PMRA# 2457317	LC50 ♂ > 2.44 mg/L LC50 ♀ > 2.17 mg/L Low toxicity
Eye irritation / Rabbit, New Zealand White PMRA# 2457319	MAS[a] = 7/110 MIS[b] = 13.7/110 (24 hrs) Minimally irritating
Dermal irritation / Rabbit, New Zealand White PMRA# 2457321	MAS[a] = 0.38/8 MIS[b] = 1.83/8 (1 hr) Minimally irritating
Dermal sensitization (maximization test of Magnusson and Kligman) / Guinea pig, Hartley albino PMRA# 2457322	Positive (mild) Potential dermal sensitizer
Toxicokinetic Study	
Metabolism/toxicokinetics ^{14}C-Polyoxin D (98.0% radiopurity) labelled in the C2 position in the pyrimidine ring / Rat, Crl:CD (SD) PMRA# 2457354	Plasma C_{max} was 0.667 to 1.33 hours after administration and then disappeared rapidly with the $t_{½}$ being 1.59 to 2.57 hours. C_{max} and AUC_{0-t} increased depending on the dose ratio without any significant sex differences. Polyoxin D has low absorption rate and more than 90% was excreted in feces. No dose dependent or sex dependent differences in the absorption, distribution, metabolism, and elimination.

Study Type/Animal/PMRA #	Study Results
Short-term Toxicity	
90-day oral (dietary) / Rat, Fischer PMRA# 2457324	**NOAEL** = 2000 ppm (♂ = 119 mg/kg/d; ♀ = 135 mg/kg/d) **LOAEL** = 20000 ppm (♂ = 1166 mg/kg/d; ♀ = 1333 mg /kg/d) Effects included lower liver and spleen weight.
90-day oral (dietary) / Beagle dog Data-waiver request PMRA# 2457326	Rationale: 1) A 90-Day oral toxicity study is available in the rat and 2) Polyoxin D Zinc Salt Technical has low mammalian toxicity. Waiver request granted
Chronic Toxicity and Oncogenicity	
24-month chronic toxicity / oncogenicity (dietary) Rat, Wistar PMRA# 2457329	NOAEL = 5% of diet (♂ = 2058.7 mg/kg/d; ♀ = 2469.8 mg/kg/d) LOAEL: Not identified No evidence of oncogenicity Non-GLP and test guidelines not specified
24-month chronic toxicity / oncogenicity (dietary) Mouse, ICR PMRA# 2457330	NOAEL = 4% of diet(♂ = 3591 mg/kg/d; ♀ = 4177 mg/kg/d) LOAEL: Not identified No evidence of oncogenicity Non-GLP and test guidelines not specified
Reproductive and Developmental Toxicity	
Multigeneration reproductive toxicity / Rat, Wistar	<u>Parental Toxicity:</u> NOAEL = 1% of diet (10000 ppm; not presented in terms of mg/kg bw/d) LOAEL: Not identified No adverse treatment-related findings <u>Reproductive Toxicity:</u> NOAEL = 1% of diet (10000 ppm) LOAEL: Not identified No adverse treatment-related findings <u>Offspring Toxicity</u> NOAEL = 1% of diet (10000 ppm) LOAEL: Not identified

