(10)

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

DEC 0 1 2004

MEMORANDUM

SUBJECT: Secondary Review of Information/data Submitted for Registration of Endorse WDG (Water Dispersable Granules) Containing Polyoxin D zinc salt as the Active Ingredient by Arvesta Corporation (66330-LA) and also by Kaken Pharmaceuticals (68173-G) [DP #308515 and 308553 for 66330-LA; and DP # 308554 and 308556 for 68173-G].

TO: Denise Greenway, RAL
Biochemical Pesticides Branch (BPB)
Biopesticides and Pollution Prevention Division (BPPD)

FROM: Roy D. Sjoblad
BPB, BPPD

Background: Arvesta Corporation, on its own behalf, and also as an agent of Kaken Pharmaceuticals, has submitted a petition to register a new turf fungicide product containing Polyoxin D zinc salt (at 11.3%) as the active ingredient.

Conclusion: The following deficiencies exist for registration of the product: The nature of the test material used in the acute toxicity studies could not be confirmed as being of the same composition as for ENDORSE WDG. The rationales set forth for the waiver of the acute inhalation toxicity study are not acceptable, and therefore, this study remains outstanding. Finally, results of the storage stability and corrosion characteristics studies need to be submitted when completed.

Data Submitted:

Product Chemistry (MRID 463402-01):

Product Identity and Composition (OPPTS 830.1550), Description of Starting Materials (OPPTS 830.1600), Description of Formulation Process (OPPTS 830.1650)and, Discussion of Formation of Impurities (OPPTS 830.1670).

The product identity/composition was adequately described. The beginning materials and formulation process were adequately described. No chemical reactions arise during formulation, and there are no impurities of toxicological concern.

Preliminary Analysis (OPPTS 830.1700), Certified Limits (OPPTS 830.1750), and Enforcement Analytical Method (OPPTS 830.1800).

Preliminary analysis was not conducted, and is not required for a non-integrated system with a previously registered active ingredient. The upper and lower certified limits for active and inert ingredients are acceptable, and an HPLC method (adequately described) is used to analyze for the active ingredient.

Physical and Chemical Characteristics (OPPTS 830.6302 - 830.7950)

The physical/chemical characteristics are summarized in the primary review (Table 2, Page 5). The product bulk density is specified as 0.561 g/ml, while on the CSF it is given a range of 0.5 to 0.8 g/ml. The pH is specified as 7.07, while on the CSF it is given a range of pH 6 to 8. The one-year storage stability study, and the corrosion characteristics study are underway, **and need to be submitted when completed.**

Mammalian Toxicology:

The acute exposure mammalian toxicity studies were done with "Polyoxin Z dry flowable," which was described as a "Brown fine granule" containing about 11.3% Polyoxin D salt and about 88.7% surfactants, etc. which is consistent with the current product, Endorse Water Dispersible Granules. However, the test material in the toxicology studies was not further described. **Note to RAL: The registrant should confirm whether the test material used in the acute toxicity studies was the same composition as Endorse Water Dispersible Granules.**

Acute oral toxicity - rat (OPPTS 870.1100) MRID 463402-02:

Five male and five female rats/group were dosed orally by gavage with "Polyoxin Z dry flowable" at either 2,500 mg/kg, 5,000 mg/kg, or 7,500 mg/kg. At 2,500 mg/kg there were no deaths, no observed clinical signs of toxicity, nor any signs of abnormality upon necropsy. At 7,500 mg/kg all animals died within 24 hours after dosing. Clinical signs observed included decreased or cessation of movement as early as 1 hour after dosing and soft feces. At 5,000 mg/kg, 2 males and 3 females died on the day following dosing. Survivors in this dose group also showed decreased movement and soft feces, but recovered by the day after dosing. Survivors also gained weight during the study. Animals that died on the day of dosing had dark reddening of the lungs. The study author reported the LD50 values for males at 4916 mg/kg, and for females at 4,404 mg/kg. **The study is Acceptable. The test material can be placed in Toxicity Category III.**

Acute dermal toxicity - rat (OPPTS 870.1200) MRID 463402-03:

The LD50 value for rats treated dermally with"Polyoxin Z dry flowable"was >2,000 mg/kg. All

rats survived and gained weight during the study. No abnormalities were noted upon cageside observation or upon necropsy. **The study is Acceptable. The test material can be placed in Toxicity Category III.**

Primary eye irritation - rabbit (OPPTS 870.2400) MRID 463402-04:

The left eyes of six rabbits each were treated with 0.1g of "Polyoxin Z dry flowable. Corneal opacity was noted in 2 rabbits, which resolved by 48 hours after dosing. Conjunctival irritation (Score = 2) was noted on all rabbits within 1 hour of dosing, and which resolved by 48 hours. The study is **Acceptable.** The test material can be placed in **Toxicity Category III.**

Primary dermal irritation - rabbit (OPPTS 870.2500) MRID 463402-05:

"Polyoxin Z dry flowable" (at 0.5 g/animal) was not irritating to the skin of rabbits. The study is **Acceptable.** The test material can be placed in **Toxicity Category IV.**

Skin sensitization - guinea pig (OPPTS870.2600) MRID 463402-06:

"Polyoxin Z dry flowable" was not a sensitizer in guinea pigs when tested by the Buehler Method. The study is **Acceptable.**

Acute inhalation toxicity (870.1300) - Waiver request; MRID Not Assigned.

A waiver for the acute inhalation study was requested based on: 1) the low acute inhalation toxicity of the Polyoxin D Technical material (LC50 .2.44 mg/L for males, and 2.17 mg/L for females; i.e., Toxicity Category IV) which comprises 47.5% of the product by weight, and 2) each inert ingredient has an acute oral toxicity (test animal species not noted) that would place them in Toxicity category III.

The registrant cited a single MSDS for each of the [redacted] inert ingredients. The MSD Sheets were not submitted. It was stated that animal studies with one of the inerts caused a slight decrease in lung function. But also, the registrant states acute inhalation data are not available for any of the inert ingredients.

The waiver request is not Acceptable. The acute inhalation study could be waived if particle size analysis showed that the end use product is not respirable. The rationale that low acute oral toxicity of each of the inert ingredients allows for the conclusion that the inerts would not cause or contribute to, pulmonary toxicity is not scientifically supportable.

DATA EVALUATION RECORD

POLYOXIN D ZINC SALT
(ENDORSE® WATER DISPERSIBLE GRANULE)

STUDY TYPES: Product Identity and Composition (OPPTS 830.1550)
Description of Beginning Materials (OPPTS 830.1600)
Description of Formulation Process (OPPTS 830.1650)
Discussion of Formation of Impurities (OPPTS 830.1670)
Preliminary Analysis (OPPTS 830.1700)
Certified Limits (OPPTS 830.1750)
Enforcement Analytical Method (OPPTS 830.1800)
Physical and Chemical Characteristics (OPPTS 830.6302-830.7950)

MRID 46340201

Prepared for
Biopesticides and Pollution Prevention Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1801 Bell Street
Arlington, VA 22202

Prepared by
Toxicology and Hazard Assessment Group
Life Sciences Division
Oak Ridge National Laboratory
Oak Ridge, TN 37830
Task Order No. 04-74

Primary Reviewer:
Susan Chang, M.S.

