United States Department of Agriculture
Agricultural Marketing Service | National Organic Program
Document Cover Sheet
https://www.ams.usda.gov/rules-regulations/organic/national-list/petitioned

Document Type:

☐ **National List Petition or Petition Update**

A petition is a request to amend the USDA National Organic Program's National List of Allowed and Prohibited Substances (National List).

Any person may submit a petition to have a substance evaluated by the National Organic Standards Board (7 CFR 205.607(a)).

Guidelines for submitting a petition are available in the NOP Handbook as NOP 3011, National List Petition Guidelines.

Petitions are posted for the public on the NOP website for Petitioned Substances.

☒ **Technical Report**

A technical report is developed in response to a petition to amend the National List. Reports are also developed to assist in the review of substances that are already on the National List.

Technical reports are completed by third-party contractors and are available to the public on the NOP website for Petitioned Substances.

Contractor names and dates completed are available in the report.

Polyoxin D Zinc Salt

Crops

Identification of Petitioned Substance

Chemical Names:
Polyoxin D, Zinc Salt; $C_{17}H_{23}N_5O_{14}Zn$; 5-Pyrimidinecarboxylic acid, 1-(5-(2-amino-2-deoxy-L-xylonamino)-5-deoxy-beta-D-allofuranuronosyl)-1,2,3,4-tetrahydro-2,4-dioxo-, monocarbamate (ester), zinc salt; Polyoxorim-zinc;Polyoxin D zinc salt;Polyoxorim-zinc [iso];beta-D-Allofuranuronic acid, 5-((2-amino-5-o-(aminocarbonyl)-2-deoxy-L-xylonoyl)amino)-1-(5-carboxy-3,4-dihydro-2,4-dioxo-1(2H)-pyrimidinyl)-1,5-dideoxy-, zinc salt (1:1); Zinc 5-[[2-amino-5-O-(aminocarbonyl)-2-deoxy-L-xylonoyl]-1-(5-carboxy-3,4-dihydro-2,4-dioxo-7 1(2H)-pyrimidinyl)-1,5-dideoxy-ß-D-8 allofuranuronate]; Allofuranuronic acid, 5-((2-amino-5-o- (aminocarbonyl)-2-deoxy-L-xylonoyl)amino)-1- 14 (5-carboxy-3,4-dihydro-2,4-dioxo-1(2H)- 15 pyrimidinyl)-1,5-dideoxy-, zinc salt (1:1); Zinc,1-[(3R,4S,5R)-5-[[[(2R,3R,4R)-2-amino-5-carbamoyloxy-3,4-dihydroxypentanoyl]amino]-carboxylatomethyl]-3,4-dihydroxyoxolan-2-yl]-2,4-dioxopyrimidine-5-carboxylate;

Other Name:
Polyoxin D, Zinc Salt
POLYOXIND-ZN
Polyoxorim-Zinc
Polyoxorim Zinc Salt
Polyoxorim-Zinc [ISO]

Trade Names:
Endorse ™; Ph-D™ Fungicide; Affirm™ Water Dispersible Granules; STOPIT™ ; Veranda™, Veggieturbo 5SC suspension concentrate fungicide; OSO™ 5% SC; TAVANO™ 5%SC Fungicide; ESTEEM™ Poloyoxin D Salt; Novel 0.5% SC Fungicide

CAS Numbers:
33401-46-6
22976-86-9 (W/O zinc salt)
146659-78-1

Other Codes:
F48U67E18L (FDA)
PC230000 (EPA)
EPA Reg. No. 68173-1
169507 (PubChem)
72476 (Polyoxin D: Parent CID)
23994, 72476 (zinc, Polyoxin D, respectively)
Ccris 9108 (PubChem)
AC1Q2375 (PubChem)
AM020580 (PubChem)
LS-189236 (PubChem)

Summary of Petitioned Use

Polyoxin D Zinc Salt is petitioned for use in the production of fungicides for use on almonds, cucurbit vegetables, fruiting, vegetables, ginseng, grapes, pistachios, pome fruits, potatoes, strawberries, ornamentals, golf courses, residential lawns, parks, and commercial and institutional grounds (EPA amendment, Nov 12, 2008).

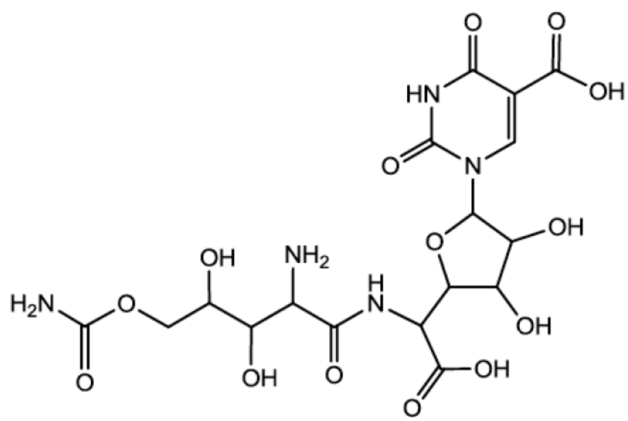
Characterization of Petitioned Substance

Composition of the Substance:

The chemical structure of Polyoxin D (without Zinc salt) is presented below in Figure 1. Polyoxin D is composed of a six membered ring, resembling a lactam analog, conjugated to a hydroxylated five membered ring resembling a substituted furan. An amide side chain is connected to the five-membered ring.