Study Type/Animal/PMRA #	Study Results
	No adverse treatment-related findings Reduced bodyweight of pups observed at birth in the offspring of the high dose group of the first generation, regained parity with controls by Day 8. Because of low number of litters observed at this time point (n = 5/group) and lack of individual data and details, the observed effect cannot be verified as treatment-related. The study has limited data: parental necropsy findings, male and female reproductive functional parameters, parental and offspring organ weights, and detailed data for histopathology were not presented. Non-GLP and test guidelines not specified
PMRA# 2457331	
Developmental toxicity / Rat, BrlHan:WIST@Jcl	<u>Maternal Toxicity</u> NOAEL = 300 mg/kg/d LOAEL = 1000 mg/kg/d Effects included gross lesions in the stomach (thickening of the limiting ridge) <u>Developmental Toxicity</u> NOAEL = 1000 mg/kg/d LOAEL: Not identified No evidence of teratogenicity
PMRA# 2457334	
Developmental toxicity / Rabbit, Japanese White	<u>Maternal Toxicity</u> NOAEL = 200 mg/kg/d LOAEL = 800 mg/kg/d (slightly lower bodyweight gain) <u>Developmental Toxicity</u> NOAEL = 800 mg/kg/d LOAEL: Not identified No evidence of teratogenicity
PMRA# 2457338	
Neurotoxicity	
90-day neurotoxicity / Rat Data-waiver request PMRA# 2457358	Rationale: Polyoxin D zinc salt is not potentially neurotoxic, not structurally related to other substances that may cause delayed neurotoxicity, has low mammalian toxicity, and has nontoxic mode of action. Waiver request granted
Immunotoxicity	
Mouse 28 day immunotoxicity study / Mouse, Crl:CD®1, ICR, ♀	NOAEL immune response ♀ = 40000 ppm (8034.2 mg/kg/d)

Study Type/Animal/PMRA #	Study Results
PMRA# 2457371	LOAEL: Not identified There were no treatment-related effects on the humoral immune response to the T-dependent antigen, sRBC. No evidence of immunotoxicity
Genotoxicity	
Gene mutation in bacteria / *Salmonella typhimurium* strains TA1535, TA1536, TA1537, TA1538 and *Escherichia coli* strains WP2hcr^{+}, WP2 hcr^{-} PMRA# 2457341	Negative Study is unacceptable due to lack of study details, data, and protocol deficiencies.
Gene mutation in bacteria / *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 and *E. coli* strain WP2 *uvrA* PMRA# 2457343	Negative Nonmutagenic
Gene mutation in bacteria / *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 and *E. coli* strain WP2 *uvrA* PMRA# 2457347	Negative Nonmutagenic
Chromosome aberrations in vitro / CHL/IU cells PMRA# 2457347	Positive Clastogenic with and without metabolic activation
Chromosome aberrations in vitro / CHL cells PMRA# 2457349	Positive Clastogenic with and without metabolic activation
Micronucleus assay in vivo / Mouse, Crj:CD-1 PMRA# 2457352	Negative Nonclastogenic

[a] MAS = Maximum Average Score for 24, 48, and 72 hrs
[b] MIS = Maximum Irritation Score (average)

Table 2 Toxicology Profile of Polyoxin D Zinc Salt 5SC Fungicide

Study Type/Animal/PMRA #	Study Results
Acute Toxicity	
Acute oral toxicity / Rat, Sprague-Dawley PMRA# 2457421	LD_{50} ♀ > 5000 mg/kg bw Low toxicity
Acute dermal toxicity / Rat, Sprague-Dawley PMRA# 2457422	LD_{50} ♂ & ♀: > 5050 mg/kg bw Low toxicity
Acute inhalation toxicity / Rat, Sprague-Dawley PMRA# 2457423	LC_{50} ♂ ♀ > 2.20 mg/L Low toxicity
Eye irritation / Rabbit, New Zealand White PMRA# 2457424	MAS[a] = 0.0, MIS[b] = 4 Non-irritating
Dermal irritation / Rabbit, New Zealand White PMRA# 2457425	MAS = 0.33, MIS = 1 Minimally irritating
Dermal sensitization (Buehler test) / Guinea pig, Hartley albino PMRA# 2457425	Positive (mild) Potential dermal sensitizer

[a] MAS = Maximum Average Score for 24, 48, and 72 hrs
[b] MIS = Maximum Irritation Score (average)