Signature: [signature]
Date: NOV 0 3 2004

Secondary Reviewers:
Sylvia Milanez, Ph.D., D.A.B.T.

Signature: [signature]
Date: NOV 0 3 2004

Robert H. Ross, M.S., Group Leader

Signature: [signature]
Date: NOV 0 3 2004

Quality Assurance:
Lee Ann Wilson, M.A.

Signature: [signature]
Date: NOV 0 3 2004

Disclaimer

This review may have been altered subsequent to the contractor's signatures above.

Oak Ridge National Laboratory managed and operated by UT-Battelle, LLC., for the U.S. Department of Energy under Contract No. DE-AC05-00OR22725.

DATA EVALUATION RECORD

EPA Secondary Reviewer: Mary D. Goldsmith 12/1/04

STUDY TYPE:	Product Identity and Composition (OPPTS 830.1550) Description of Beginning Materials (OPPTS 830.1600) Description of Formulation Process (OPPTS 830.1650) Discussion of Formation of Impurities (OPPTS 830.1670) Preliminary Analysis (OPPTS 830.1700) Certified Limits (OPPTS 830.1750) Enforcement Analytical Method (OPPTS 830.1800) Physical and Chemical Characteristics (OPPTS 830.6302-830.7950)
MRID NO:	46340201
DP BARCODE NO:	DP308515
CASE NO:	Not reported
DECISION NOS:	346783 and 346781
TEST MATERIAL:	Endorse Water Dispersible Granule (EPA Reg Nos. 66330-LA and 68173-G; 11.3% w/w polyoxin D zinc salt, a.i.)
PROJECT NO:	Arvesta Corporation: TMN-0213 and TMN-0214
SPONSORS:	Arvesta Corporation, San Francisco, CA and Arvesta Corporation as agent for Kaken Pharmaceutical Co. Ltd., Bunkyo, Tokyo, Japan
TESTING FACILITY:	Toxikon Corporation, Jupiter, FL and TNO Prins Maurits Laboratory, 2280 AA Rijswijk, The Netherlands
TITLE OF REPORT:	U.S. EPA Product Properties Test Guidelines - Group A and B of Endorse WDG (TM-43802)
AUTHORS:	Stephen R. Cornes, Yiting Li, and Kacia Baldwin
STUDY COMPLETED:	June 14, 2004
GOOD LABORATORY PRACTICE:	GLP Compliant

Inert ingredient information may be entitled to confidential treatment

CONCLUSION: Endorse Water Dispersible Granule is an end-use product (EP) and is a systemic, foliar applied turf fungicide. The active ingredient is 11.3% w/w polyoxin D zinc salt and the TGAI Polyoxin D Zinc Salt Technical (EPA Reg. No. 68173-1) containing 23.8% Polyoxin D Zinc Salt is 47.5% of the EP. The inerts are [redacted] Two CSFs and labels were submitted for the same EP, one by Arvesta Corporation, and one other by Kunimine Industries (with Arvesta Corporation as their agent). The two labels agree with the corresponding CSFs concerning the concentration of the active ingredient. The beginning materials and formulation process are adequately described. No chemical reactions occur during the manufacturing process and no formulation impurities are created. Preliminary analysis was not conducted since it is not required for a non-integrated system with registered active ingredients. The upper and lower certified limits of the active and inert ingredients are within the recommended range in guideline OPPTS 830.1750. The enforcement analytical method is HPLC to determine polyoxin D zinc salt. The physical/chemical characteristics data are from the "Summary of the Physical/Chemical Properties (PR Notice 98-1)" and are adequately addressed except that the one-year storage stability study and corrosion characteristics study are in progress.

CLASSIFICATION: **ACCEPTABLE**, but the registrant needs to submit the results of the storage stability and corrosion characteristics upon completion of the study.

CONTAINS CONFIDENTIAL BUSINESS INFORMATION

Test Material: Endorse Water Dispersible Granule (Endorse WDG) containing 11.3% w/w polyoxin D zinc salt

I. **PRODUCT IDENTITY AND COMPOSITION:** Endorse Water Dispersible Granule (EPA Reg. Nos. 66330-LA and 68173-G) is an end-use product (EP) for use on golf courses, residential lawns, parks, commercial and institutional grounds composed of cool and warm season grasses such as bluegrass, bentgrass, fescue, ryegrass, zoysiagrass, or mixtures of these grasses. The EP is a systemic, foliar applied turf fungicide for control of brown patch and large patch caused by *Rhizoctonia* spp. The EP also controls cool weather brown patch (yellow patch) (*Rhizoctonia* cerealis), foliar and basal anthracnose (*Colletotrichum graminicola*), gray snow mold (*Typhula ishikariensis* and Typhula

incarnata), leaf spot/melting out (Dreschlera poae), pink snow mold (microdochium nivale), red thread (*Laetisaria fuciformis*), Rhizoctonia damping off (*Rhizoctonia solani*), and zoysia patch (*Rhizoctonia solani*) on cool and warm season turf grasses. The EP also aids in the suppression of gray leaf spot (*Pyricularia grisea*) and may be applied as a preventive or curative treatment in conjunction with good turf management practices. The active ingredient is 11.3% w/w polyoxin D zinc salt and the TGAI in the EP is 47.5% w/w Polyoxin D Zinc Salt Technical (EPA Reg. No. 68173-1) which contains 23.8% Polyoxin D Zinc Salt. The inerts are [redacted] Two CSFs and labels were submitted for the same EP, one by Arvesta Corporation, and one other by Kunimine Industries (with Arvesta Corporation as their agent). The two labels agree with the corresponding CSFs concerning the concentration of the active ingredient.

Deficiencies: None

II. **DESCRIPTION OF BEGINNING MATERIALS:** The beginning materials are Polyoxin D Zinc Salt Technical containing 23.8% Polyoxin D Zinc Salt, [redacted] The MSDSs of the ingredients are provided in the study.

Deficiencies: None

III. **DESCRIPTION OF FORMULATION PROCESS:** [redacted]

Deficiencies: None

IV. **DISCUSSION OF FORMATION OF IMPURITIES:** No chemical reactions occur during manufacturing process and no formulation impurities are created.

Deficiencies: None

V. **PRELIMINARY ANALYSIS:** Preliminary analysis was not conducted since it is not required for a non-integrated system with registered active ingredient.