Polyoxin D Zinc Salt is a fungicide with the ability to fight a range of agricultural pests such as: *Alternaria* leaf blight, *Botrytis*, powdery mildew. It is produced by the naturally occurring microbe: *Streptomyces cacaoi* var *asoensis* and *S. piomogenus* (Certis USA, 2012 Press release). Molecular Formula: C17H23N5O14 · Zn (Chemical Register, 2012).

Figure 1
Polyoxin D



Source: ChemBioFinder: 2012
Note: The zinc salt is of the form polyoxin D · Zn

Source or Origin of the Substance:

Naturally produced by microbe: *Streptomyces cacaoi* var *asoensis* and *S. piomogenus* (Certis USA, 2012 Press release).

The physical properties of Polyoxin D Zinc Salt can be found in Table 1.

Table 1: Physical Properties of Polyoxin D Zinc Salt

Physical or Chemical Property	Value
Molecular Weight	586.8
Physical State	Powder
Appearance	Brown
Odor	Musty
Melting Point	Approximately 170 °C
Water Solubility (25 °C)	At pH 5 – Measured concentration = 663 mg/L for an initial concentration of 2060 mg/L (32.2%) and 2250 mg/L for 30900 mg/L (7.3 %) At pH 7: Measured concentration = 1770 mg/L for an initial concentration of 2060 mg/L (85.9%) and 3160 mg/L for 30900 mg/L (10.2%)

	At pH 9: Measured concentration = 931 mg/L for an initial concentration of 2060 mg/L (45.2%) and 1120 mg/L for 30900 mg/L (3.6%)
Water Solubility of Polyoxin D (without zinc)	35.4 g/L at 30°C and pH = 3.5
Dissociation Constants	pKa = 3.25, 41.6, 8.00, 9.56, 10.5
Density	1.8392 g/mL at 26.9 °C
pH	7.19 at 25 °C, 1% aqueous mixture
Viscosity	800 mPs.s at 23 °C, 515 mPs.s at 43.5 °C
Flammability	Flash Point > 232 °C
Stability	Stable at 0 and 12 °C (96 hrs); Complete degradation (95.8%) at 54 °C for 14 days; no change to metals zinc and iron foil; unstable in sunlight 39.3 % degradation in 24 hrs
Storage Stability	100% up to 12 months, slightly decreased 3% during 24 months, and in 4 yrs decreased about 5%

Source: EPA Staff report for ESTEEM™ November 2015 and EPA office of pesticide programs July 2003

Specific Uses of the Substance:

Agricultural fungicide; antifungal pharmaceutical.

Approved Legal Uses of the Substance:

EPA Registered (EPA Reg. No. 68173-1)
FDA Registered. (F48U67E18L)

Action of the Substance:

Polyoxin D Zinc Salt stops the growth of the target fungal plant pathogens by competing with uridine diphosphate-N-acetylglycosamine, which is required to form chitin. Insufficient chitin leads to reduced cell wall growth and loss of pathogenicity. (EPA Staff report for ESTEEM™ November 2015)

Combinations of the Substance:

Polyoxin D Zinc Salt pesticides that are used by farmers are formulated with undisclosed inert ingredients. The preferred surfactants used in the dry flowable form are formalin sodium naphthalenesulfonate or nonionic polyoxyethylene alkyl ethers (Tokumura, et al., 2001). Polyoxin D Zinc Salt may also be mixed with 60 other fungicides (Source: NOP report 2012).

Status

Historic Use:

First discovered from cultured *Streptomyces cacaoi ver. Asonesis* from Kumamoto in Japan in 1962. First registered in Japan in 1968 and used as a fungicide (EPA Staff report for ESTEEM™ November 2015). In 1994, Kaken Pharmaceutical Company, Ltd submitted applications to register Polyoxin D Zinc Salt technical and product STOPIT™ Wettable Powder Turf. In 1995 the Biopesticides and Pollution Prevention Division (BPPD) classified Polyoxin D zinc salt as a 'gray area pesticide.' (EPA office of pesticide programs July 2003). In 2008, Polyoxin D Zinc Salt was registered for food use. Recently, the EPA established a tolerance for Polyoxin D Zinc Salt residues in/on all food commodities. (Certis USA, 2012 Press release). Use by country: Japan (Food use: over 40 years; Non-food use: over 31 years), Taiwan (Food use: over 29 years), Korea (Food use: over 25 years), US (Food use: over 6 years, non-food use: over 17 years), Mexico (Food use: over 4 years, non-food use: over 7 years) (source: Esteem™ Kaken Pharmaceutical report 2015) In US specifically Polyoxin D Zinc Salt has been used as a fungicide on a variety of crops such as: tree nuts, vegetables, and fruit.