Table 3 Toxicology Profile of Polyoxin D Zinc Salt 11.3% WDG

Study Type/Animal/PMRA #	Study Results
Acute Toxicity	
Acute oral toxicity / Rat, Crj:CD (SD) SPF strain PMRA# 2457464	LD_{50} ♂ ♀ = 5000 mg/kg bw Low toxicity
Acute dermal toxicity / Rat, Crj:CD (SD) SPF strain PMRA# 2457467	LD50 ♂ ♀ > 2000 mg/kg bw Low toxicity

Study Type/Animal/PMRA #	Study Results
Acute inhalation toxicity / Rat, Sprague Dawley SD strain PMRA# 2457468	LC_{50} ♂ ♀ > 2.41 mg/L Low toxicity
Eye irritation / Rabbit, New Zealand White PMRA# 2457469	MAS [a] = 5.66, MIS [b] = 10.83 Minimally irritating
Dermal irritation / Rabbit, New Zealand White PMRA# 2457470	MAS = 0.39, MIS = 1.83 Minimally irritating
Dermal sensitization (Beuhler test) / Guinea pig, Hartley albino PMRA# 2457472	Negative Non-sensitizer

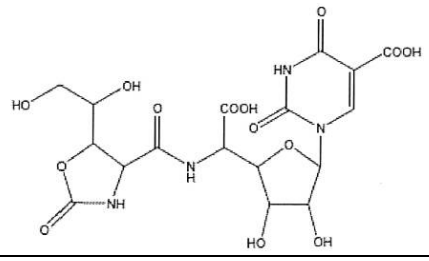
[a]MAS = Maximum Average Score for 24, 48, and 72 hrs
[b]MIS = Maximum Irritation Score (average)

Table 4 Polyoxin D Fate and Behaviour in the Environment

Study	Half-life (days)	pH	Comment	PMRA#
Hydrolysis 25 ºC	32.5	7.0	pH dependant; increased transformation under basic conditions	2457403
	9.1	9.0		
Aqueous photolysis in sterile medium (continuous irradiation)	0.4	natural		2457404
	4.0	5.0		
	2.4	7.0		
	1.6	9.0		
Aerobic soil metabolism	15.9 (non-sterile)	NA	Slightly persistent; major transformation route. Volatile organic chemicals were not detected.	2457398
	59.2 (sterile)	NA		2457399

NA = not applicable

Table 5 Polyoxin D Transformation Products Formed in the Environment

Name	Chemical structure	Related Studies
Polyoxin d1a		Hydrolysis Photolysis

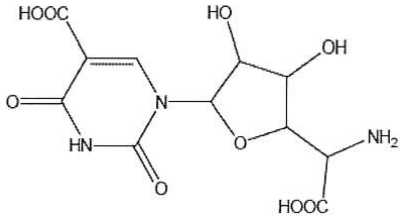
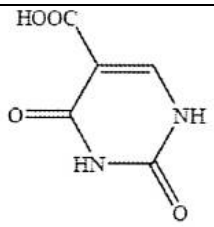
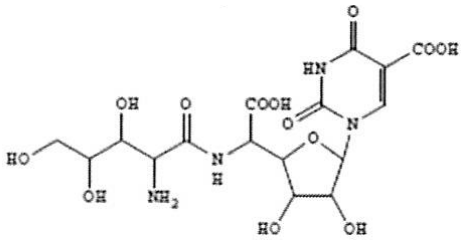
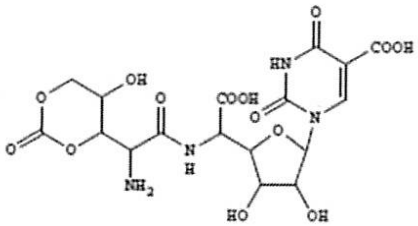
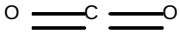
Name	Chemical structure	Related Studies
Polyoxin C acid Polyoxin C-acid zinc salt; 5-amino-1,5-dideoxy-1-(1,2,3,4-tetrahydro-5-carboxy-2,4-dioxopyrimidinyl)-β-D-allofuranuronic acid		Hydrolysis Photolysis Aerobic soil
Uracil-5-Carboxylic Acid		Hydrolysis Photolysis Aerobic soil
Polyoxin d2		Hydrolysis Photolysis
Polyoxin d1b		Hydrolysis Photolysis
Carbon dioxide		Photolysis Aerobic soil