Deficiencies: None

VI. **CERTIFIED LIMITS:** Endorse Water Dispersible Granule contains 11.3% by weight (limits of 10.7-11.9%, by weight) polyoxin D zinc salt. The TGAI in EP is 47.5% by weight (limits of 45.1-49.8%, by weight) Polyoxin D Zinc Salt Technical. The lower and

Inert ingredient information may be entitled to confidential treatment

upper certified limits for the inerts are [redacted] The upper and lower certified limits of the TGAI are outside (±5%) of the recommended range (±3%) in guideline OPPTS 830.1750, but the upper and lower certified limits of the pure active and inert ingredients are within the recommended range. The registrant indicated in a letter dated 7/21/04 that "due to the fact that the active ingredient content in the technical grade Polyoxin D Zinc Salt is very low (23.8% nominal) elected to have certified limits at 5% to better control the production."

Deficiencies: None

TABLE 1. Nominal CSF concentrations and limits for Endorse Water Dispersible Granule[a]

Ingredients (CAS number)	PC Code	Purpose	Concentration (% by weight)		
			Nominal	Lower	Upper
Active Ingredient					
Polyoxin D Zinc Salt Technical containing 23.8%			47.5%	45.1%	49.8%
Polyoxin D zinc salt (146659-78-1)	230000		11.3%, a.i.	10.7%, a.i.	11.9%, a.i.
Inert ingredient					
[redacted]					

[a] Data from CSFs.

VII. **ENFORCEMENT ANALYTICAL METHOD:** The enforcement analytical method uses HPLC to determine polyoxin D zinc salt. The column is a Zorbax-300-SCX 4.6 mm x 150 mm, 5 µm particle size. The mobile phase is 5 mM ammonium formate (pH 3), the detector wavelength is 276 nm, the flow rate is 0.50 mL/min, the column temperature is 40°C, and injection volume is 10 µL. TM-43802 test sample (0.1 g) was dissolved in 5 mM ammonium formate in a 100 mL volumetric flask and filtered through a 0.45 µm millipore disk filter. Two mL of the filtrate is diluted to 100 mL with distilled water for HPLC analysis. The polyoxin D content and polyoxin D zinc salt content are calculated.

Deficiencies: None

VIII. **PHYSICAL AND CHEMICAL CHARACTERISTICS:**

1. **Methods:** The data are from the "Summary of the Physical/Chemical Properties (PR Notice 98-1)." The self-certification statement is included in MRID 46340201.

2. **Results:** The physical/chemical properties are listed in Table 2. There is discrepancies concerning the pH and bulk density between the CSF and the study report. This is not a deficiency since the CSF is the legal document.

3. **Deficiencies:** The one-year storage stability study and corrosion characteristics study are in progress.

TABLE 2. Physical and Chemical Properties for Endorse Water Dispersible Granule[a]

Guideline Reference No./Property	Description of Result	Methods/Report No.
830.6302 Color	Dusty sable brown	TMN-0213
830.6303 Physical State	Fine powder (granule)	TMN-0213
830.6304 Odor	Clay-like, earthy	TMN-0213
830.6313 Stability	Not required for EP	
830.6314 Oxidation/Reduction: Chemical Incompatibility	No reaction with water, zinc powder, or monoammonium phosphate. Significant temperature increases and evolution of bubbles when placed in contact with household bleach.	TMN-0213
830.6315 Flammability	Product is not a combustible liquid.	
830.6316 Explodability	Product has no explosive properties.	TMN-0213
830.6317 Storage Stability	In progress (expected completion date 2/7/05)	TMN-0214
830.6319 Miscibility	Not applicable	
830.6320 Corrosion Characteristics	In progress (expected completion date 2/7/05)	TMN-0214
830.6321 Dielectric Breakdown Voltage	Not required for EP; product is not a liquid and is not intended for use around electrical equipment.	
830.7000 pH	7.07 at 22°C; 6-8 (CSF)	TMN-0213
830.7050 UV/Visible	Not required for EP	
830.7100 Viscosity	Not applicable; product is not a liquid.	
830.7200 Melting Range	Not required for EP	
830.7220 Boiling Range	Not required for EP	
830.7300 Bulk Density	0.561 g/mL; 0.5-0.8 g/mL (CSF)	TMN-0213
830.7370 Dissociation Constant in Water	Not required for EP	
830.7550 Partition Coefficient	Not required for EP	
830.7840 Water Solubility	Not required for EP	
830.7950 Vapor Pressure	Not required for EP	

[a] Data from MRID 46340201.

IX. **ADDITIONAL REVIEWER'S COMMENTS:** The registrant should consider adding an "s" to the end of the name of their product on the label (i.e., change "granule" to "granules") to more accurately describe its contents.

DATA EVALUATION RECORD

POLYOXIN D ZINC SALT
(POLYOXIN Z DRY FLOWABLE)

STUDY TYPE: ACUTE ORAL TOXICITY - RAT (870.1100)
MRID 46340202

Prepared for
Biopesticides and Pollution Prevention Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1801 Bell Street
Arlington, VA 22202

Prepared by
Toxicology and Hazard Assessment Group
Life Sciences Division
Oak Ridge National Laboratory
Oak Ridge, TN 37831
Task Order No. 04-75

Primary Reviewer:
Susan Chang, M.S.

Signature: _____
Date: NOV 17 2004

Secondary Reviewers:
H. Tim Borges, M.T.(A.S.C.P.), Ph.D., D.A.B.T.

Signature: _____
Date: NOV 17 2004

Robert H. Ross, M.S., Group Leader

Signature: _____
Date: NOV 17 2004

Quality Assurance:
Lee Ann Wilson, M.A.

Signature: _____
Date: NOV 17 2004

Disclaimer

This review may have been altered subsequent to the contractor's signatures above.

Oak Ridge National Laboratory managed and operated by UT-Battelle, LLC., for the U.S. Department of Energy under Contract No. DE-AC05-00OR22725.