Presently (and according to the previous NOP report), Polyoxin D Zinc Salt is not approved for organic use as it does not appear on the list of allowed substances for crop production (Sources: NOP report 2012 & 2017 GPO regulation, Title 7)

Organic Foods Production Act, USDA Final Rule:
Not listed in OFPA or USDA NOP

International

Describe the status of the substance among international organizations. Specifically, the report should address whether the petitioned substance is allowed or prohibited for use in other international organic standards such as:

Canada - Canadian General Standards Board Permitted Substances List.
As observed in the previous NOP report, Polyoxin D Zinc Salt does not appear on the CGSB permitted substances List (CGSB, 2015)

CODEX Alimentarius Commission, Guidelines for the Production, Processing, Labelling and Marketing of Organically Produced Foods (GL 32-1999) -
ftp://ftp.fao.org/docrep/fao/010/a1385e/a1385e00.pdf

As observed in the previous NOP report, Polyoxin D Zinc Salt does not appear on the Codex Alimentarius Commission's guidelines for the *Production, Processing, Marketing and Labelling of Organically Produced Foods*. (Codex 2007)

European Economic Community (EEC) Council Regulation, EC No. 834/2007 and 889/2008
http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2008:250:0001:0084:EN:PDF

As observed in the previous NOP report, the European Union regulation requires all authorized plant protection products to appear on a list of 85 permitted inputs (EC, 2007). Polyoxin D Zinc Salt does not appear on the list of authorized plant protection 86 products and is therefore not allowed (EC, 2008 and Biopesticides Data Base University of HertfordShire).

Japan Agricultural Standard (JAS) for Organic Production—
http://www.maff.go.jp/e/jas/specific/criteria_o.html

As observed in the previous NOP report, the Japanese Agricultural Standard for Organic Production does not include Polyoxin D Zinc Salt on Table 2. (JMAFF, 2012).

International Federation of Organic Agriculture Movements (IFOAM) –
http://www.ifoam.bio/en/ifoam-norms

Polyoxin D Zinc Salt does not appear on Appendix 2 of the 2014 IFOAM Basic Standards (IFOAM, 2005). No dossier has been received at the time of this report.

Evaluation Questions for Substances to be used in Organic Crop or Livestock Production

Evaluation Question #1: Indicate which category in OFPA that the substance falls under: (A) Does the substance contain an active ingredient in any of the following categories: copper and sulfur compounds, toxins derived from bacteria; pheromones, soaps, horticultural oils, fish emulsions, treated seed, vitamins and minerals; livestock parasiticides and medicines and production aids including netting, tree wraps and seals, insect traps, sticky barriers, row covers, and equipment cleansers? (B) Is the substance a synthetic inert ingredient that is not classified by the EPA as inerts of toxicological

concern (i.e., EPA List 4 inerts) (7 U.S.C. § 6517(c)(1)(B)(ii))? Is the synthetic substance an inert ingredient which is not on EPA List 4, but is exempt from a requirement of a tolerance, per 40 CFR part 180?

Polyoxin D Zinc Salt is a toxin derived from *Streptomyces cacaoi* var. asoensis, a soil-borne microorganism.

Evaluation Question #2: Describe the most prevalent processes used to manufacture or formulate the petitioned substance. Further, describe any chemical change that may occur during manufacture or formulation of the petitioned substance when this substance is extracted from naturally occurring plant, animal, or mineral sources (7 U.S.C. § 6502 (21)).

Polyoxin D is produced by controlled aerobic fermentation of the naturally occurring soil microorganism *Streptomyces cacaoi ver. Asonesis*. The precise details of this fermentation and the insertion of the zinc salt are not disclosed in the public version. However, information is presented such that Polyoxin D without the zinc salt is extremely water soluble, and therefore not as useful as a fungicide product. By using it as zinc salt, it becomes much more stable and increases the longevity of the fungicide (Source: Fungicide Review 2010).

Evaluation Question #3: Discuss whether the petitioned substance is formulated or manufactured by a chemical process, or created by naturally occurring biological processes (7 U.S.C. § 6502 (21)).

Poloxin D without the zinc salt is isolated through a natural, aerobic fermentation process. Polyoxin D is then converted into the zinc salt using an aqueous process. Because Polyoxin D Zinc Salt is not found naturally, it is usually considered a synthetic compound (Kaken Pharmaceutical Petition, 2016).

Evaluation Question #4: Describe the persistence or concentration of the petitioned substance and/or its by-products in the environment (7 U.S.C. § 6518 (m) (2)).

Soil half-life from aerobic microbial metabolism is reported to be 15.9 days (Esteem Report). Polyoxin D Zinc Salt was shown to undergo aqueous abiotic hydrolysis at pH = 7 and pH = 9 (Esteem Report). Photolytic degradation was observed, DT_{50} = 1.6 d in spring conditions (Esteem Report). Data reviewed by EPA indicated that polyoxin D Zinc Salt biodegrades within 2-3 days of application, with a low toxicity profile [73 FR 69559]. Polyoxin D Zinc Salt degrades very quickly in alkaline soil or in alkaline solutions, and some sources recommend a pH a buffer in the spray tank (Vincelli and Williams, 2012).

Evaluation Question #5: Describe the toxicity and mode of action of the substance and of its breakdown products and any contaminants. Describe the persistence and areas of concentration in the environment of the substance and its breakdown products (7 U.S.C. § 6518 (m) (2)).