Table 6 Polyoxin D Zinc Salt Toxicity to Non-Target Species

Organisms	Exposure	Endpoint value	Degree of toxicity[a]	PMRA Number
Terrestrial organisms				
Invertebrates				
Earthworm (*Eisenia fetida*)	Acute	14-day LC_{50} > 1000 mg a.i/kg dw of soil (highest dose tested)	NA[b]	2533900
Honeybee (*Apis mellifera* L)	48-h acute contact	LD_{50}> 100 µg a.i./bee (highest dose tested) NOEL: 100µg a i./bee (highest dose tested)	Relatively non-toxic	2533901

Organisms	Exposure	Endpoint value	Degree of toxicity[a]	PMRA Number
Honeybee (*Apis mellifera* L)	48-h acute oral	LD_{50}: 32.885 µg a.i./bee	Relatively non-toxic	2533902
Marmalade hoverfly (*Epistrophus balteatus*)	Acute contact	Adults: 5-day LC_{50}>2100 mg a.i./L (highest dose tested). Larvae: 10-day NOEL: 2100 mg a.i./L (highest dose tested).	NA	2533904
Green Lacewing (*Chrysoperia carnea)*	Acute contact	14-day LC_{50}>2100 mg a.i./L (highest dose tested) 14-day NOEL: 2100 mg/L (highest dose tested)	NA	2533903
Ladybird beetle (adults and third instar larvae) Family *Coccinellidae*	Acute contact (adult) developmental (emergence as adults)	3-day NOEL was 150 mg a.i./L. (mortality and emergence)	NA	2533906
Wolf Spider (*Pardosa laura)*	Acute contact	10-day LC_{50}>2100 mg a.i./L (highest dose tested) 10-day NOEL: 2100 mg a.i./L (highest dose tested)	NA	2533907
Silkworm (*Bombyx mori)*	Developmental dietary toxicity	28-day NOEL was 2100 mg a.i./L (highest dose tested).	NA	2533905
Two spotted mite (*Tetranychus urticae Koch*)	48-h Acute and 5-day mortality and molting (second instar larvae)	LC_{50}>400 µg a.i./mL	NA	2675021
Brown plant hopper (Nilaparvata lugens)	Acute and molting inhibition (third instar larvae)	96-h LC_{50} >400 µg a.i./mL	NA	2675021
Diamond back moth (*Plutella xylostella* L)	48-h molting inhibition; 5-day Cocoon formation ; 10-day occurrence of eclosion	LC_{50}>400 µg a.i./mL	NA	2675021
Vertebrates				
Mallard Duck (*Anas platyrhynchos*)	21-d acute oral	LD_{50}> 2150 mg a.i./kg Highest dose tested	Practically non-toxic	2533915
Mallard Duck (*Anas platyrhynchos*)	8-d acute dietary	LC_{50}> 5000 ppm or LD_{50}>1642 mg a.i./kg bw/day (measured)	Practically non-toxic	2533917
Rat Sprague-Dawley, albino	Acute oral	LD_{50} 10,000 mg a.i./kg bw	Practically non-toxic	2457310

