UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF PESTICIDES AND TOXIC SUBSTANCES

CONTAINS CONFIDENTIAL BUSINESS INFORMATION

MEMORANDUM

DATE: **08/18/2008**

SUBJECT: Science Review in Support of a Tolerance Exemption Petition for Polyoxin D Zinc Salt [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)]. Old Active Ingredient, First Food Use.

Tolerance Exemption Petition No.:	**7F7252**
EPA Reg. Nos.:	**68173-1 (TGAI); 68173-3/66330-56 (EP)**
Decision No.:	**378876, 378878, & 382351**
DP Barcode:	**352135, 352136, & 352137**
Chemical Class:	**Biochemical**
PC Code:	**230000**
CAS No.	**146659-78-1**
MRIDs:	**471209-01 & -04; 471451-01 & 02;**
Tolerance Exemptions:	**Proposed**

FROM: Russell S. Jones, Ph.D., Senior Biologist /s/ 08/18/2008
Biochemical Pesticides Branch
Biopesticides & Pollution Prevention Division (7511P)

TO: Chris Pfeifer, Regulatory Action Leader
Biochemical Pesticides Branch
Biopesticides & Pollution Prevention Division (7511P)

ACTION REQUESTED

On behalf of Kaken Pharmaceutical Co., Ltd., D. Bujor (Arysta LifeScience North America) requests an expansion of the labels for Polyoxin D Zinc Salt Technical (EPA Reg. No. 68173-1) and Endorse Water Dispersible Granules (EPA Reg. No. 68173-3/66330-56; these are identical products registered in 2005) to add first food crop uses (almonds, cucurbit vegetables, fruiting vegetables, ginseng, grapes, pistachio, pome fruits, potato, and strawberry). In support of the request, the registrant submitted a petition for an exemption from the requirements of tolerances for Polyoxin D Zinc Salt, additional toxicological studies to support the proposed food uses, and Confidential Statements of Formula for the TGAI and EP, and draft product labels.

Inert ingredient information may be entitled to confidential treatment

Polyoxin-D
PC Codes: 230000

DP Number: 378876, 358878, & 382351
EPA Reg Nos.: 66356-1 & 66356-3
PP# 7F7252

RECOMMENDATIONS AND CONCLUSIONS

1a. The Tolerance Exemption Request for Polyoxin D Zinc Salt (CAS No. 146659-78-1; PC Code 230000) and amendment of the product labels for Polyoxin D Zinc Salt Technical (EPA Reg No. 68173-1) and Endorse Water Dispersible Granules (EPA Reg No. 67176-3/66330-56; these are identical products) to permit the requested food crop uses **is supported**.

NOTE 1: The food use clearance for the inert, [redacted] As of the date of this report (08/18/2008), this inert was approved for pre-harvest food use under 40 CFR 180.920.

1b. All other inert ingredients contained in Endorse® Water Dispersible Granules (EPA Reg. No. 68173-3/66330-56), are cleared for pre- and post-harvest food use under 40 CFR 180.910.

1c. All existing product chemistry studies and information previously submitted to support the registrations of EPA Reg No. 68173-1 and EPA Reg No. 68173-3/66330-56 are acceptable. No additional product chemistry data are required.

2b. No meaningful acute, subchronic, or chronic toxicological endpoints were identified for Polyoxin-D, zinc salt technical (See Table 2 and Review of Tier I Toxicity Data). The current toxicological profile for Polyoxin-D, Zinc Salt is adequate to support the Tolerance Exemption Petition

2c. Acute oral toxicological endpoints were identified for the end-use product Endorse® Water Dispersible Granules (EPA Reg. No. 68173-3/66330-56), although they were near the upper limit of Toxicity Category III [4404 mg/kg (male rat)- 4916 mg/kg (female rat)]. It is not likely that the observed endpoints resulted from the presence of the active ingredient. The TGAI has an acute oral LD50 > 10,000 mg/kg (male rat) – 15,000 mg/kg (female rat).

2d. The extremely low application rates of the end-use product on food commodities (no more than 0.3875 lb product/A/application) and active ingredient (0.04375 lb/A/application) would result in residues on food commodities that are well below the highest doses used in acute oral or chronic toxicity testing. There will be no more than 6 applications (on pome fruits) for a seasonal application of 2.325 lbs product/A and 0.2625 lbs active ingredient/A. These application rates result in maximum residues of no more than approximately 360 ppm product and approximately 40 ppm a.i., respectively.

2e. The current toxicological profile for the end-use product, Endorse Water Dispersible Granules, is adequate to support the Tolerance Exemption Petition.

3a. The current non-target organism/environmental fate profile for Polyoxin-D, zinc salt contained in the Polyoxin-D, Zinc Salt BRAD is adequate to support the uses specified on the product label for the end-use product, Endorse Water Dispersible Granules. There are no concerns for non-target organisms, including threatened and endangered species.

3b. Based on the extremely low application rate and highly specific mode of action of the active ingredient as a fungal chitin synthetase inhibitor, a **No Effects (NE)** determination on threatened and endangered species is made for Polyoxin-D, Zinc Salt.