In animal models, Polyoxin D Zinc Salt was shown to have very low acute toxicity by oral, dermal, and inhalation routes. Only very minor skin irritation was observed for Polyoxin D Zinc Salt, which was not sufficient to warrant classification. Polyoxin D Zinc Salt was shown to cause mild eye irritation. Polyoxin D Zinc Salt was shown not to be a contact sensitizer. Polyoxin D did not demonstrate a mutagenic potential though it did reveal some clastogenic potential with and without metabolic activation. In general, low toxicity was observed for Polyoxin D Zinc Salt in all investigations. During toxicity studies, Polyoxin D Zinc Salt is poorly absorbed with the vast majority of the product (>90%) being excreted unchanged directly in the feces. Polyoxin D Zinc Salt has been used for many years without any notable, consistent adverse human reactions being recorded. Polyoxin D Zinc Salt has been in use as an antifungal agent for over 40 years in Japan on rice, and approved in the USA and Mexico on food crops for over 5 and 3 years respectively and for non-food crops in the USA for over 16 years. The product is derived naturally in Japan from *Streptomyces cacaoi* var *asoensis* and has a unique mode of activity by inhibiting fungal cell wall synthesis. The risk to humans is considered to be extremely low.

The toxicity tests performed and their results can be found in Table 2.

Table 2. Toxicity of Polyoxin D Zinc Salt

Toxicological Study	Toxicity	EPA Category
Acute Oral (rats)	LD_{50}: >15000 mg/kg bw (males) >10000<1500 mg/kg bw (females)	A0 (oral)
Acute dermal (rats)	LD_{50}: >2000 mg/kg bw	B0 skin/eye irritation
Acute inhalation (rats)	LD_{50}: >2.44 mg/L (males), >2.17 mg/L (females), >2,78 mg/L (combined sexes)	C0 (inhalation)
Acute dermal (rabbits)	Not irritating	B0 skin/eye irritation
Acute eye irritation (rabbits)	Irritating	B0 skin/eye irritation
Sensitization (guinea pigs)	A contact dermal sensitizer at concentrations greater than or equal to 5%	B3 (may cause a skin sensitization reaction)
Sensitization (local lymph nodes assay in mice)	Not a contact dermal sensitizer at concentrations less than or equal to 25%	B3 (may cause a skin sensitization reaction)
Ames reverse mutation test	Non mutagenic, negative with and without metabolic activation	-
Chromosome aberration in CHL cells	Clastogenic with and without metabolic activation	-
Chromosome aberration in CHL/IU cells	Clastogenic potential with and without metabolic activation	-
Carcinogenicity/chronic toxicity (rats)	Polyoxin D Zinc Salt did not demonstrate oncogenic potential	-
Carcinogenicity/chronic toxicity (Mice)	Polyoxin D Zinc Salt did not demonstrate oncogenic potential	-
Embryofoetal development (rats)	Polyoxin D Zinc Salt did not adversely affect embryofoetal development	-
Embryofoetal development (rabbits)	Polyoxin D Zinc Salt did not adversely affect embryofoetal development	-
Multigeneration study (rats)	Polyoxin D Zinc Salt did not adversely affect reproductive capacity or survival over generations	-
Toxicity study (Rat, 90 day)	No target organ was clearly identified. (EPA Staff note: The highest dose exceeded the generally acknowledged limit does of 1000 mg/kg bw/day with only limited effects.)	-
Toxicity study (dog, 1 year)	No target organ was clearly identified. (EPA Staff note: The highest dose exceeded the generally acknowledged limit does of 1000 mg/kg bw/day with only limited effects.)	-

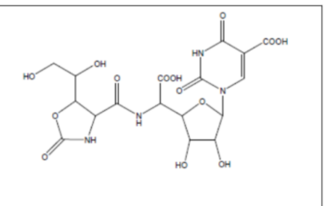
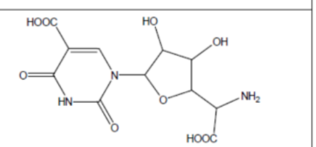
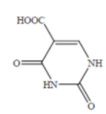
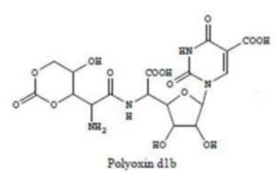
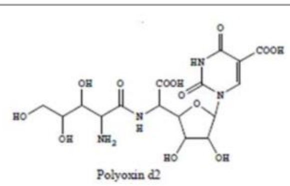
Immunotoxicity study (mouse 28 day)	Polyoxin D Zinc Salt did not exhibit any immunotoxicological potential.	-

Sources: EPA Staff report for ESTEEM™ November 2015 and California Department of Pesticide regulation output reporting

<u>Evaluation Question #6:</u> Describe any environmental contamination that could result from the petitioned substance's manufacture, use, misuse, or disposal (7 U.S.C. § 6518 (m) (3)).

In the study of Polyoxin D as a contaminating agent, it is important to analyze what the products of Polyoxin D Zinc Salt's decomposition are. Figure 2 presents a list of known metabolites of Polyoxin D Zinc salt. The metabolites, Polyoxin d1a and d1bmost closely resembles the cyclization or modification of the amide side chain off of the five-membered furan-like ring. Polyoxin C acid and Uracil-5-carboxylic acid are likely the products of severance of the amide side chain or the five-membered ring, respectively. Polyoxin d2 is likely the product of modification of the amide bond at the end of the chain.

Figure 2. Known Metabolites

Polyoxin d1a	
Polyoxin C acid	
Uracil-5-Carboxylic Acid	
Polyoxin d1b	
Polyoxin d2	

Polyoxin D Zinc Salt underwent a variety of environmental studies. The tests as well as the results can be found in Table 3.

