Health Canada Santé Canada

Evaluation Report for Category A, Subcategory 1.3 Application

Application Number: 2014-3908
Application: New Active Ingredient – Maximum Residue Limits (MRL)s only
Product: Polyoxin D Zinc Salt Technical
Registration Number: N/A
Active ingredient (a.i.): Polyoxin D Zinc Salt
PMRA Document Number: 2643583

Purpose of Application

The purpose of this application was to determine if an import MRL for Polyoxin D Zinc Salt Technical on food commodities treated in the United States would be required.

Chemistry Assessment

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	$C_{17}H_{21}N_5O_{14}Zn$
Molecular weight	584.8

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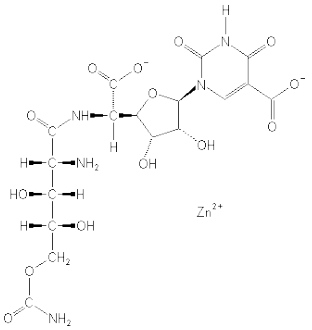
Structural formula



Purity of the active ingredient 23.8%

Physical and Chemical Properties of the Active Ingredient

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	< 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	Very soluble Polyoxin D solubility: 35.4 g/L, pH 3.5, 30°C
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
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.

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.

Methods for Residue Analysis
No methods are required to quantify residues of polyoxin D zinc salt due to its low toxicity.

Health Assessments

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 to 2.7% and 91.8 to 94.1% of the dose, respectively by 96 hours postdosing, i.e., more than 90% of the dose was excreted into 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 to 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% to 90% of the radioactivity in each sample, while the major metabolite in liver was uracil-5 carboxylic acid accounting for 54% to 80% of the radioactivity. Two unknown metabolites were detected only in feces, which were considered to be degradates produced by the gastrointestinal tract (GIT). 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.

In a 90-Day oral toxicity study on rats, polyoxin D zinc salt had a low subchronic oral toxicity. 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 for 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, 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 embryofoetal 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 embryofoetal development parameters at any doses.

In a two-generation reproductive study in rats, treatment with polyoxin D zinc salt up to 1% of diet did not produce any adverse effects on reproductive capacity of the F_0, F_1 and F_2 generations or survival over all generations. Also, there were no treatment-related adverse effects on embryofoetal development from selected animals of the F_1 and F_2 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.

The results of the toxicology studies conducted in vitro and on laboratory animals with polyoxin D zinc salt are summarized in Appendix I Table 1.

Occupational and Residential Risk Assessment
As this was an import MRL application, an occupational or a residential risk assessment was not required.

Food Residue Exposure Assessment

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. Residue levels on crops are expected to be low based on the residue data from metabolism studies, application rates which are very low and the expected degradation of residues in the field. For these reasons, no adverse effects are anticipated from the presence of residues on imported food commodities.

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

Drinking Water
As the current application pertains to imported food commodities only, there is no risk due to exposure from drinking water.

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 commodities 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 (PCPA) for the purposes of the adulteration provision of the Food and Drugs Act (FDA). 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 very 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 (i.e., washing) will also further reduce residue levels on crops and processed commodities. Furthermore, application rates are very low and the use pattern of polyoxin D zinc salt is unlikely to change due to the fungicide resistance management recommendations presented on products containing polyoxin D zinc salt as the active ingredient which strictly limits the number of applications per season. Consequently, an import MRL for food commodities treated with polyoxin D zinc salt will not be specified.

Antimicrobial Resistance Assessment

No health risk of concern is expected due to the development of antimicrobial resistance from importation of food commodities treated with polyoxin D zinc salt.

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 U.S. as human or veterinary drugs. Polyoxin D has been shown to be 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.

Resistance to polyoxins has been noted in plant pathogenic fungi and this has been attributed to changes in the uptake of polyoxin into fungal cells or efflux by drug transporters. Polyoxin-resistant mutants of *Candida albicans* exhibited cross-resistance with other dipeptide antibiotics (e.g., bacilysin). There have, however, been no reports of the use of dipeptide antibiotics for treatment of fungal diseases in humans or animals.