General Information Regarding the Active Ingredient

"Polyoxins are antibiotics produced by *Streptomyces cacaoi* var. *asoensis* that are specifically active against a few species of phytopathogenic fungi. Polyoxins consist of several structurally analogous components designated alphabetically from A to N. Commercial production of *S. cacaoi* [yields] a variety of polyoxins for the control of fungal diseases on fruits, vegetables, flowers, rice, and turf " [see Memorandum from S. Lewis (EPA) to R. Engler (EPA), dated 04/04/1990].

Review of the Confidential Statements of Formula (CSFs)

Two CSFs were submitted for review: one each for Technical Grade Active Ingredient (TGAI; dated 03/25/1997) and the End-Use Product (EP; dated 02/07/2005).

The Active Ingredient: The Technical Grade Active Ingredient (TGAI) contains 23.8% Polyoxin-D [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)] as its active ingredient. The TGAI is manufactured by one source: Kaken Pharmaceuticals (Tokyo, JAPAN) [Polyoxin D Zinc Salt Technical (23.8%); EPA Reg. No. 68173-1] and contains the following inert (other) ingredients (Table 1a):

Inert ingredient information may be entitled to confidential treatment

Polyoxin-D
PC Codes: 230000

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Table 1a. Inert Ingredients in Polyoxin D Zinc Salt Technical (EPA Reg. No. 68173-1)

[redacted]

The most recent CSF for Endorse® Water Dispersible Granules (EPA Reg. No. 66330-56) is dated 02/07/2005. It is identical to 68173-3 The formulation contains the following:

The Active Ingredient: The end-use product contains 11.3% Polyoxin-D, zinc salt as its active ingredient. The Technical Grade Active Ingredient (TGAI) may be obtained from one manufacturing source: Kaken Pharmaceuticals (Tokyo, JAPAN) [Polyoxin D Zinc Salt Technical (23.8%); EPA Reg. No. 68173-1]. The following inerts are contained in the EP:

Table 1b. Inert Ingredients in Endorse® Water Dispersible Granules (EPA Reg. No. 68173-3/66330-56)

[redacted]

CONCLUSION: The existing product chemistry data are acceptable to support the requested permanent tolerance exemption on food.

Polyoxin-D
PC Codes: 230000

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Review of Tier I Toxicity Data

No acute toxicity data for the TGAI or the end-use product were submitted for review. The end-use product, Endorse® Water Dispersible Granules (EPA Reg. No. 68173-3/66330-56) was unconditionally registered in 2005 for non-food use on turf sites (golf courses, residential lawns, parks, and commercial and institutional grounds) as a fungicide. Toxicity data for the TGAI contained in the Polyoxin-D Zinc Salt Biopesticide Registration Eligibility Document (BRAD; ca. 1997) are summarized in the following table:

Table 2. Acute Toxicity Data for the Polyoxin-D Zinc Salt TGAI in the BRAD

Data Requirement	LD50/LC50	Toxicity Category	MRID
Acute Oral Toxicity	>10000 mg/kg	IV	432618-23
Acute Dermal Toxicity	>2000 mg/kg	III	432618-25
Acute Inhalation Toxicity	>2.17 mg/L	IV	432618-27
Primary Eye Irritation	Slight to moderate (Draize)	III	432618-29
Primary Dermal Irritation	Slight irritation (Draize)	IV	432618-31
Dermal Sensitization	Mild sensitizer	N/A	432618-33
Hypersensitivity Incidents	None Reported	N/A	N/A

Tier I Toxicity studies were submitted in support of the non-food use registration of Endorse® Water Dispersible Granules (EPA Reg. No. 68173-3/66330-56) and reviewed in a Memorandum from R. Sjoblad to D. Greenway (dated 12/01/2004); a separate review of an acute toxicity study was also conducted (see Memorandum from C. Frazer to D. Greenway, dated 09/22/2005). The reported acute toxicity data are summarized in the following table:

Table 3. Acute Toxicity Data for the End-Use Product, Endorse Water Dispersible Granules [11.3% Polyoxin-D, Zinc Salt as its Active Ingredient (EPA Reg. No. 66356-3/66330-56)]

Data Requirement	LD50/LC50	Toxicity Category	MRID
Acute Oral Toxicity	4404 - 4916 mg/kg	III	463402-02
Acute Dermal Toxicity	>2000 mg/kg	III	463402-03
Acute Inhalation Toxicity	>2.41 mg/L	III[1]	465820-01
Primary Eye Irritation	Mild irritation (Draize)	III	463402-04
Primary Dermal Irritation	Non-irritant (Draize)	IV	463402-05
Dermal Sensitization	Non-sensitizer	N/A	463402-06
Hypersensitivity Incidents	None Reported	N/A	N/A

[1] Only the water dispersible granules were tested and it is unlikely that there will be any acute inhalation toxicity via exposure to the dry granules. However, no data are available for the EP under conditions of use. Until the diluted product is tested, a classification of Tox Category III is appropriate for acute inhalation toxicity and associated product label language.