Table 3. Environmental Studies of Polyoxin D Zinc Salt

Environmental Study	Toxicity
Fish acute toxicity (freshwater species)	LC_{50} > 100 mg ai/L
Test solutions of the carp acute test	LC_{50} is 5.1mg TGAI/L (equivalent to 1.0 mg Polyoxin D/L)
Invertebrate acute toxicity	The EC50 = 1.4 mg TGAI/L equivalent to 0.29 mg Polyoxin D/L
Algae acute toxicity	E_rC_{50} is 7.05 mg ai/L and E_bC_{50} is 6.47 mg ai/L at 72 hours, NOEC = 5 mg a.i./L (Growth rate)
Soil macro-invertebrates acute toxicity	LC_{50} > 1000 mg Polyoxin D Zinc Salt/ Kg dry soil
Terrestrial vertebrate (other than birds) toxicity: Oral acute toxicity Dietary acute toxicity	 LD_{50} > 2150 mg Polyoxin D Zinc Salt/ kg bw LD_{50} > 5000 mg Polyoxin D Zinc Salt/ kg diet
Ecotoxicity to terrestrial vertebrates Bees (acute oral) Bees (acute contact)	 Oral LD_{50} = 28.7 µg Polyoxin D Zinc Salt/ bee LD_{50} > 100 µg a.i./ bee
Water compartment Hydrolysis Aqueous photolysis	 Aqueous abiotic hydrolysis would be a major route of elimination of Polyoxin D from the environment at pH 7 and 9 Photolysis contributes to the degradation of the substance, DT50 = 1.6 d in spring conditions in Tokyo
Aerobic degradation in soil	Polyoxin D: DT50 = 15.9 days Major metabolite (> 10%): Polyoxin C acid, its DT50 is 67.9 days

Source: EPA Staff report for ESTEEM™ November 2015

Based on the results in Table 3, Polyoxin D Zinc Salt is presumed to carry very low environmental risk and because Polyoxin D Zinc Salt is formed through fermentation, it is considered to be less toxic to the environment than a fungicide that was chemically manufactured such as cupper, sulfur or petroleum distillates.

In 2017 the EPA accepted a technical label for Polyoxin D Zinc Salt, which labels the fungicide as "moderately toxic to aquatic invertebrates and fish." The label continues to provide instructions for proper disposal to avoid any minor issues with improperly stored/discarded product (EPA PRIA amendment, 2017).

<u>Evaluation Question #7:</u> Describe any known chemical interactions between the petitioned substance and other substances used in organic crop or livestock production or handling. Describe any environmental or human health effects from these chemical interactions (7 U.S.C. § 6518 (m) (1)).

Polyoxin D Zinc Salt is considered to degrade quickly in the environment and is therefore considered to not be of concern even for spills/environmental exposure (ESTEEM). Polyoxin D Zinc Salt's effects on non-target plants are likely to be low based on its relatively low toxicity towards algae. In regard to other substances, Polyoxin D Zinc Salt is considered to be, like most fungicides, most beneficial as a preventative measure used alongside a variety of other known fungicides (Dernoeden, P.H, 2001)

Because Polyoxin D Zinc salt is a fungicide, it could have a negative impact on beneficial fungi. However, it has also been proven to encourage a beneficial effect on controlling Bacillus subtilis and of encouraging *Alternaria mali* expression.

When Polyoxin D Zinc salt is combined with *Agip*MNPV (Agrotis ipsilon multicapsid nucleopolyhedrovirus) it reduces the efficacy of the NPV in controlling black cutworm (*Agrotis ipsilon*) populations (Source: NOP Report, Appendix 2, 2012).

<u>Evaluation Question #8:</u> Describe any effects of the petitioned substance on biological or chemical interactions in the agro-ecosystem, including physiological effects on soil organisms (including the salt index and solubility of the soil), crops, and livestock (7 U.S.C. § 6518 (m) (5)).

Because of Polyoxin D Zinc Salt's unique mode of action, it does not kill fungi, but instead prevents their growth. Various tests were conducted on soil organisms to better understand the environmental risks. Soil macro-invertebrate toxicity studies were performed on earthworms, two-spotted mites, brown plant hoppers, diamond back moths, marmalade hoverflies, green lacewings, silkworms, wolf spiders, ladybird beetles. Only in earthworms the data recovered was reliable (LC50 > 1000 mg Polyoxin D zinc salt/kg dry soil). In regard to earthworms, the results are below the level of concern. (EPA Staff report for ESTEEM™ November 2015) The other studies were classified as 'disregarded.'

There was not enough data to accurately judge a risk assessment for target plants. Based on the summary of tests addressed in Evaluation Question #6, and because of Polyoxin D Zinc Salt's rapid degradation, the risk for non-target plants and the environment is considered to be minimal.

<u>Evaluation Question #9:</u> Discuss and summarize findings on whether the use of the petitioned substance may be harmful to the environment (7 U.S.C. § 6517 (c) (1) (A) (i) and 7 U.S.C. § 6517 (c) (2) (A) (i)).