DATA EVALUATION RECORD

EPA Secondary Reviewer: [signature] 12/01/04

STUDY TYPE:	Acute Oral Toxicity - Rats (OPPTS 870.1100)
MRID NO:	46340202
DP BARCODE NOS:	DP308553 and DP308556
CASE NO:	Not reported
DECISION NOS:	346783 and 346781
TEST MATERIAL:	Polyoxin Z Dry Flowable (11.25% polyoxin D zinc salt, a.i.)
PROJECT NO:	BOZO/B-3301
SPONSOR:	Kaken Pharmaceutical Co., Ltd., Tokyo, Japan
TESTING FACILITY:	Bozo Research Center, Inc., Tokyo, Japan
TITLE OF REPORT:	An Oral Acute Toxicity Study of Polyoxin Z Dry Flowable in Rats
AUTHOR:	S. Oda
STUDY COMPLETED:	August 30, 1996
GOOD LABORATORY PRACTICE:	GLP Compliant (8/10/84, Japan)
CONCLUSION:	The study author reported that the oral LD_{50}'s for males and females were 4916 mg/kg (95% C.L. 4297-5624 mg/kg) and 4404 mg/kg (95% C.L. 3850-5039 mg/kg), respectively. The reviewer calculated that the oral LD_{50}'s for the male, female, and combined were approximately 5268, 4573, and 5000 mg/kg, respectively.
CLASSIFICATION:	ACCEPTABLE -- TOXICITY CATEGORY III

I. STUDY DESIGN:

1. **Test Material:** Polyoxin Z Dry Flowable containing 11.25% polyoxin D zinc salt, a.i.; Lot No. RUN6

2. **Test Animals:** Thirty-one male and 31 female Crj:CD(SD) strain SPF rats were received from Charles River Japan Inc., Atsugi. Groups of five males and five females were assigned and weighed 237-272 g (males) and 146-171 g (females) on the day of dosing. The young adult animals, 7 weeks old, were housed in groups of five in stainless steel wire mesh cages. The animals were fed pellet diet CRF-1 (radiation sterilized: Oriental Yeast Co., Ltd.), *ad libitum*. Tap water was available *ad libitum*. The environmental conditions of the animal

room were as follows: temperature, 20-26°C; relative humidity, 30-70%; air changes, 10-15 per hour; and photoperiod, 12 hour light/dark cycle.

3. **Methods:** Rats were tail-marked: males (Nos. 1001-1005, 2002-2005, 3001-3005, and 4001-4005) and females (Nos. 1101-1105, 2101-2105, 3101-3105, and 4101-4105). The rats were quarantined for one week and fasted overnight prior to dosing. The test material (0, 2500, 5000, or 7500 mg/kg body weight) was dosed in distilled water at a volume of 2 mL/100 g body weight by gavage (Table 1). Body weight was recorded prior to dosing, and on days 1, 2, 3, 7, 10, and 14 and at death. The test animals were observed for mortality and clinical signs of toxicity frequently post-dosing and at least daily for 14 days. All decedent or euthanized animals were necropsied.

II. RESULTS:

1. **Mortality:** Mortality is given in Table 1. Two males and three females in the 5000 mg/kg group and all animals in the 7500 mg/kg group died during the study. The 5000 mg/kg rats died on the day following dosing and the 7500 mg/kg rats died one hour after dosing through the day following dosing. All 2500 mg/kg rats survived the study.

TABLE 1. Doses, mortality/animals treated

Dose (mg/kg)	Males	Females	Combined
0	-	-	-
2500	0/5	0/5	0/10
5000	2/5	3/5	5/10
7500	5/5	5/5	10/10

Data taken from p. 16, MRID 46340202.

2. **Body Weight:** The body weight of the 2500 mg/kg rats was comparable with that of the control group. Body weight of the 5000 mg/kg group decreased on the day following dosing, but increased thereafter.

3. **Clinical Observations:** All 2500 mg/kg rats were normal throughout the study. Within 15 minutes, the 5000 mg/kg rats showed decreased movement and/or soft feces. The survivors recovered by the day following dosing. The 7500 mg/kg rats showed clinical signs within 5 minutes of dosing. Prior to death, decreased movement, prone position, soft feces, and oligopnea were observed in the 7500 mg/kg rats.

4. **Gross Necropsy:** The decedents that died on day of dosing had dark reddening of the lung. The other decedents and the survivors had no abnormalities.

III. DISCUSSION:

The study author reported that the oral LD_{50}'s for males and females were 4916 mg/kg (95% C.L. 4297-5624 mg/kg) and 4404 mg/kg (95% C.L. 3850-5039 mg/kg), respectively. The LD_{50} for male should be between 5000 mg/kg and 7500 mg/kg due to the mortality pattern shown in Table 1. Therefore, the reviewer calculated that the oral LD_{50}'s for the male, female, and combined were approximately 5268, 4573, and 5000 mg/kg, respectively. This

DATA EVALUATION RECORD

POLYOXIN D ZINC SALT
(POLYOXIN Z DRY FLOWABLE)

STUDY TYPE: ACUTE DERMAL TOXICITY - RAT (870.1200)
MRID 46340203

Prepared for
Biopesticides and Pollution Prevention Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1801 Bell Street
Arlington, VA 22202

Prepared by
Toxicology and Hazard Assessment Group
Life Sciences Division
Oak Ridge National Laboratory
Oak Ridge, TN 37831
Task Order No. 04-75

Primary Reviewer:
Susan Chang, M.S.

Signature: _____
Date: NOV 17 2004

Secondary Reviewers:
H. Tim Borges, M.T.(A.S.C.P.), Ph.D., D.A.B.T.

Signature: _____
Date: NOV 17 2004

Robert H. Ross, M.S., Group Leader

Signature: _____
Date: NOV 17 2004

Quality Assurance:
Lee Ann Wilson, M.A.

Signature: _____
Date: NOV 17 2004

Disclaimer

This review may have been altered subsequent to the contractor's signatures above.

Oak Ridge National Laboratory managed and operated by UT-Battelle, LLC., for the U.S. Department of Energy under Contract No. DE-AC05-00OR22725.

DATA EVALUATION RECORD

EPA Secondary Reviewer: [signature] 12/01/04

STUDY TYPE:	Acute Dermal Toxicity - Rats (OPPTS 870.1200)
MRID NO:	46340203
DP BARCODE NO:	DP308553 and DP308556
CASE NO:	Not reported
DECISION NO:	346783 and 346781
TEST MATERIAL:	Polyoxin Z Dry Flowable (11.25% polyoxin D zinc salt, a.i.)
PROJECT NO:	BOZO/B-3302
SPONSOR:	Kaken Pharmaceutical Co., Ltd., Tokyo, Japan
TESTING FACILITY:	Bozo Research Center, Inc., Tokyo, Japan
TITLE OF REPORT:	An Dermal Acute Toxicity Study of Polyoxin Z Dry Flowable in Rats
AUTHOR:	S. Oda
STUDY COMPLETED:	August 30, 1996
GOOD LABORATORY PRACTICE:	GLP Compliant
CONCLUSION:	The dermal LD_{50} for males, females, and combined was greater than 2000 mg/kg.
CLASSIFICATION:	ACCEPTABLE -- TOXICITY CATEGORY III

I. STUDY DESIGN:

1. **Test Material:** Polyoxin Z Dry Flowable containing 11.25% polyoxin D zinc salt, a.i.; Lot No. RUN6

2. **Test Animals:** Twenty-one male and 21 female Crj:CD(SD) strain SPF rats were received from Charles River Japan Inc., Atsugi. Groups of five males and five females were assigned and weighed 255-277 g (males) and 156-171 g (females) on the day of treatment. The young adult animals, 7 weeks old, were housed individually in stainless steel wire mesh cages. The animals were fed pellet diet CRF-1 (radiation sterilized: Oriental Yeast Co., Ltd.), *ad libitum*. Tap water was available *ad libitum*. The environmental conditions of the animal room were as follows: temperature, 20-26°C; relative humidity, 30-70%; air changes, 10-15 per hour; and photoperiod, 12 hour light/dark cycle.