Additional Toxicity Studies to Support New Food Use

Mutagenicity

Mammalian Erythrocyte Micronucleus Study – Tier II (OPPTS 870.5395; MRID 47145102): In a mouse bone marrow micronucleus range-finding assay, five male mice per dose were treated once via oral gavage with Polyoxin D zinc salt technical at doses of 0, 500, 1000 or 2000 mg/kg body weight. Bone marrow cells were harvested at 24 hours following treatment at all doses and additionally at 48 hours following treatment at 2000 mg/kg. The bone marrow polychromatic erythrocytes (PCEs) were evaluated for the presence of micronuclei and the PCE/total erythrocyte ratio was determined. The vehicle was 0.5% methylcellulose. The test material was not toxic to male mice in at any dose tested and there were no reported sex difference in response to the test material and an LD_{50} of >9600 mg/kg.

In a definitive study, Polyoxin D zinc salt technical was tested to the limit dose of 2000 mg/kg. The mice showed no clinical signs or mortality during the micronucleus test. No statistically or biologically significant increase in the frequency of micronucleated PCEs was seen at any test material dose at either harvest time and the PCE/total erythrocyte ratio was not decreased. The vehicle and Mitomycin C positive control values were appropriate. **There was no increase in the frequency of micronucleated bone marrow PCEs as tested in this study.**

Conclusion: ACCEPTABLE, no additional data are required (see Overall Conclusions for Muagenicity below).

Previously Reviewed Mutagenicity Studies: In previously submitted studies, Polyoxin-D was shown to be weakly mutagenic in an Ames Assay (MRID 433230-01) but in a follow-up battery of three mutagenicity tests (see Polyoxin-D Brad), the data supported negative conclusions for mutagenicity. No maternal toxicity or developmental toxicity was observed in a developmental toxicity study (MRID 432618-36).

Overall Conclusions for Mutagenicity: Based on the existing data, Polyoxin-D is not a mutagen. These data are acceptable to support the new food uses and the permanent Tolerance Exemption petition.

Subchronic Testing

90-Day Oral Toxicity – Rat (OPPTS 870.3100; MRID 47145101): In a 90-day oral toxicity study Polyoxin D Zinc Salt Technical was administered to ten rats/sex/dose in the diet at levels of 0, 200, 2000 and 20,000 ppm (equivalent to 0, 11.6, 119 and 1166 mg/kg/day in males and 0, 13.7, 135 and 1333 mg/kg/day in females, respectively) for 13 weeks.

There were no toxicologically significant treatment-related effects on mortality, clinical signs, neurological assessments, urinalysis, ophthalmology, hematology, clinical chemistry or gross and histologic pathology. Decreased body weight gain (decreased 6-16%), food consumption ($p \leq 0.01$ and 0.05; decreased 4.7-8.3%) and food efficiency (decreased 0.5-34%) were seen in the 20,000 ppm (1166 mg/kg/day) males, when compared to the control males.

The NOAEL in this study is 20,000 ppm (1333 mg/kg/day) in females and 2000 ppm (119 mg/kg/day) in males. The LOAEL in males is 20,000 ppm (1166 mg/kg/day) based on decreased body weight gain, food consumption and food efficiency; a LOAEL was not observed in females.

Conclusions: ACCEPTABLE, no additional data are required. Based on the lack of meaningful subchronic toxicological endpoints for the TGAI, the mode of action as a chitin synthetase inhibitor, and the extremely low application rate of the EP (no more than 0.3875 lb product/A/application) and active ingredient (0.04375 lb/A/application), there are no subchronic oral toxicity concerns when the end-use product is used in accordance with approved labeling (see also Overall Conclusions for Subchronic Toxicity below).

Previously Reviewed Subchronic Toxicity Information: Since the original end-use product was intended for non-food use and the use patterns did not indicate repeated and/or long-term exposure by oral dermal or inhalation routes, no 90-studies (oral, inhalation, dermal) were conducted at the time of the original registration. Although the proposed new uses are for food crops, the proposed label use pattern does not result in any repeated and/or long-term exposure by dermal or inhalation routes.

The proposed application rate of Polyoxin-D, Zinc Salt is practically identical to the rate originally assessed in the 1997 BRAD. Therefore, any potential for adverse health effects will be no greater than that identified in the 1997 BRAD. No subchronic toxicity concerns were noted in the 1997 BRAD.

Overall Conclusions for Subchronic Toxicity: Based the data, there are no concerns for subchronic oral exposure. Based on the current and proposed new use patterns, it is highly unlikely that there will be any repeated exposure humans (consumers, workers, applicators, handlers) by the dermal or inhalation routes of exposure. These data are acceptable to support the new food uses and the permanent Tolerance Exemption petition.

Developmental Toxicity

Two Generation Reproduction Toxicity Study-Rat – Tier III (OPPTS 870.3800; MRID 47120904): In a Non-Guideline two-generational reproduction toxicity study, 35 male and 35