Organisms	Exposure	Endpoint value	Degree of toxicity[a]	PMRA Number
Vascular plants				
Terrestrial/Aquatic Vascular Plants	NA	Waiver rationale based on low toxicity to algae, non-toxic mode of action and no phytotoxicity	NA	2533920
Aquatic Organisms				
Invertebrates				
Daphnia magna	48-h acute	EC_{50}: 1.4 mg a.i./L NOEC: 0.11 mg a.i./L	Moderately toxic	2533909
Freshwater Fish				
Rainbow Trout (*Oncorhynchus mykiss*)	96-h acute	LC_{50}: 5.1 mg a.i./L NOEC: 3.5 mg a.i./L	Moderately toxic	2533910
Common Carp, (*Cyprinus carpio)*	96-h acute	LC_{50} > 100 mg a.i./L NOEC: 100 mg a.i./L	Practically non-toxic	2533911
Freshwater Algae				
Green alga, (*Selenastrum capricornutum)*	48-h acute[c] 72-h acute	E_rC_{50}: 7.19 mg a.i./L (growth rate); E_bC_{50}: 6.47 mg a.i./L (biomass)	NA	2533919

[a] USEPA classification, where applicable
[b] NA: not applicable

Table 7 Screening Level Risk Assessment for Bees

Organism	Exposure	Endpoint value	EEC	RQ	LOC* exceeded?
Bee	Contact	48-h LD_{50} > 100 µg a.i./bee	0.73 µg a.i./bee[a]	<0.007	No
	Oral	48-h LD_{50} : 32.885 µg a.i./bee	8.85 µg a.i./bee[b]	0.27	No

[a]An EEC for contact toxicity to bees is calculated by multiplying the single application rate, in units of kg (that is, 0.305 kg a.i./ha) by a factor of 2.4 µg a.i./bee, which gives an EEC in units that match the toxicity endpoint (µg a.i./bee).
[b]An EEC for oral toxicity to bees is calculated by multiplying the single application rate, in units of kg (that is, 0.305 kg a.i./ha) by a factor of 29 µg a.i./bee, which gives an EEC in units that match the toxicity endpoint (µg a.i./bee).
*Level of Concern (LOC) = 0.4 for bees.

Table 8 Screening Level Risk Assessment for Birds and Mammals

Organism	Acute Toxicity (mg a.i./kg bw/d)	Feeding Guild (food item)	EDE* (mg a.i./kg bw)	RQ	LOC** Exceeded?
Small bird (0.02 kg)	2150.00	Insectivore	49.53	0.02	No
Medium sized bird (0.1 kg)	2150.00	Insectivore	38.66	0.02	No
Large sized bird (1 kg)	2150.00	Herbivore (short grass)	24.97	0.01	No
Small mammal (0.015 g)	1000.00	Insectivore	28.49	0.03	No
Medium sized mammal (0.035 kg)	1000.00	Herbivore (short grass)	55.26	0.06	No
Large sized mammal (1 kg)	1000.00	Herbivore (short grass)	29.53	0.03	No

*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 ≤200 g): FIR (g dry weight/day) = $0.398(\text{bw in g})^{0.850}$
All birds Equation (body weight >200 g): FIR (g dry weight/day) = $0.648\ (\text{bw in g})^{0.651}$
For mammals, the "all mammals" equation was used: FIR (g dry weight/day) = $0.235(\text{bw in g})^{0.822}$ (Note: For birds, the acute toxicity value was not adjusted as there were no effects seen at the highest concentration tested. For mammals, the acute toxicity value was adjusted for the risk assessment, that is, toxicity value/10).
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.
**Level of concern (LOC) = 1 for birds.*

Table 9 Screening Level Risk Assessment for Aquatic Organisms

Organism	Exposure	Endpoint value[1]	EEC[2]	RQ[3]	LOC[4] exceeded?
Freshwater invertebrates					
Daphnia magna	48 h Acute	EC_{50}: 0.7 mg a.i./L	0.11 mg a.i./L	0.15	No
Freshwater vertebrates					
Oncorhynchus mykiss	96 h Acute	LC_{50}: 0.51 mg a.i./L	0.11 mg a.i./L	0.21	No
Amphibians (surrogate: *Oncorhynchus mykiss*)	96 h Acute	LC_{50}: 0.51 mg a.i./L	0.61 mg a.i./L	1.2	Yes[5]
Freshwater algae					
Green algae (*Selenastrum capricornutum*)	48 h	EC_{50}: 3.6 mg a.i./L	0.11 mg a.i./L	0.03	No