3. **Methods:** Rats were tail-marked: males (Nos. 1001-1005 and 2001-2005) and females (Nos. 1101-1105 and 2101-2105). The rats were quarantined for one week. The test material (2000 mg/kg body weight) was moistened with 0.5 mL of distilled water and applied to a 4 cm x 5 cm gauze lined with a polyethylene film that was placed on the clipped dorsal trunk in an area of approximately 20 cm^2 of the body surface. Then, it was covered with surgical tape. The control rats were treated with distilled water instead of the test material. The coverings were removed after 24 hours and the excess test material was removed with gauze. The test animals were observed frequently after treatment for mortality and for clinical signs of toxicity daily thereafter for 14 days. The rats were weighed prior to treatment and on days 1, 2, 3, 7, 10, and 14. The rats were euthanized on day 14 and necropsied.

II. RESULTS:

1. **Mortality:** All rats survived the study.

2. **Clinical Observations:** No abnormalities were noted in any animal and no dermal irritation was noted.

3. **Body Weight:** All animals lost weight on the day following treatment, but recovered thereafter.

4. **Gross Necropsy:** No gross abnormalities were noted.

III. DISCUSSION:

The dermal LD_{50} for males, females, and combined was greater than 2000 mg/kg. This places Polyoxin Z Dry Flowable in TOXICITY CATEGORY III. The packet classification is **ACCEPTABLE.**

IV. COMMENTS: The Tables and Appendices mentioned in the MRID 46340203 text were not included in the report.

DATA EVALUATION RECORD

POLYOXIN D ZINC SALT
(POLYOXIN Z DRY FLOWABLE)

STUDY TYPE: PRIMARY EYE IRRITATION - RABBIT (870.2400)
MRID 46340204

Prepared for
Biopesticides and Pollution Prevention Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1801 Bell Street
Arlington, VA 22202

Prepared by
Toxicology and Hazard Assessment Group
Life Sciences Division
Oak Ridge National Laboratory
Oak Ridge, TN 37831
Task Order No. 04-75

Primary Reviewer:
Susan Chang, M.S.

Signature: Susan Chang
Date: NOV 17 2004

Secondary Reviewers:
H. Tim Borges, M.T.(A.S.C.P.), Ph.D., D.A.B.T.

Signature: H.T Borges
Date: NOV 17 2004

Robert H. Ross, M.S., Group Leader

Signature: Robert H. Ross
Date: NOV 17 2004

Quality Assurance:
Lee Ann Wilson, M.A.

Signature: L.A. Wilson
Date: NOV 17 2004

Disclaimer

This review may have been altered subsequent to the contractor's signatures above.

Oak Ridge National Laboratory managed and operated by UT-Battelle, LLC., for the U.S. Department of Energy under Contract No. DE-AC05-00OR22725.

DATA EVALUATION RECORD

EPA Secondary Reviewer: Mary D. Barbieri 12/01/04

STUDY TYPE:	Acute Eye Irritation - Rabbits (OPPTS 870.2400)
MRID NO:	46340204
DP BARCODE NO:	DP308553 and DP308556
CASE NO:	Not reported
DECISION NO:	346783 and 346781
TEST MATERIAL:	Polyoxin Z Dry Flowable (11.25% polyoxin D zinc salt, a.i.)
PROJECT NO:	BOZO/B-3304
SPONSOR:	Kaken Pharmaceutical Co., Ltd., Tokyo, Japan
TESTING FACILITY:	Bozo Research Center, Inc., Tokyo, Japan
TITLE OF REPORT:	A Primary Eye Irritation Study of Polyoxin Z Dry Flowable in Rabbits
AUTHOR:	R. Shibata
STUDY COMPLETED:	October 22, 1996
GOOD LABORATORY PRACTICE:	GLP Compliant
CONCLUSION:	Corneal opacity was noted on one rabbit with unwashed eyes one hour after test material instillation and on another rabbit in the same group 24 hours after test material instillation with resolution by 48 hours. No corneal opacity was noted on any rabbit with washed eyes. No iritis was noted on any rabbit. Positive conjunctival irritation was noted on all rabbits one hour after test material instillation with resolution on washed eyes by 24 hours and on unwashed eyes by 48 hours. The maximum average scores for unwashed eyes and washed eyes were 10.83 and 8.00, respectively, one hour after test material instillation. Polyoxin Z Dry Flowable was mildly irritating.
CLASSIFICATION:	ACCEPTABLE -- TOXICITY CATEGORY III

I. STUDY DESIGN:

1. **Test Material:** Polyoxin Z Dry Flowable containing 11.25% polyoxin D zinc salt, a.i.; Lot No. RUN6

2. **Test Animals:** Twelve female Japanese White rabbits were received from Japan Laboratory Animals Inc. The animals were housed individually in aluminum cages with wire mesh bottoms. The animals were 15 weeks old and weighed 2.64-2.96 kg on the day of treatment. The animals were fed RC4 pellet diet (Oriental Yeast Co., Ltd.), *ad libitum*. Tap water was available *ad libitum*. The environmental conditions of the animal room were as follows: temperature, 23±5°C; relative humidity, 55±25%; air changes, 8-10 per hour; and photoperiod, 12 hour light/dark cycle.

3. **Methods:** Rabbits were ear-marked: Nos. 1101-1106 (Group 1: without eye washing) and 2101-2103 (Group 2: with eye washing). The rabbits were quarantined for 13 days. The test material (0.1 g/eye/animal) was applied in the conjunctival sac of the left eye, and the eye held closed for approximately one second. The right eye served as control. The eyes were examined and scored 1, 24, 48, 72, and 96 hours after test material instillation. The eyes of the animals in Group1 were washed with distilled water 24 hours after test material instillation. The eyes of the animals in Group 2 were washed with distilled water immediately after test material instillation. The animals were observed for clinical signs frequently after test material instillation and once daily thereafter.

II. RESULTS:

1. **Mortality:** All rabbits survived the study.

2. **Ocular Lesions:** Group 1 (eyes not washed): Corneal opacity was noted on one rabbit one hour after test material instillation with resolution by 48 hours and on another rabbit 24 hours after test material instillation with resolution by 48 hours (Table 1). No iritis was noted on any rabbit. Positive conjunctival irritation (score ≥2) was noted on all rabbits one hour after test material instillation with resolution by 48 hours (Table 2). The maximum average score was 10.83 at one hour after test material instillation (Table 3). Group 2 (eyes washed): No corneal opacity or iritis were noted on any rabbit (Table 1). Positive conjunctival irritation was noted on all rabbits one hour after test material instillation with resolution by 24 hours (Table 2). The maximum average score was 8.00 one hour after test material instillation (Table 3). Evaluation of eye irritation was done according to the method of Kay and Calandra.