female Wistar rats were administered 0.01% or 1% Polyoxin D zinc salt in the feed 20 weeks prior to mating. From weeks 6-20, P parental animals had a mean intake of 144.79 mg/kg at 0.01% and 15, 013 mg/kg at 1% of the test material. Animals were mated (P), allowed to reproduce and wean a litter and mated again. No parental systemic toxicity or differences in body weight gain of each generation were observed in the study. No abnormal clinical signs were observed during the study period in any generation. **The parental systemic NOAEL for Polyoxin D zinc salt (Lot in Wistar rats is 1% for males and females. Due to a lack of any observed effects at the doses tested, a LOAEL was not identified.** The body weight of surviving offspring of FI-b dams fed 1% Polyoxin D zinc salt was significantly reduced at birth compared to control offspring body weight, but at one week after birth, the offspring body weight was significantly increased compared to control offspring body weight; body weights of treated offspring were comparable to that of control offspring at two weeks post birth. No significant differences were found between treated and control groups with regard to the average number of live births per litter, average body weight of live pups, ossification failure of the chest ossification center, or bone variation. No differences were found in the number of stillbirths and weaning rate. No specific abnormalities in postnatal growth or general behavior was found between treated and control groups. **The offspring NOAEL for Polyoxin D zinc salt is 0.01%, and the LOAEL was 1% based on significantly reduced body weight at birth.** Reproductive toxicity was not evident in the study. No differences were detected in mating, pregnancy, delivery, or nursing rate by generation between the treated and control groups. No chemical effects were found in males or females. **For male and female Wistar rats, the reproductive NOAEL for Polyoxin D zinc salt is 1%, and the LOAEL was not identified.**

Conclusion: **ACCEPTABLE** to fulfill the data requirements under OPPTS 870.3800; no additional data are required. **Based on the data, Polyoxin D Zinc Salt is not a developmental or reproductive toxicant.** Reduced body weight was observed prior to and at birth in the offspring of the high dose group of the first generation. However, the low number of litters observed at this timepoint (n=5/group) make it difficult to determine if the effect was treatment-related. No reproductive indices or viability indices were adversely affected by the treatment. Although some data were not provided, including but not limited to, parental postmortem observations, male and female reproductive function parameters, parental and offspring organ weights, and detailed data for histopathology; the lack of effects in parental animals and offspring give weight to the lack of toxicity of the test material.

Immunotoxicity

Immunotoxicity following dietary exposure - Special Testing (OPPTS 870.7800; MRID 47120901): Polyoxin D Zinc Salt Technical was administered to ten female mice in the diet for 28 days at concentrations of 0, 400, 4000, and 40,000 ppm (equivalent to 0, 86, 832, and 8,034 mg technical/kg bw/day, respectively; equivalent a.i. dosage was 19, 184, 1776 mg/kg bw/day). A

positive control group of ten mice received cyclophosphamide, a known immunosuppressant, at 50 mg/kg bw/day by intraperitoneal injection on days 24-27. There were no compound-related deaths or effects on clinical observations, body weight or food consumption. There were no compound-related macroscopic findings noted and organ weights were unaffected. There were no compound-related effects on the humoral immune response to the T-dependent antigen, sRBC. The cyclophosphamide-treated group had small spleens and thymuses which correlated with the lower spleen and thymus organ weights noted at necropsy. The humoral immune response to the T-dependent antigen, sRBC, was decreased (100%) when compared to the control group. These changes are consistent with the expected immunological effects of this positive control agent.

No LOAEL for immunotoxicity was demonstrated for Polyoxin D Zinc Salt Technical in female mice. The NOAEL for immunotoxicity is 40,000 ppm (equivalent a.i. dose of 1776 mg/kg bw/day).

Conclusion: **ACCEPTABLE**; no additional data are required. No meaningful immunotoxicity endpoints were identified. Polyoxin D is not immunotoxic on a dietary basis.

OTHER PREVIOUSLY REVIEWED STUDIES/DATA IN 1997 BRAD

Chronic Exposure/Oncogenicity (from Polyoxin-D, Zinc Salt BRAD)

According to the Polyoxin-D, Zinc Salt BRAD, results of chronic toxicity/oncogenicity studies indicated that there were no significant toxicity or oncogenic responses in mice dosed with the TGAI at up to 5% dose levels in 24-month studies (NOELs = 2058.7 to 3591 mg/kg/day; MRIDs 432618-38 and -39).

Conclusion: Based on the data, Polyoxin-D, Zinc Salt is not a chronic toxicant or oncogen. These data are acceptable to support the new food uses and the permanent Tolerance Exemption petition.

Effects on Immune and Endocrine Systems (from Polyoxin-D, Zinc Salt BRAD)

Polyoxin-D, zinc salt is a relatively specific, competitive inhibitor of fungal chitin synthetases (Endo et al., 1970; Suzuki et al., 1965). There is no available evidence demonstrating that Polyoxin-D, Zinc Salt acts as an endocrine disruptor in humans.

Conclusion: Based on negative responses obtained from developmental toxicity studies, chronic exposure studies, and oncogenicity studies (MRIDs 432618-36, -38 and -39) no adverse effects

to the endocrine or immune systems are known or expected. These data are acceptable to support the new food uses and the permanent Tolerance Exemption petition.

No toxicological endpoints were identified for Polyoxin-D, Zinc Salt Technical (see Table 2 above). Although acute oral toxicological endpoints were identified for the end-use product Endorse® Water Dispersible Granules (EPA Reg. No. 66330-56; Table 3), these endpoints are just slightly below the threshold of Tox Category IV (see Table 3 above), and it is not likely that the observed endpoints resulted from the presence of the active ingredient.

The proposed maximum application rate of Polyoxin-D, Zinc Salt is practically identical to the rate originally assessed in the 1997 BRAD. Therefore, any potential for adverse health effects will be no greater than that identified in the 1997 BRAD. No immune response or endocrine systems concerns were noted in the 1997 BRAD.