[1] The endpoint value from the toxicity study is adjusted by dividing it by an uncertainty factor (2 for invertebrates and 10 for vertebrates) for calculating the risk quotient. This is to account for potential differences in species sensitivity as well as varying protection goals (that is, protection at the community, population, or individual level).
[2] Estimated environmental concentration (EEC) was based on the cumulative total of three applications of 305 g a.i./ha, and no dissipation between applications (915 g a.i./ha), in an 80 cm (0.11 mg a.i./L) and 15 cm (0.61 mg a.i./L) depth of water.
[3] Risk quotient (RQ) = [EEC / Endpoint value $_{adjusted}$]
[4] Level of concern (LOC) = 1 for aquatic organisms.
[5] In a refined risk assessment, considering only 11% spray drift deposition to aquatic habitats, the LOC was not exceeded.

Table 10 Registered Alternatives, based on mode of action, for the uses on Polyoxin D Zinc Salt 5SC Fungicide (current to February 2016)

Crop	Pest	Mode of Action (FRAC Fungicide Group No.)	
		Conventional	Non-conventional
Ginseng	Botrytis blight (*Botrytis cinerea*)	7, 9, 12, 17, 29, 9+12, M5	NC (Suppression)
Potato	Early blight (*Alternaria solani*)	3, 4, 7, 9, 11, 22, 28, 40, 44, M1, M3, M5, M3+4, M3+11, M3+22, M5+3, M5+4, M5+7, 3+11, 7+9, 11+27	
Tomato	Early blight (*Alternaria solani*)	3, 7, 9, 11, 28, M1, M3, 3+11, 11+27	44 (Suppression)
Cucurbit Vegetables	Gummy stem blight (*Didymella bryoniae*)	3, 7, 11, 29, M3, 3+9, 3+11, 7+11	44, NC (Suppression)
	Powdery mildew (*Podosphaera xanthii*)	3, 7, 11, 13, M2, M3, M4, M5, 3+11, 7+M5, 7+11, 9+12	44, P5, NC (Suppression)

Apples and Pears	Powdery mildew (*Podosphaera leucotricha*)	3, 7, 11, U8, 3+9, 7+9, 7+11	44, P5, NC (Suppression)
Blueberries	Grey mold (*Botrytis cinerea*)	1, 7, 9, 17, M3, 7+11, 9+12	44, P5 (Suppression)
Grapes	Grey mold (*Botrytis cinerea*)	1, 2, 7, 9, 17, 7+9, 9+12	44, P5, NC (Suppression)
	Powdery mildew (*Erysiphe necator*)	3, 7, 11, 13, 17, 22, U8, M1, M2, M3, M4, 7+9, 7+11	44, P5, NC (Suppression)
Strawberries	Grey mold (*Botrytis cinerea*)	1, 2, 7, 9, 17, 29, M5, 7+11, 9+12	44, P5, NC (Suppression)
	Powdery mildew (*Sphacelotheca macularis*)	3, 7, 11, M2, 7+11	P5, NC (Suppression)
Ornamentals (Greenhouse)	Botrytis blight, grey mold (*Botrytis cinerea*)	1, 2, 11, 14, M1, M4, M5	44, NC (Suppression)

Table 11 Registered Alternatives, based on mode of action, for the uses on Polyoxin D Zinc Salt 5SC 11.3% WDG Fungicide, Commercial or Domestic (current to February 2016)