TABLE 1. Individual Male (M) and Female (F) Eye Scores w/ Time: Cornea (A=Density of Opacity, B=Area of Opacity)										
Animal No.	1 hour		24 hours		48 hours		72 hours		96 hours	
	A	B	A	B	A	B	A	B	A	B
Group 1 (eyes not washed)										
1101	0	0	0	0	0	0	0	0	0	0
1102	0	0	1	1	0	0	0	0	0	0
1103	0	0	0	0	0	0	0	0	0	0
1104	0	0	0	0	0	0	0	0	0	0
1105	0	0	0	0	0	0	0	0	0	0
1106	1	1	1	1	0	0	0	0	0	0
Group 2 (eyes washed)										
2101	0	0	0	0	0	0	0	0	0	0
2102	0	0	0	0	0	0	0	0	0	0
2103	0	0	0	0	0	0	0	0	0	0

TABLE 2. Summary of Eye Irritation Scores with Time: Conjunctiva and Iris					
Score Conditions	1 hour	24 hours	48 hours	72 hours	96 hours
Group 1 (eyes not washed)					
Conjunctiva					
Erythema	1	1 to 2	0 to 1	0 to 1	0
Chemosis	2 to 3	1	1	0	0
Discharge	1 to 2	1 to 2	0 to 1	0 to 1	0
Iris	0	0	0	0	0
Group 2 (eyes washed)					
Conjunctiva					
Erythema	1	1	0	0	0
Chemosis	2	1	0	0	0
Discharge	1	0 to 1	0	0	0
Iris	0	0	0	0	0

Irritation score is based on Draize Method

Scale for Scoring Ocular Lesions

Cornea

A. Opacity-degree of density (area most dense taken for reading)

No Opacity 0
Scattered or diffuse area, details of iris clearly visible 1
Easily discernible translucent areas, details of iris slightly obscured 2
Opalescent areas, no details of iris visible, size of pupil barely discernible 3
Opaque cornea, iris not discernible through the opacity 4

B. Area of cornea involved

No opacity 0
One quarter (or less) but not zero 1
One quarter or greater, but less than half 2
One half or greater, but less than three quarters 3
Three quarters or greater, up to whole area 4
Score = A x B x 5 Theoretical Maximum Score = 80

Iris

A. Values

Normal 0
Marked congestion, swelling, circumcorneal injection (any or all of these or combination of any thereof), iris still reacting to light (sluggish reaction is positive). 1
No reaction to light, hemorrhage, gross destruction (any or all of these). 2
Score = A x 5 Theoretical Maximum Score = 10

Conjunctivae

A. Redness (refers to palpebral and bulbar conjunctive excluding cornea and iris)

Vessels normal 0
Vessels definitely injected above normal 1
More diffuse, deeper crimson red, individual vessels not easily discernible 2
Diffuse beefy red 3

B. Chemosis

No swelling 0
Any swelling above normal (includes nictitating membrane) 1
Obvious swelling with partial eversion of lids 2
Swelling with lids about half closed 3
Swelling with lids about half closed to completely closed 4

C. Discharge

No discharge (including small amounts observed in inner canthus) 0
Any amount different from normal 1
Discharge with moistening of the lids and hairs adjacent to lids 2
Discharge with moistening of the lids and hairs, and considerable area around the eye 3
Score = (A + B + C) x 2 Theoretical Maximum Score = 20

TABLE 3. Summary of Total[a] and Primary Eye Irritation Scores with Time					
Animal #	1 h	24 h	48 h	72 h	96 h
Group 1 (eyes not washed)					
1101	10	8	6	0	0
1102	10	15	4	0	0
1103	10	8	4	0	0
1104	10	10	6	4	0
1105	8	6	6	0	0
1106	17	15	6	4	0
[b]Total	10.83	10.33	5.33	1.33	0
Group 2 (eyes washed)					
2101	8	4	0	0	0
2102	8	4	0	0	0
2103	8	6	0	0	0
[c]Total	8.00	4.67	0	0	0

[a]Formula: Total Irritation Score = I + II + III, where,
I = Corneal Score = [Density (A) x Area (B)] x 5
II = Iris Score = Severity x 5
III = Conjunctival Score = [Erythema (A) + Chemosis (B) + Discharge (C)] x 2
[b]Primary Irritation = Sum of Total Irritation Scores ÷ 6
[c]Primary Irritation = Sum of Total Irritation Scores ÷ 3

III. DISCUSSION:

Corneal opacity was noted on one rabbit with unwashed eyes one hour after test material instillation with resolution by 48 hours and on another rabbit in the same group 24 hours after test material instillation with resolution by 48 hours. No corneal opacity was noted on any rabbit with washed eyes. No iritis was noted on any rabbit. Positive conjunctival irritation (score 2) was noted on all rabbits one hour after test material instillation with resolution on washed eyes by 24 hours and on unwashed eyes by 48 hours. The maximum average scores for unwashed eyes and washed eyes were 10.83 and 8.00, respectively, one hour after test material instillation. Polyoxin Z Dry Flowable was mildly irritating and is in TOXICITY CATEGORY III. The packet classification is **ACCEPTABLE.**

Page 22- *Non-Responsive*

DATA EVALUATION RECORD

POLYOXIN D ZINC SALT
(POLYOXIN Z DRY FLOWABLE)

STUDY TYPE: PRIMARY DERMAL IRRITATION - RABBIT (870.2500)
MRID 46340205

Prepared for
Biopesticides and Pollution Prevention Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1801 Bell Street
Arlington, VA 22202

Prepared by
Toxicology and Hazard Assessment Group
Life Sciences Division
Oak Ridge National Laboratory
Oak Ridge, TN 37831
Task Order No. 04-75

Primary Reviewer:
Susan Chang, M.S.

Signature: [signature]
Date: NOV 17 2004

Secondary Reviewers:
H. Tim Borges, M.T.(A.S.C.P.), Ph.D., D.A.B.T.

Signature: [signature]
Date: NOV 17 2004

Robert H. Ross, M.S., Group Leader

Signature: [signature]
Date: NOV 17 2004

Quality Assurance:
Lee Ann Wilson, M.A.

Signature: [signature]
Date: NOV 17 2004

Disclaimer

This review may have been altered subsequent to the contractor's signatures above.

Oak Ridge National Laboratory managed and operated by UT-Battelle, LLC., for the U.S. Department of Energy under Contract No. DE-AC05-00OR22725.