Occupational, Residential, School, and Daycare Exposure and Risk Characterization

Based on the proposed use pattern for Endorse® Water Dispersible Granules (EPA Reg. No. 66330-56), there is the potential for dermal, ocular, and inhalation exposure. However, due to the lack of significant mammalian acute and chronic toxicity, the specific mode of action as a fungal chitin synthetase inhibitor, and the low use rate (no more than 0.3875 lb product/A/application) and active ingredient (0.04375 lb/A/application) data on occupational exposure is not required at this time. Occupational exposure will be further mitigated via appropriate Tox Category III PPE and appropriate precautionary labeling. All proposed uses are agricultural or commercial.

Conclusion: There are no concerns for occupational exposure and the proposed new food uses will not result in any indoor residential, school, or daycare exposure.

Drinking Water Exposure and Risk Characterization

There is a potential for Polyoxin-D, Zinc salt to enter ground water or other drinking water sources after a significant rainfall and surface water runoff, and from incidental spray drift. However, health risk to humans is considered negligible based on the lack of meaningful toxicological endpoints for the TGAI and the EP, the mode of action as a chitin synthetase inhibitor, and the extremely low application rate of the EP (no more than 0.3875 lb product/A/application) and active ingredient (0.04375 lb/A/application). The proposed application rate of Polyoxin-D, Zinc Salt is practically identical to the rate originally assessed in the 1997 BRAD). Therefore, any potential for adverse health effects will be no greater than that identified in the 1997 BRAD. No drinking water exposure concerns were noted in the 1997 BRAD.

Conclusion: There are no drinking water exposure concerns in regard to the new food uses.

Acute and Chronic Dietary Risks for Sensitive Subpopulations, Particularly Infants and Children

Health risk to humans, including infants and children is considered negligible based on the lack of meaningful toxicological endpoints for the TGAI and the EP, the mode of action as a chitin synthetase inhibitor, and the extremely low application rate of the EP (0.3875 lb product/A/application) and the active ingredient (0.04375 lb/A/application), with no more than 6 applications/season. The Agency has no information to indicate that infants and children would be more sensitive than adults to Polyoxin-D, Zinc

The proposed application rate of Polyoxin-D, Zinc Salt is practically identical to the rate originally assessed in the 1997 BRAD). Therefore, any potential for adverse health effects will no greater than that identified in the 1997 BRAD. No acute and chronic dietary risks for sensitive subpopulations were noted in the 1997 BRAD.

Conclusion: There are no acute and chronic dietary risk concerns for sensitive subpopulations.

Aggregate Exposure from Multiple Routes Including Dermal, Oral, and Inhalation

Aggregate exposure would occur primarily amongst workers/applicators via dermal and inhalation routes. Health risk to humans is considered negligible based on the lack of meaningful toxicological endpoints for the TGAI and the EP via the dermal and inhalation routes of exposure (see Tables 2 & 3 above) and the mode of action as a chitin synthetase inhibitor.

The proposed application rate of Polyoxin-D, Zinc Salt is practically identical to the rate originally assessed in the BRAD). Therefore, any potential for adverse health effects will be no more than that identified in the 1997 BRAD. No aggregate exposure concerns were noted in the 1997 BRAD.

OVERALL TOXICOLOGICAL CONCLUSIONS FOR THE NEW FOOD USES AND THE PERMANENT TOLERANCE EXEMPTIONS: No toxicological endpoints were identified for Polyoxin-D, Zinc Salt technical . These data are acceptable to support the new food uses and the permanent Tolerance Exemption petition. Although acute oral toxicological endpoints were identified for the end-use product Endorse® Water Dispersible Granules (EPA

Reg. No. 66330-56), these endpoints are just below the threshold of Tox Category IV. It is not likely that the observed endpoints resulted from the presence of the active ingredient.

The original acute toxicity hazard assessment and health risk assessment conducted in support of the Polyoxin-D, Zinc Salt BRAD EPA, 1997) was based on a field application rate of 117 g a.i./A. **The maximum proposed seasonal application rate of Polyoxin-D, Zinc Salt for Endorse Water Dispersible Granules on food crops is approximately 119 g/A (approximately 1.02x the original assessed rate). Therefore, any potential for adverse health effects will be no greater than that identified in the 1997 BRAD.** No acute, subchronic, or chronic toxicity concerns were noted in the 1997 BRAD.

In addition, no meaningful toxicological endpoints were identified in four new studies (mutagenicity, 90-day oral toxicity, a two-generation reproduction study, and a dietary immunotoxicity study) submitted to support the new food uses and the permanent tolerance exemption.

For this review, the Terrestrial Exposure Model (T-Rex, v. 1.2.3; EPA, 2005) was used to calculate new terrestrial residue data for the active ingredient and the end-use product based on the proposed maximum label application rates on food (no more than 0.3875 lb product/A/application and 0.04375 lb active ingredient/A/application with no more than 6 applications) for a seasonal application of 2.325 lbs product/A and 0.2625 lbs active ingredient/A. These application rates result in maximum residues of **no more than approximately 360 ppm product and approximately 40 ppm a.i., respectively** (see Appendices A and B). These levels are well below the highest doses used in toxicity testing.