Therefore, any residues that may remain on treated crops are not of concern as polyoxins, nikkomycins and dipeptide antibiotics are not considered to be clinically important antimicrobial drugs.

Environmental and Value Assessments

Environmental and value assessments were not required for this application.

Conclusion

The Pest Management Regulatory Agency has completed an assessment of the information provided in support of the product, Polyoxin D Zinc Salt Technical, and has found the information sufficient to determine that an import MRL for polyoxin D zinc salt is not required.

Appendix I Tables and Figures

Table 1 Acute Toxicity of Polyoxin D Zinc Salt Technical

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	LC_{50} ♂ > 2.44 mg/L LC_{50} ♀ > 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] = 0.39/8 MIS [b] = 1.83/8 (1 hr) Minimally irritating
Dermal Sensitization (Maximization test of Magnusson and Kligman) Guinea pig/Hartley albino PMRA# 2457322	Positive Potential dermal sensitizer

Study Type/Animal/PMRA #	Study Results
Toxicokinetic Study	
Metabolism/Toxicokinetics ^{14}C-Polyoxin D (98.0% radiopurity) labelled in the C2 position in the pyrimidine ring Rats, 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 into feces. No dose dependent or sex dependent differences in the absorption, distribution, metabolism, and elimination.
Short-term toxicity	
90-day oral (dietary) Rat (Fischer) PMRA# 2457324	**NOAEL** = 2000 ppm (♂ = 119 mg/kg bw/d; ♀ = 135 mg/kg bw/d) **LOAEL** = 20000 ppm (♂ = 1166 mg/kg bw/d; ♀ = 1333 mg /kg bw/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 bw/d; ♀ = 2469.8 mg/kg bw/d) LOAEL: Not identified No evidence of oncogenicity Non-GLP and test guidelines not specified
24-month chronic toxicity / oncogenicity (dietary) Mice (ICR) PMRA# 2457330	NOAEL = 4% of diet(♂ = 3591 mg/kg bw/d; ♀ = 4177 mg/kg bw/d) LOAEL: Not identified No evidence of oncogenicity Non-GLP and test guidelines not specified

Study Type/Animal/PMRA #	Study Results
Reproductive and developmental toxicity	
Multigeneration reproductive toxicity Rat (Wistar) PMRA# 2457331	<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 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
Developmental toxicity Rat (BrlHan:WIST@Jcl) PMRA# 2457334	<u>Maternal Toxicity</u> NOAEL = 300 mg/kg bw/d LOAEL = 1000 mg/kg bw/d Effects included gross lesions in the stomach (thickening of the limiting ridge) <u>Developmental Toxicity</u> NOAEL = 1000 mg/kg bw/d LOAEL: Not identified No evidence of teratogenicity

Study Type/Animal/PMRA #	Study Results
Developmental toxicity Rabbit (Japanese White rabbits) PMRA# 2457338	<u>Maternal Toxicity</u> NOAEL = 200 mg/kg bw/d LOAEL = 800mg/kg bw/d (slightly lower bodyweight gain) <u>Developmental Toxicity</u> NOAEL = 800 mg/kg bw/d LOAEL: Not identified No evidence of teratogenicity
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, ♀) PMRA# 2457371	NOAEL immune response ♀ = 40000 ppm (8034.2 mg/kg bw/d) 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 *Escherichia coli* strains WP2hcr$^+$ WP2 hcr$^-$ PMRA# 2457341	Negative Study is unacceptable due to lack of study details, data, and protocol deficiencies.

Study Type/Animal/PMRA #	Study Results
Gene mutation in bacteria *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 *E. coli* strain WP2 *uvrA* PMRA# 2457343	Negative Nonmutagenic
Gene mutation in bacteria *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 *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 PMRA# 2457349	Positive Clastogenic with and without metabolic activation
Micronucleus assay (*in vivo*) Mouse (Crj:CD-1) PMRA# 2457352	Negative Nonclastogenic

References

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