Polyoxin D Zinc Salt is considered to have minimal impact on the environment. The following studies were conducted and showed little prohibitively noxious properties:

Tests on rats, rabbits, and pigs showed that Polyoxin D Zinc salt is only a minor skin/eye irritant. Tests on fish, invertebrates, macro-invertebrates, algae, and terrestrial vertebrates and Bees came back with very high LD_{50} levels relative to the species tested implying that in practical doses, Polyoxin D Zinc salt is not considered harmful on the environment. (Source: EPA Staff report for ESTEEM™ November 2015)

The results of these individual tests can be seen in greater detail in the preceding answers to questions #5 and #6.

<u>Evaluation Question #10:</u> Describe and summarize any reported effects upon human health from use of the petitioned substance (7 U.S.C. § 6517 (c) (1) (A) (i), 7 U.S.C. § 6517 (c) (2) (A) (i)) and 7 U.S.C. § 6518 (m) (4)).

The tables below (4 and 5) describe the tests performed to simulate human health effects from use of Polyoxin D Zinc Salt as both an operator (Table 4) and a bystander (Table 5).

Table 4. Effects Upon Human Health from Polyoxin D Zinc Salt OPERATOR Exposure

Exposure scenario	Estimated operator exposure Mg/kg bw/day	Risk Quotient
Airblast		
No PPE during mixing, loading and application	0.0402	0.034

Gloves only during mixing and loading	0.0397	0.033
Gloves only during application	0.0378	0.032
Full PPE during mixing, loading and application (excluding respirator)	0.0022	0.002
Full PPE during mixing, loading and application (including respirator)	0.0018	0.002

Table 5. Effects Upon Human Health from Polyoxin D Zinc Salt BYSTANDER Exposure

Exposure Scenario	**Estimated exposure of 15 kg toddle exposed through contact to surfaces 8 m from an application area µg/kg bw/day**	**Risk Quotient**
Airblast		
Airblast sparse orchard	8.36	0.0070
Airblast dense orchard	2.79	0.0023
Airblast vineyard	0.39	0.0003

Source: EPA Staff report for ESTEEM™ November 2015

The risk for humans is considered low because personal protective equipment (PPE) is not considered necessary. However, it is appropriate to retain the requirement for PPE since that is good practice for working with agrochemicals (EPA Staff report for ESTEEM™ November 2015). According to the EPA, Polyoxin D Zinc Salt has been considered in regard to the nine safety factors listed in the Food Quality Protection Act (FQPA) and has been considered it to be of no harm. The BPPD has not identified any subchronic, chromic, immune, endocrine, or non-dietary cumulative exposure that may affect infants, children, and the general public. (EPA office of pesticide programs July 2003)

Evaluation Question #11: Describe all natural (non-synthetic) substances or products which may be used in place of a petitioned substance (7 U.S.C. § 6517 (c) (1) (A) (ii)). Provide a list of allowed substances that may be used in place of the petitioned substance (7 U.S.C. § 6518 (m) (6)).

Because Polyoxin D Zinc Salt is considered to be safer than previous fungicides, based on its mode of action and quick dissipation rate as discussed in questions #8, 9, and 10, alternative fungicides do not seem like improvements of the petitioned substance.

Table 6 compares the disease control and suppression labels of various alternatives reviewed by OMRI. Formulations that are subregistrations of OMRI listed products and products that make broad claims of suppression without specific crop-pathogen pairs are excluded. The number of options that organic farmers have is greater than Table 6 suggests. More information can be found in the previous, 2012, technical report on Polyoxin D Zinc Salt.

Table 6. Comparison of the Endorse WDG Label with Alternative Pesticides

Crop	**Pathogens**	**EPA Registered and OMRI Listed Products Labeled for Use**
Almonds	*Alternaria* spp.	Actinovate SP (Natural Industries); Regalia Concentrate (Marrone); Regalia Maxx (Marrone); Sonata ASO (Agraquest).
Cucurbits (Cucumbers, melons,	*Alternaria* spp.	Actinovate SP (Natural Industries); Badge X2 (Isagro); Basic Copper 53 (Albaugh); Champ WG (NuFarm); Chem Copp 50 (apples only) (American Chemet); COC WP (Albaugh); Cueva Fungicide Concentrate (Neudorff); Organic JMS Stylet Oil (JMS);