Based on the data, it is highly unlikely that there will adverse effects resulting from the use of the end-use product via the oral route of exposure, especially in view of the extremely low application rate (no more than 0.3875 lb product/A/application and 0.04375 lb active ingredient/A/application with no more than 6 applications) and lack of meaningful toxicological endpoints. Acute inhalation exposure can be mitigated with appropriate Tox Category III PPE and appropriate precautionary labeling. There are no acute, subchronic, or chronic oral toxicity or acute inhalation toxicity human health concerns for the active ingredient when the product is used in accordance with approved labeling.

NOTE 2: It is noted that a waiver request for acute inhalation toxicity for the end-use product was deemed Unacceptable (see Memorandum from R. Sjoblad to D. Greenway, dated 12/01/2004). Since the product (EPA Reg. No. 66330-56; 11.3% a.i.) was registered in October 2005, this deficiency was evidently resolved. However, no decision document is available explaining how this resolution was achieved. The TGAI (23.8% a.i.) was placed in Tox Category IV for acute inhalation toxicity, based on a acute inhalation toxicity study (MRID 432618-27). Similarly, an EP containing 2.5%

a.i. (EPA Reg. No. 068173-2) containing the same inerts, was also placed in Tox Category IV (MRID 432618-28). Due to the similarity of inerts in both EPs, the higher level of inerts in EPA Reg. No. 068173-2, and the Tox Category IV classification for EPA Reg. No. 068173-2 and the TGAI (EPA Reg. No. 068173-1), it is likely that an acute inhalation Tox Category IV could be classified for Endorse (EPA Reg. No. 068173-3/66330-56).

Polyoxin-D
PC Codes: 230000

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EPA Reg Nos.: 66356-1 & 66356-3
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ENVIRONMENTAL ASSESSMENT

Except for a non-guideline Honey Bee Study, no non-target organism studies or environmental fate data were submitted for review. However, studies for other taxa were submitted in support of the registration of the TGAI [Polyoxin-D Zinc Salt Technical (23.8%); EPA Reg. No. 68173-1). All submitted data are summarized in Table 4 below:

Table 4. Tier I Non-target Organism Data for Polyoxin-D Zinc Salt Technical (23.8%); EPA Reg. No. 68173-1

Data Requirement	LD50/LC50	Toxicity Category	MRID
Avian Acute Oral Toxicity	>2150 mg/kg (Mallard duck)	Practically non-toxic	432618-40
Avian Dietary Toxicity	>5000 ppm (Mallard duck)	Practically non-toxic	432618-41
Freshwater Fish 96-hr LC50	5.06 ppm	Moderately toxic	432618-42
Freshwater Aquatic Invertebrate Toxicity	1.35 ppm	Moderately toxic	432618-43
Non-Target Plants	Waiver requested	N/A	Waived [1]
Non-Target Insects	>400 ppm [2]	Practically non-toxic	432618-44
Honeybee Test	Waiver requested		Waived [3]
	24-hr LD50 = 88.1 *u*g/bee 48-hr LD50 = 32.9 *u*g/bee	Practically non-toxic	See footnote 4

[1] Mode of action is specific to fungal chitinases and the product is intended to be applied to plants to control fungal pathogens.

[2] Tests were conducted on eggs, nymphs, and larva of two-spotted mites, brown leafhoppers, and Diamondback moth. The study was classified as Supplemental since it did not follow established Guideline protocols and used Asian insect pests of agricultural crops instead of beneficial insects. However, the study was considered Acceptable to support the data requirements since it demonstrated that three different non-target insects were unaffected by Polyoxin-D, zinc salt when applied at rates 10x the field rate estimated in the 1997 BRAD. The field application rate proposed under the Section 18 request is only 0.45x the rate assessed in the 1997 BRAD.

[3] Waiver request deemed acceptable based on results of non-target insect study submitted in MRID 432618-44

[4] Unpublished study submitted by Kaken Pharmaceutical Co. Ltd. on 07/01/2008; study conducted by the Japan Plant Protection Association , dated 10/28/2001

Environmental Fate and Groundwater

Aquatic Organisms: In the Polyoxin-D, Zinc Salt BRAD (EPA, 1997), aquatic Estimated Environmental Concentrations (EECs) were calculated to be approximately 1.6 ppb per 1% residue runoff following each application. Since the maximum proposed single application rate for the new food uses practically identical to the single application rate assessed in the 1997 BRAD, the EEC is not expected to change with new uses. Based on the existing non-target organism data (Table 4), these levels, which are well below any known toxic endpoints for quatic organisms (see Table 4 above), are not expected to pose any risk to aquatic organisms.

Terrestrial Organisms: In the Polyoxin-D, Zinc Salt BRAD (EPA, 1997), terrestrial Estimated Environmental Concentrations (EECs) were calculated to be approximately 9 ppm to 62 ppm on foliage depending on the plant type. Since the maximum proposed single application rate for the new food uses practically identical to the single application rate assessed in the 1997 BRAD, the EEC is not expected to change with new uses. Based on the toxicological data for rodents (Table 2), birds, and non-target insects (Table 4), these levels are no expected to pose any risk to non-target mammalian and avian wildlife, plants, and insects.