DATA EVALUATION RECORD

EPA Secondary Reviewer: [signature] 12/01/04

STUDY TYPE:	Primary Dermal Irritation - Rabbits (OPPTS 870.2500)
MRID NO:	46340205
DP BARCODE NO:	DP308553 and DP308556
CASE NO:	Not reported
DECISION NO:	346783 and 346781
TEST MATERIAL:	Polyoxin Z Dry Flowable (11.25% polyoxin D zinc salt, a.i.)
PROJECT NO:	BOZO/B-3305
SPONSOR:	Kaken Pharmaceutical Co., Ltd., Tokyo, Japan
TESTING FACILITY:	Bozo Research Center, Inc., Tokyo, Japan
TITLE OF REPORT:	A Primary Dermal Irritation Study of Polyoxin Z Dry Flowable in Rabbits
AUTHOR:	R. Shibata
STUDY COMPLETED:	October 22, 1996
GOOD LABORATORY PRACTICE:	GLP Compliant
CONCLUSION:	No dermal irritation was noted on any rabbit. Polyoxin Z Dry Flowable was not irritating.
CLASSIFICATION:	ACCEPTABLE -- TOXICITY CATEGORY IV

I. STUDY DESIGN:

1. **Test Material:** Polyoxin Z Dry Flowable containing 11.25% polyoxin D zinc salt, a.i.; Lot No. RUN6

2. **Test Animals:** Ten female Japanese White rabbits were received from Japan Laboratory Animals Inc. The animals were housed individually in aluminum cages with wire mesh bottoms. The animals were 15 weeks old and weighed 2.60-3.10 kg on the day of treatment. The animals were fed RC4 pellet diet (Oriental Yeast Co., Ltd.), *ad libitum*. Tap water was available *ad libitum*. The environmental conditions of the animal room were as follows: temperature, 23±5°C; relative humidity, 55±25%; air changes, 8-10 per hour; and photoperiod, 12 hour light/dark cycle.

3. **Methods:** Rabbits were ear-marked: Nos. 1101 to 1106 (female). The rabbits were quarantined for 12 days. The fur on the dorsal trunk of each rabbit was clipped on the day

prior to treatment. The rabbits were given an approximate 0.5 g dose of test material moistened with water applied on a 2.5 cm x 2.5 cm lint and placed on the clipped site. The site was covered with oil-paper and then with an elasticated dressing. On the negative control sites, a lint sheet was placed and covered with an elasticated dressing. The animals were held in restrainers. The covering and the restrainer were removed 4 hours later and the site wiped with cotton soaked with water to remove any residual test material. The animals were observed once daily for clinical signs during the study. Dermal examination was recorded at 1, 24, 48, and 72 hours after removal of the patch.

II. RESULTS:

1. **Mortality:** All rabbits survived the study.

2. **Dermal responses:** No dermal irritation was noted on any rabbit. The primary irritation index was 0.

Irritation Scores:

TABLE 1. Summary of individual rabbit's dermal irritation scores with time

	Hours			
Animal No.	1	24	48	72
4876	0/0 [a]	0/0	0/0	0/0
4877	0/0	0/0	0/0	0/0
4878	0/0	0/0	0/0	0/0

Data taken from Appendix 1, p. 22, MRID 46340205.
[a]Erythema/Edema

Description of rating method:

Evaluation of Skin Reaction:	Score
Erythema formation:	
No erythema	0
Very slight erythema (barely perceptible)	1
Well-defined erythema	2
Moderate to severe erythema	3
Severe erythema (beet redness) to slight eschar formation (injuries in depth)	4

Edema Formation:	
No edema	0
Very slight edema (barely perceptible)	1
Slight edema (edges of area well-defined by definite raising)	2
Moderate edema (raised approximately 1 mm)	3
Severe edema (raised by more than 1 mm extending beyond the area of exposure)	4

III. DISCUSSION:

No dermal irritation was noted on any rabbit. Polyoxin Z Dry Flowable was not irritating and is in TOXICITY CATEGORY IV. The packet classification is **ACCEPTABLE.**

DATA EVALUATION RECORD

POLYOXIN D ZINC SALT
(POLYOXIN Z DRY FLOWABLE)

STUDY TYPE: SKIN SENSITIZATION - GUINEA PIG (870.2600)
MRID 46340206

Prepared for
Biopesticides and Pollution Prevention Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1801 Bell Street
Arlington, VA 22202

Prepared by
Toxicology and Hazard Assessment Group
Life Sciences Division
Oak Ridge National Laboratory
Oak Ridge, TN 37831
Task Order No. 04-75

Primary Reviewer: Susan Chang, M.S.	Signature: Date:	NOV 17 2004
Secondary Reviewers: H. Tim Borges, M.T.(A.S.C.P.), Ph.D., D.A.B.T.	Signature: Date:	NOV 17 2004
Robert H. Ross, M.S., Group Leader	Signature: Date:	NOV 17 2004
Quality Assurance: Lee Ann Wilson, M.A.	Signature: Date:	NOV 17 2004

Disclaimer

This review may have been altered subsequent to the contractor's signatures above.

Oak Ridge National Laboratory managed and operated by UT-Battelle, LLC., for the U.S. Department of Energy under Contract No. DE-AC05-00OR22725.

DATA EVALUATION RECORD

EPA Secondary Reviewer: [signature] 12/8/04

STUDY TYPE:	Skin Sensitization - Guinea Pigs (OPPTS 870.2600)
MRID NO:	46340206
DP BARCODE NO:	DP308553 and DP308556
CASE NO:	Not reported
DECISION NO:	346783 and 346781
TEST MATERIAL:	Polyoxin Z Dry Flowable (11.25% polyoxin D zinc salt, a.i.)
PROJECT NO:	BOZO/B-3306
SPONSOR:	Kaken Pharmaceutical Co., Ltd., Tokyo, Japan
TESTING FACILITY:	Bozo Research Center, Inc., Tokyo, Japan
TITLE OF REPORT:	A Skin Sensitization Study of Polyoxin Z Dry Flowable in Guinea Pigs
AUTHOR:	R. Shibata
STUDY COMPLETED:	October 22, 1996
GOOD LABORATORY PRACTICE:	GLP Compliant
CONCLUSION:	After three consecutive inductions, the test and control animals showed no signs of reactivity at 24 and 48 hours after challenge. The study included a DNCB positive control study and the results were appropriate. Polyoxin Z Dry Flowable was not a dermal sensitizer.
CLASSIFICATION:	ACCEPTABLE

I. STUDY DESIGN:

1. **Test Material:** Polyoxin Z Dry Flowable containing 11.25% polyoxin D zinc salt, a.i.; Lot No. RUN6

2. **Test Animals:** Seventy female Hartley guinea pigs received from Japan Laboratory animals Inc. were assigned to groups and weighed 355-451 g at experiment start. The young adult animals (6 or 7 weeks old) were housed in groups of two in stainless steel wire mesh cages. The animals were fed RC4 pellet diet (Oriental Yeast Co., Ltd.), *ad libitum*. Tap water was available *ad libitum*. The environmental conditions of the animal room were as follows: temperature, 22.5±3.5°C; relative humidity, 50±20%; air changes, 10-15 per hour; and photoperiod, 12 hour light/dark cycle.