Crop	Pathogens	EPA Registered and OMRI Listed Products Labeled for Use
squash and others)		Nordox 75 WG (Nordox); Nu Cop DF (Albaugh); Nu Cop WP (Albaugh); Oxidate (BioSafe); Prestop Biofungicide Powder (Verdura Oy); Regalia Concentrate (Marrone).
	Gray mold (*Botrytis* spp.)	Actinovate SP (Natural Industries); Cueva Fungicide Concentrate (Neudorff).
	Gummy stem blight (*Didymella bryoniae)*	Badge X2 (Isagro); Basic Copper 53 (Albaugh); Chem Copp 50 (apples only) (American Chemet); Champ WG (NuFarm); COC WP (Albaugh); Cueva Fungicide Concentrate (Neudorff); Organic JMS Stylet Oil (JMS); Nordox 75 WG (Nordox); Oxidate (BioSafe); Regalia Concentrate (Marrone); Regalia Maxx (Marrone); Sonata ASO (Agraquest).
	Leaf spot (*Corynespora cassicola*)	Oxidate (BioSafe).
	Powdery mildew (*Spthaerotheca* spp.)	Actinovate SP (Natural Industries); Badge X2 (Isagro); Basic Copper 53 (Albaugh); Champ WG (NuFarm); COC WP (Albaugh); Cosavet DF (Sulphur Mills); CSC 80% Thiosperse (Martin); Cueva Fungicide Concentrate (Neudorff); CSC Dusting Sulfur (Martin); Kaligreen (Otsuka); M-Pede Insecticide-Miticide-Fungicide (Dow); Nordox 75 WG (Nordox); Oxidate (BioSafe); Regalia Concentrate (Marrone); Regalia Maxx (Marrone); Sonata ASO (Agraquest).
	Scab (*Cladosporium* spp.)	Prestop Biofungicide Powder (Verdura Oy).
Fruit Vegetables (Eggplant, pepper, pepinos, tomatillos and tomatoes)	Early blight (*Alternaria solani*)	Actinovate SP (Natural Industries); Badge X2 (Isagro); Basic Copper 53 (Albaugh);); Chem Copp 50 (apples only) (American Chemet); Champ WG (NuFarm); COC WP (Albaugh); Camelot O (SePRO); Cueva Fungicide Concentrate (Neudorff); Organic JMS Stylet Oil (JMS); Nordox 75 WG (Nordox); Nu Cop DF (Albaugh); Nu Cop WP (Albaugh); Oxidate (BioSafe); Prestop Biofungicide Powder (Verdura Oy); Regalia Concentrate (Marrone); Regalia Maxx (Marrone); Sonata ASO (Agraquest).
	Anthracnose (*Colletotrichum coccodes*)	Actinovate SP (Natural Industries); Badge X2 (Isagro); Basic Copper 53 (Albaugh); Champ WG (NuFarm); Chem Copp 50 (apples only) (American Chemet); COC WP (Albaugh); Organic JMS Stylet Oil (JMS); Nordox 75 WG (Nordox); Nu Cop DF (Albaugh); Nu Cop WP (Albaugh); Oxidate (BioSafe).
	Gray molds (*Botrytis* sp.)	Actinovate SP (Natural Industries); Cueva Fungicide Concentrate (Neudorff); Oxidate (BioSafe); Regalia Concentrate (Marrone); Regalia Maxx (Marrone); Sonata ASO (Agraquest).
	Powdery mildew (*Leveillula taurica* and *Oidiopsis sipula*)	Actinovate SP (Natural Industries); Cosavet DF (Sulphur Mills); CSC Dusting Sulfur (Martin); Organic JMS Stylet Oil (JMS); Kaligreen (Otsuka); M-Pede Insecticide-Miticide-Fungicide (Dow); Oxidate (BioSafe); Regalia Concentrate (Marrone); Regalia Maxx (Marrone); Sonata ASO (Agraquest); several other sulfur products by various manufaturers.
Ginseng	*Alternaria panax* spp.	Badge X2 (Isagro); Basic Copper 53 (Albaugh); Champ WG (NuFarm); Cueva Fungicide Concentrate (Neudorff); Nordox 75 WG (Nordox); Nu Cop DF (Albaugh); Nu Cop WP (Albaugh); Oxidate (BioSafe); Regalia Concentrate (Marrone); Regalia Maxx (Marrone); Sonata ASO (Agraquest).
	Botrytis cinerea	Cueva Fungicide Concentrate (Neudorff); Regalia Concentrate (Marrone); Regalia Maxx (Marrone).

Crop	Pathogens	EPA Registered and OMRI Listed Products Labeled for Use
	Cylinderocarpon destructans	None found.
	Rhizoctonia solani	Oxidate (BioSafe); Prestop Biofungicide Powder (Verdura Oy); Regalia Concentrate (Marrone).
Grapes	Bunch rot or Gray mold (*Botrytis cinerea)*	CSC Copper Sulfur Dust (Martin); Cueva Fungicide Concentrate (Neudorff); Cueva Fungicide RTU (Neudorff); Organic JMS Stylet Oil (JMS); Oxidate (BioSafe); Regalia Concentrate (Marrone); Regalia Maxx (Marrone).
	Powdery mildew (*Unicula necator*)	Badge X2 (Isagro); Basic Copper 53 (Albaugh); Champ WG (NuFarm); Copper Sulfate Crystals (Chem One); Chem Copp 50 (American Chemet); COC WP (Albaugh); Cosavet DF (Sulphur Mills); CSC 80% Thiosperse (Martin); CSC Copper Sulfur Dust (Martin); CSC Dusting Sulfur (Martin); Cueva Fungicide Concentrate (Neudorff); Cueva Fungicide RTU (Neudorff); Kaligreen (Otsuka); Organic JMS Stylet Oil (JMS); Quimag Quimicos Aguila Copper Sulfate Crystal (Fabrica de Sulfato El Aguila, S.A. de C.V.); Quimag Quimicos Aguila Copper Sulfate Crystal - Crop (Fabrica de Sulfato El Aguila, S.A. de C.V.); Nordox 75 WG (Nordox); Nordox 30/30 WG (Nordox); Nu Cop DF (Albaugh); Nu Cop WP (Albaugh); Oxidate (BioSafe); Regalia Concentrate (Marrone); Regalia Maxx (Marrone); Most OMRI Listed sulfur products.