For this review, the Terrestrial Exposure Model (T-Rex, v. 1.2.3; EPA, 2005) was used to calculate new terrestrial residue data for the active ingredient and the end-use product based on the proposed maximum label application rates on food (no more than 0.3875 lb product/A/application and 0.04375 lb active ingredient/A/application with no more than 6 applications) for a seasonal application of 2.325 lbs product/A and 0.2625 lbs active ingredient/A. These application rates result in maximum residues of **no more than approximately 360 ppm product and approximately 40 ppm a.i., respectively** (see Appendices A and B).

Conclusion: There are no concerns for non-target terrestrial organisms. Based on the moderately toxic category obtained from laboratory studies with freshwater fish and daphnids, it is appropriate to have aquatic mitigating language on the product label. However, the use of Polyoxin D, Zinc Salts is highly unlikely to pose more than minimal concerns to aquatic organisms when used in accordance with approved labeling.

Ecological Exposure and Risk Characterization

Exposure and Risk to Non-Target Organisms

Non-target organism studies [see Tables 2 & 3 (rodents), & 4 (other taxa) above] indicated that there was no significant toxicity to mammals and birds when exposed to Polyoxin-D, zinc salt at limit doses. Non-target terrestrial insects were unaffected by exposure to the active ingredient at up to 400 ppm (equivalent to approximately 10x the expected residue level when he product is applied at the maximum proposed label rate). Non-target plants will be unaffected due to the unique mode of action as a fungal chitin synthetase inhibitor; plants do not possess fungal chitin synthetase. Furthermore, the product is intended for use on plants to control fungal pathogens. Polyoxin-D, Zinc salt was demonstrated to be moderately toxic to both freshwater fish and freshwater aquatic invertebrates in laboratory studies. However, based on the application rate and the proposed use patterns, the aquatic EECs do not exceed any LOCs for any aquatic non-targets, including threatened and endangered species.

Polyoxin-D
PC Codes: 230000

DP Number: 378876, 358878, & 382351
EPA Reg Nos.: 66356-1 & 66356-3
PP# 7F7252

Conclusion: There are no concerns for non-target organisms, including threatened and endangered species. Based on the data, a **No Effects (NE)** determination is made for Polyoxin-D, Zinc Salt on threatened and endangered species.

REFERENCES

Endo, A., K. Kakiki, and T. Misato. 1970. J. Bacteriol. 104(1): 189-196.

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cc: R. S. Jones, C. Pfeifer, BPPD Subject File/BPB File/IHAD/Archives
R. S. Jones, Ph.D., Sr. Biologist, FT, OPY: 08/18/2008

Polyoxin-D
PC Codes: 230000

DP Number: 378876, 358878, & 382351
EPA Reg Nos.: 66356-1 & 66356-3
PP# 7F7252

APPENDIX A: TERRESTRIAL EXPOSURE ANALYSIS OF ENDORSE WATER DISPERSIBLE GRANULES

Upper Bound Kenaga Residues For RQ Calculation

[redacted]

Acute and Chronic RQs are based on the Upper Kenaga Residues.

The maximum single day residue estimation is u both the acute and reproduction RQs.

RQs reported as "0.00" in the RQ tables below should be noted as <0.01 in your assessment. This is due to rounding and significant figure issues in Excel.

Endpoints

[redacted]

	359.88
	164.95
	202.43
	22.49

Avian Results

[redacted]

[redacted]

	409.87	233.72	104.64
	187.86	107.12	47.96
	230.55	131.47	58.86
	25.62	14.61	6.54

	#DIV/0!	#DIV/0!	#DIV/0!
	#DIV/0!	#DIV/0!	#DIV/0!
	#DIV/0!	#DIV/0!	#DIV/0!
	#DIV/0!	#DIV/0!	#DIV/0!

	Acute	Chronic
	#DIV/0!	#DIV/0!
	#DIV/0!	#DIV/0!
	#DIV/0!	#DIV/0!
	#DIV/0!	#DIV/0!

Note: To provide risk management with the maximum possible information, it is recommended that both the dose-based and concentration-based RQs be calculated when data are available

Polyoxin D Zinc Salt | Food and Turf | Upper bound Kenaga Residues

Mammalian Results

[redacted]

[redacted]

[redacted]

343.12	237.14	54.98			
157.26	108.69	25.20			
193.00	133.39	30.93			
21.44	14.82	3.44	4.77	3.29	0.76

[redacted]

Acute	Chronic	Acute	Chronic	Acute	Chronic
0.04	#DIV/0!	0.03	#DIV/0!	0.02	#DIV/0!
0.02	#DIV/0!	0.01	#DIV/0!	0.01	#DIV/0!
0.02	#DIV/0!	0.02	#DIV/0!	0.01	#DIV/0!
0.00	#DIV/0!	0.00	#DIV/0!	0.00	#DIV/0!
0.00	#DIV/0!	0.00	#DIV/0!	0.00	#DIV/0!