Crop	Pest	Mode of Action (FRAC Fungicide Group No.)	
		Conventional	Non-conventional
Turf	Anthracnose (*Colletotrichum cereale*)	3, 7, 11, 12, M5, 3+11, 3+M5, 2+3+11	44, P5 (Suppression), NC
	Brown patch (*Rhizoctonia solani*)	1, 2, 3, 7, 11, 12, M3, M5, 3+11, 3+M5	44 (Suppression)
	Brown ring patch / Waitea patch (*Waitea circinata* var. *circinata*)	3, 11, 3+11	
	Fairy ring (various Basidiomycetes)	11, 3+11	
	Red thread (*Laetisaria fuciformis*)	3, 3+11, 3+M5	
	Leaf spot and melting-out disease (*Drechslera poae*)	2, 3, 11, 12, M3, M5, 3+11, 3+M5	
	Yellow patch *(Rhizoctonia cerealis*)	3, 3+M5	
	Pink snow mould (*Microdochium nivale)*	1, 2, 3, 11, 12, M5, 3+11, 2+3+11, 3+12+M5	NC (Suppression)
	Grey snow mould (*Typhula incarnata*)	2, 3, 11, M5, 3+11	

Crop	Pest	Mode of Action (FRAC Fungicide Group No.)	
	(*Typhula ishikariensis*)		
Outdoor ornamentals	Botrytis blight, grey mould (*Botrytis cinerea*)	1, 2, 11, 12, 17, M1, M4, M5	44, NC (Suppression)

Table 12 List of Supported Uses

Supported use claims for Polyoxin D Zinc Salt 5SC Fungicide
1. Preventative control of botrytis blight (*Botrytis cinerea*) on ginseng at rates of 611–1222 mL/1000 L (33–66 g a.i./1000 L) with three applications per season, apply on a 7 day interval.
2. Preventative suppression of early blight (*Alternaria solani*) on potato and tomato at rates of 537–926 mL/ha (29–50 g a.i./ha) with maximum 150 g a.i./ha per season, apply on a 7-14 day interval.
3. Preventative suppression of gummy stem blight (*Didymella bryoniae*), and preventative control and curative suppression of powdery mildew (*Podosphaera xanthii*) on cucurbit vegetables (Crop Group 9) at rates of 463-926 mL/ha (25-50 g a.i./ha) with maximum 150 g a.i./ha per season, apply on a 7-14 day interval.
4. Preventative suppression of powdery mildew (*Podosphaera leucotricha*) on apple and pear (Crop Group 11) at rates of 259-926 mL/ha (14 - 50 g a.i./ha) with maximum 150 g a.i./ha per season, apply on a 7-14 day interval.
5. Preventative suppression of botrytis blight and grey mold (*Botrytis cinerea*) on berries and small fruits, *excluding* grapes (Crop Croup 13) at rates of 463-926 mL/ha (25-50 g a.i./ha) with maximum 150 g a.i./ha per season, apply on a 7-14 day interval.
6-1. Preventative suppression of bunch rot and grey mold *(Botrytis cinerea)* on grape at rates of 463-926 mL/ha (25-50 g a.i./ha) with maximum 150 g a.i./ha per season, apply with a re-application interval based on grape growth stages as described on the label. 6-2. Preventative control of powdery mildew (*Erysiphe necator*) on grape at rates of 259-926 mL/ha (14 - 50 g a.i./ha) with maximum 150 g a.i./ha per season, apply on a 7-14 day interval.
7-1. Preventative suppression of grey mold (*Botrytis cinerea*) on strawberries (Crop Croup 13) at rates of 259-926 mL/ha (14-50 g a.i./ha) with maximum 150 g a.i./ha per season, apply on a 7-14 day interval. 7-2. Preventative suppression of powdery mildew (*Podosphaera aphanis*) on strawberries (Crop Croup 13) at rates of 259-926 mL/ha (14-50 g a.i./ha) with maximum 150 g a.i./ha per season, apply on a 7-10 day interval.
8. Preventative suppression of botrytis blight and grey mold (*Botrytis cinerea*) on greenhouse ornamentals at rates of 315–1222 mL/1000 L (17–66 g a.i./1000 L) with maximum three applications per growing season, apply on a 7-14 day interval.