3. **Methods:** Female guinea pigs were marked and grouped: Test – Nos. 1101 to 1120; Control – Nos. 2101 to 2120; Positive Control – Nos. 3101 to 3110; Control for Positive Control – Nos. 4101 to 4110. The guinea pigs were quarantined for 12 days. The animals were induced and challenged according to the method of Buehler. The dorsal and flank areas of 20 test guinea pigs and 20 naive control animals were clipped prior to each treatment. For the induction, 0.2 mL of 50% w/w test material in distilled water was applied to a patch 2.5 cm in diameter and placed on the application site on the test animals then secured with a polyethylene-film plaster. The control group was treated with water instead of the test material. The patch was removed after six hours and the application site was wiped with water. The procedure was repeated once each week for three consecutive weeks. Fourteen days after the third induction, the test animals were challenged with 0.2 mL of 50% test material in distilled water under occlusion to naive sites. At challenge, the control group (20 animals) was treated with 0.2 mL of 50% w/w test material in distilled water. The positive control animals (10 animals) were induced with 0.2 mL 1% DNCB in olive oil and challenged with 0.2 mL 0.25% DNCB in olive oil using the same procedure as for the test animals. The control group for the positive control (10 animals) was treated with water instead of DNCB at the induction and challenged with 0.2 mL 0.25% DNCB in olive oil. The reactions were scored at approximately 24 and 48 hours following challenge application.

II. RESULTS:

1. **Mortality:** No deaths were observed in any group.

2. **Body weight:** All guinea pigs gained weight during the study.

3. **Skin effects:** The reaction after induction was not addressed. No reaction was noted on any test or control animals after challenge. The results of the positive control study were appropriate.

TABLE 1. Summary of Individual Erythema Challenge Scores with Time [a]

Time	24 hours				48 hours			
Erythema Score	0	0.5	1	2	0	0.5	1	2
Treated	20	0	0	0	20	0	0	0
Control	20	0	0	0	20	0	0	0

[a]Number of animals affected
Evaluation score is based on Buehler Grading Scale.

Scale for Scoring Skin Reaction

Buehler sensitization scoring scale

Erythema and eschar formation	Score
No erythema	0
Very slight erythema (barely perceptable)	1
Well-defined erythema	2
Moderate to severe erythema	3
Severe erythema (beet redness) to slight eschar formation (injures in depth)	4

Maximum possible 4

Edema formation	
No edema	0
Very slight edema (barely perceptable)	1
Slight edema (edges of area well defined by definite raising)	2
Moderate edema (raised approximately 1 mm)	3
Severe edema (raised more than 1 mm and extending beyond area of exposure)	4

Maximum possible 4

III. DISCUSSION:

The test and control animals showed no signs of reactivity at 24 and 48 hours after challenge. The study included a DNCB positive control study and the results were appropriate. Polyoxin Z Dry Flowable was not a dermal sensitizer. The packet is classified as **ACCEPTABLE.**

DATA EVALUATION RECORD

POLYOXIN D ZINC SALT
(POLYOXIN Z DRY FLOWABLE)

STUDY TYPE: ACUTE INHALATION TOXICITY - RAT (870.1300)
MRID not assigned

Prepared for
Biopesticides and Pollution Prevention Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1801 Bell Street
Arlington, VA 22202

Prepared by
Toxicology and Hazard Assessment Group
Life Sciences Division
Oak Ridge National Laboratory
Oak Ridge, TN 37831
Task Order No. 04-75

Primary Reviewer:
Susan Chang, M.S.

Signature:
Date: NOV 17 2004

Secondary Reviewers:
H. Tim Borges, M.T.(A.S.C.P.), Ph.D., D.A.B.T.

Signature:
Date: NOV 17 2004

Robert H. Ross, M.S., Group Leader

Signature:
Date: NOV 17 2004

Quality Assurance:
Lee Ann Wilson, M.A.

Signature:
Date: NOV 17 2004

Disclaimer

This review may have been altered subsequent to the contractor's signatures above.

Oak Ridge National Laboratory managed and operated by UT-Battelle, LLC., for the U.S. Department of Energy under Contract No. DE-AC05-00OR22725.

DATA EVALUATION RECORD

EPA Secondary Reviewer: [signature] 12/01/04

STUDY TYPE:	Acute Inhalation Toxicity - Rats (OPPTS 870.1300)
MRID NO:	Not assigned
DP BARCODE NO:	DP308553 and DP308556
CASE NO:	Not reported
DECISION NO:	346783 and 346781
TEST MATERIAL:	Endorse DF (47.4% Polyoxin D Technical, a.i.)
PROJECT NO:	N/A
SPONSOR:	Arvesta Corporation
TESTING FACILITY:	N/A
TITLE OF REPORT:	Endorse DF: Acute Toxicity Inhalation Study Waiver Requests
AUTHOR:	J. Kinzell and C. Ma
STUDY COMPLETED:	N/A
GOOD LABORATORY PRACTICE:	Non GLP Compliant
CONCLUSION:	Based on the low acute inhalation toxicity of the active ingredient and the low acute oral toxicity of all ingredients, it is unlikely that the EP will have a greater acute inhalation toxicity than the active ingredient. The reviewer supports this waiver request.
CLASSIFICATION:	ACCEPTABLE

Test Material: Endorse DF is a granular formulation of a biological fungicide, Polyoxin D, containing 47.4% Polyoxin D Technical, [redacted] surfactants, and [redacted] inert carrier.

Waiver Request: The registrant is requesting a waiver for the acute inhalation toxicity study for Endorse DF.

Rationale: The registrant presented a Table including the information on the acute oral and inhalation toxicity of the components in a dry flowable formulation of Polyoxin D Zinc Salt Technical. The 4-hour LC_{50} for the active ingredient Polyoxin D Zinc Salt Technical (CAS No. 146659-78-1) was > 2.44 mg/L (males) and > 2.17 mg/L (females) and the oral LD_{50} was > 5000 mg/kg. The oral LD_{50}'s for the surfactant [redacted] The author referenced all information from MSDSs, but the MSDSs were not included.

Polyoxin D Technical has a low toxicity when inhaled. Although no inhalation studies were carried out on the surfactants, based on the low oral toxicity of these surfactants and [redacted] it is reasonable to expect that they also have a low order of inhalation toxicity. It is unlikely that the surfactants and [redacted] will contribute to the inhalation toxicity of the EP such that it would be greater than that of the active ingredient.

Therefore, an acute inhalation toxicity study is unwarranted and would constitute an unnecessary use of laboratory animals.

Reviewer's Conclusion: The reviewer finds the information submitted in support of the waiver request to be acceptable.