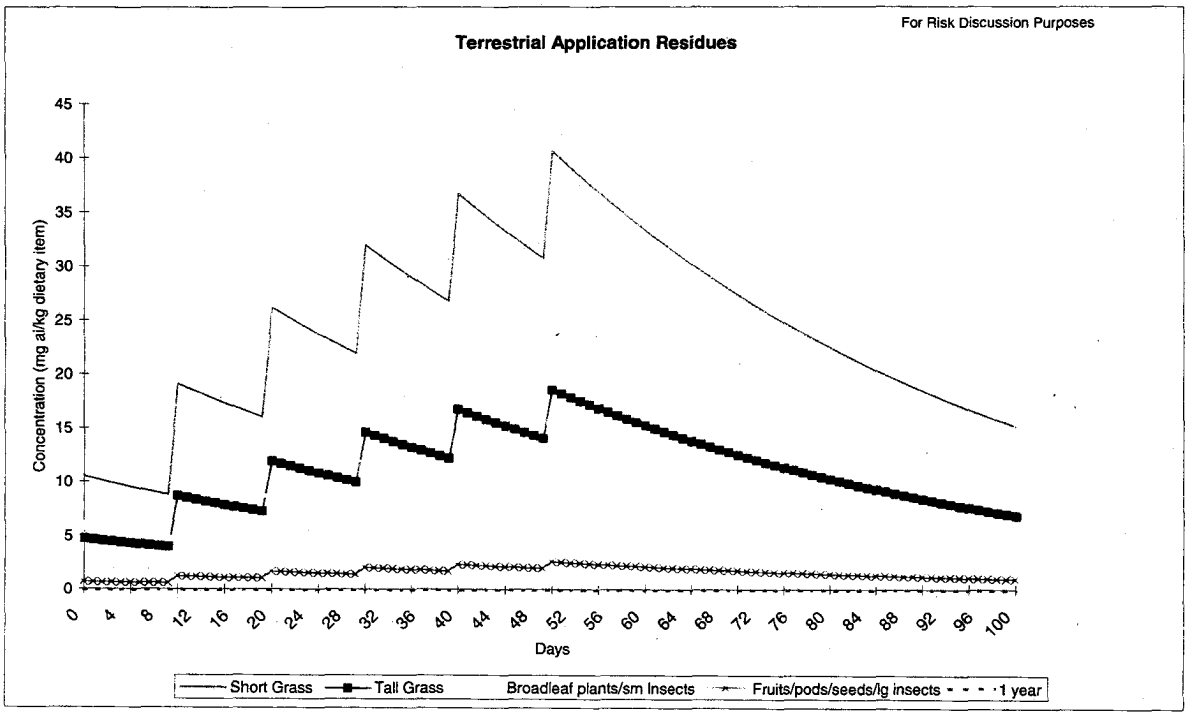
[redacted]

Acute	Chronic
#DIV/0!	#DIV/0!
#DIV/0!	#DIV/0!
#DIV/0!	#DIV/0!
#DIV/0!	#DIV/0!

Note: To provide risk management with the maximum possible information, it is recommended that both the dose-based and concentration-based RQs be calculated when data are available

Polyoxin D Zinc Salt **Food and Turf** **Upper bound Kenaga Residues**

Terrestrial Residues Graph



Polyoxin-D
PC Codes: 230000

DP Number: 378876, 358878, & 382351
EPA Reg Nos.: 66356-1 & 66356-3
PP# 7F7252

APPENDIX B: TERRESTRIAL EXPOSURE ANALYSIS OF POLYOXIN D ZINC SALT TECHNICAL

Upper Bound Kenaga Residues For RQ Calculation

[redacted]

Acute and Chronic RQs are based on the Upper Kenaga Residues.

The maximum single day residue estimation is u both the acute and reproduction RQs.

RQs reported as "0.00" in the RQ tables below should be noted as <0.01 in your assessment. This is due to rounding and significant figure issues in Excel.

Endpoints

[redacted]

40.63
18.62
22.86
2.54

Avian Results

[redacted]

[redacted]

[redacted]

46.28	26.39	11.81
21.21	12.09	5.41
26.03	14.84	6.65
2.89	1.65	0.74

[redacted]

0.04	0.02	0.01
0.02	0.01	0.00
0.02	0.01	0.00
0.00	0.00	0.00

[redacted]

Acute	Chronic
0.01	0.01
0.00	0.00
0.00	0.00
0.00	0.00

Note: To provide risk management with the maximum possible information, it is recommended that both the dose-based and concentration-based RQs be calculated when data are available

Polyoxin D Zinc Salt | Food and Turf | Upper bound Kenaga Residues

Mammalian Results

[redacted]

[redacted]

[redacted]

38.74	26.77	6.21			
17.76	12.27	2.85			
21.79	15.06	3.49			
2.42	1.67	0.39	0.54	0.37	0.09

[redacted]

Acute	Chronic	Acute	Chronic	Acute	Chronic
0.00	0.01	0.00	0.01	0.00	0.00
0.00	0.00	0.00	0.00	0.00	0.00
0.00	0.00	0.00	0.00	0.00	0.00
0.00	0.00	0.00	0.00	0.00	0.00
0.00	0.00	0.00	0.00	0.00	0.00

[redacted]

Acute	Chronic
#DIV/0!	0.00
#DIV/0!	0.00
#DIV/0!	0.00
#DIV/0!	0.00

Note: To provide risk management with the maximum possible information, it is recommended that both the dose-based and concentration-based RQs be calculated when data are available

Polyoxin D Zinc Salt **Food and Turf** **Upper bound Kenaga Residues**

Terrestrial Residues Graph