Supported use claims for Polyoxin D Zinc Salt 11.3% WDG Fungicide (Commercial or Domestic)
1. Preventative and curative control of anthracnose (*Colletotrichum cereale*), brown ring patch/waitea patch (*Waitea circinata*, var. *circinata*) and red thread (*Laetisaria fuciformis*) on turfgrass at a rate of 27 g/100 m^2 when applied maximum three times per growing season on a 14 day interval.
2. Preventative control of brown patch (*Rhizoctonia solani*), leaf spot/melting out disease (*Drechslera poae*) and yellow patch (*Rhizoctonia cerealis*) on turfgrass at a rate of 27 g/100 m^2 when applied maximum three times per growing season on a 14 day interval.
3. Preventative suppression of pink snow mould (*Microdochium nivale*) and grey snow mould (*Typhula incarnata* and *Typhula ishikariensis*) on turfgrass before spring green-up or curative suppression of the same diseases at spring green-up at a rate of 27 g/100 m^2 when applied with maximum three times per growing season on a 21 day interval.
4. Preventative and curative control of type I and type II fairy ring (various Basidiomycetes) on turfgrass at a rate of 27 g/100 m^2 when applied maximum three times per growing season on a 7-14 day interval. A non-ionic surfactant is required for the use.
5. Preventative suppression of botrytis blight, grey mold (*Botrytis cinerea*) on outdoor ornamentals at rates of 150–584 g/1000 L (17–66 g a.i./1000 L) with maximum three times per growing season, apply on a 7-14 day interval.

References

A. List of Studies/Information Submitted by Registrant

1.0 Chemistry

PMRA Document Number	Reference
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2457263	2013, Polyoxin D Zinc Salt Technical: USEPA Accepted Confidential Statement of Formula (November 8, 2013), DACO: 2.12 CBI
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2457267	2013, Polyoxin D Zinc Salt Technical: Preliminary Analysis and Certified Limits (Final Report): CONFIDENTIAL APPENDIX, DACO: 2.12.1,2.13.2,2.13.3,2.13.4 CBI
2457268	2013, Polyoxin D Zinc Salt Technical: Analytical Methods for the Quantification of Polyoxin D Zinc Salt and Selected Impurities: CONFIDENTIAL APPENDIX, DACO: 2.13.1 CBI
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2457272	1994, Physical and Chemical Properties of Polyoxin D Zinc Salt Technical Grade Active Ingredient (Color, Physical State, Odor, Melting Point, Density, Solubility, Dissociation Constant, pH, and Stability): Amended Final Report, DACO: 2.14.1,2.14.10,2.14.12,2.14.13,2.14.2,2.14.3,2.14.4,2.14.6,2.14.7, 2.14.8,2.16 CBI
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2457413	2012, Polyoxin D Zinc Salt 5SC: Analytical Method Validation for the Determination of Polyoxin D Zinc Salt, DACO: 3.4.1 CBI
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2553861	2015, Polyoxin D Zinc Salt 11.3% WDG Fungicide and Polyoxin D Zinc Salt 11.3% WDG Domestic Fungicide: Description of Starting Materials: Confidential Appendix, DACO: 3.2.1 CBI

PMRA Document Number	Reference
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2457437	2004, Product Chemistry, Composition and Analysis of Endorse WDG (TM-43802), DACO: 3.2.1,3.2.2,3.2.3,3.3.1,3.4.1,3.6 CBI
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2457457	2014, ENDORSE Water Dispersible Granules: Physical-Chemical Characteristics Data Waiver Request Rationales, DACO: 3.5.11,3.5.13,3.5.15,3.5.9 CBI
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2617068	2004, Enforcement method validation WDG 02-25-2016, DACO: 3.4.1 CBI

2.0 Human and Animal Health

PMRA Document Number	Reference
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2457293	2011, Toxicology Summary for a Tolerance Exemption Petition, DACO: 4.1
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3.0 Environment

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4.0 Value

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