Crop	Pathogens	EPA Registered and OMRI Listed Products Labeled for Use
Pistachios	*Alternaria* spp.	Badge X2 (Isagro); Basic Copper 53 (Albaugh); COC WP (Albaugh); Nordox 75 WG (Nordox); Nordox 30/30 WG (Nordox); Nu Cop DF (Albaugh); Nu Cop WP (Albaugh); Regalia Concentrate (Marrone); Regalia Maxx (Marrone); Sonata ASO (Agraquest).
	Botryosphaeria spp.	Badge X2 (Isagro); Basic Copper 53 (Albaugh); COC WP (Albaugh); Nordox 75 WG (Nordox); Nordox 30/30 WG (Nordox); Nu Cop DF (Albaugh); Nu Cop WP (Albaugh); Regalia Concentrate (Marrone); Regalia Maxx (Marrone); Sonata ASO (Agraquest).
Pome fruit	Alternaria blotch (*Alternaria mali*)	Regalia Concentrate (Marrone).
	Leaf blotch (*Diplocarpon mali*)	None found.
	Powdery mildew (*Podosphaera leucotricha* in apples; *Phyllactinia mali* in pears)	Golden Micronized Sulfur (Wilbur-Ellis); Organic JMS Stylet Oil (JMS); Kaligreen (Otsuka); Regalia Concentrate (Marrone); Regalia Maxx (Marrone).
	Scab (*Venturia* spp.)	Badge X2 (Isagro); Basic Copper 53 (Albaugh); Blue Shield DF[a] (Albaugh); Camelot O (SePRO); Chem Copp 50[a] (American Chemet); CSC 80% Thiosperse (Martin); Nordox 75 WG (Nordox); Nordox 30/30 WG[a] (Nordox); Oxidate (BioSafe); Regalia Concentrate (Marrone); Regalia Maxx (Marrone).
Potatoes	Early blight (*Alternaria solani*)	Basic Copper 53 (Albaugh); Blue Shield DF (Albaugh); Chem Copp 50 (American Chemet); Champ WG (NuFarm); COC WP (Albaugh); Cueva Fungicide Concentrate (Neudorff); Nordox 75 WG (Nordox); Nu Cop DF (Albaugh); Nu Cop WP (Albaugh); Oxidate (BioSafe); Prestop Biofungicide Powder (Verdura Oy); Regalia Maxx (Marrone); Sonata ASO (Agraquest).
Strawberries	Anthracnose (*Colletotrichum* spp.)	Cueva Fungicide Concentrate (Neudorff); Regalia Concentrate (Marrone); Regalia Maxx (Marrone).
	Gray mold (*Botrytis cinerea*)	Cueva Fungicide Concentrate (Neudorff); Organic JMS Stylet Oil (JMS); Regalia Concentrate (Marrone); Regalia Maxx (Marrone).
	Powdery mildew (*Spthaerotheca*)	Cosavet DF (Sulphur Mills); CSC Dusting Sulfur (Martin); Cueva Fungicide Concentrate (Neudorff); Golden Micronized Sulfur (Wilbur-Ellis); Kaligreen (Otsuka); M-Pede Insecticide-Miticide-Fungicide (Dow); Organic JMS Stylet Oil (JMS); Regalia Concentrate (Marrone); Regalia Maxx (Marrone); several other sulfur products by various manufacturers.

[a] Apples only

Sources: 2012 Polyoxin D Zinc Salt: Technical Evaluation Report

Information regarding on-farm use of the above-mentioned alternatives should be available from accredited certification agents and access to organic system plans. The reviewers found only a limited number of studies that compare efficacy of Polyoxin D Zinc Salt with pesticides that are currently approved for organic production.

<u>Evaluation Question #12:</u> Describe any alternative practices that would make the use of the petitioned substance unnecessary (7 U.S.C. § 6518 (m) (6)).

Polyoxin D Zinc Salt is one example of a fungicide.

According to NOP standards, specific management practices must be implemented including: crop rotations, sanitation to remove disease vectors and the use of resistant species and varieties [7 CFR 205.206(a)]. Before any chemical on the National List can be used, a producer must document that current, non-synthetic biological, botanical, or mineral techniques were insufficient to prevent or suppress diseases [7 CFR 205.206(d) & (e)].

One of the pests that Polyoxin D Zinc Salt treats and defends against is, Brown Patch (*Rhizoctonia solani*) and Large Patch, both of which affect cool season grasses. Another method for treating these issues is through proper irrigation timing that can avoid severe cases of these diseases (Dernoeden, P.H, 2001).

Because of Polyoxin D Zinc Salt's unique method of action and dissipation, it is considered a low hazard alternative to current generation fungicides. (EPA Staff report for ESTEEM™ November 2015)

Antibiosis as a mode of action for plant disease suppression in soils is a relatively new approach. The use of live organisms rather than their extracts offers a more ecological approach to manage plant pathogens and is seen as more consistent with organic farming principles (Milner, et al., 1997). Beneficial antagonistic *Streptomyces* spp. may be promising biological control agents (Liu, et al., 1997), but development and commercialization has been slow.

Improved monitoring techniques can help ginseng growers avoid planting into soils that are infested with *Cylinderocarpon descructans* (Kernaghan et al., 2007). Rotations with brassicas, such as mustard cover crops, can biofumigate soils and suppress *C. destructans* when an infestation has occurred (Crosby, et al., 2010).

Report Authorship

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All individuals are in compliance with Federal Acquisition Regulations (FAR) Subpart 3.11—Preventing Personal Conflicts of Interest for Contractor Employees Performing Acquisition Functions.

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