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Biopesticide Registration Action Document for
Pythium oligandrum DV 74
U.S. Environmental Protection Agency

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U.S. Environmental Protection Agency
Biopesticides and Pollution Prevention Division
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I. EXECUTIVE SUMMARY/FACT SHEET

Active Ingredient and Proposed Use

The active ingredient, *Pythium oligandrum* DV 74 (PC Code 028816, ATCC No. 38472¹) (also referred to in this document as *P. oligandrum*), is one of four mycoparasites found in the *Pythium* family. The DV 74 strain was originally isolated in the Czech Republic; however, this mycoparasite is widely distributed throughout the world, including the United States. *Pythium oligandrum* is common in soil and in or on plants.

Pythium oligandrum DV 74 acts as a hyperparasite by colonizing other plant pathogenic fungi in and around seeds and the rhizosphere of treated plants, thereby suppressing the growth of at least 20 soil-borne pathogenic fungi, including *Alternaria*, *Botrytis*, *Fusarium*, *Gaeumannomyces*, *Ophiostoma*, *Phoma*, *Pseudocercospora*, *Pythium*, *Sclerotinia* and *Sclerotium* in or around growing plants. *P. oligandrum* produces the name-sake protein oligandrin and other compounds that stimulate plants' cell walls to fend off pathogen invasion, and also stimulates natural plant defense mechanisms called pathogenesis-related (PR) proteins which help plants resist disease, without harming the plant.

P. oligandrum has been formulated into one manufacturing use product, Technical DV 74 (a powder containing 5% *P. oligandrum*), and one end-use product, Polyversum® (a powder containing 1% *P. oligandrum*). This product may be applied to agricultural crops, ornamental plants, and turf grasses as a seed dressing, pre-plant soak, overhead spray, soil drench, or through irrigation system application to agricultural crops, ornamental plants and turf grasses. To function effectively, the *P. oligandrum* requires a moist environment and a temperature range of 20-35°C during the infection period, which can last for three to four hours. Under dry conditions, the onset of infection may be delayed until increased moisture is available.

Toxicology, Human Exposure and Risks

Evaluations of mammalian toxicology data comply with the Food Quality Protection Act (FQPA) of 1996, and are sufficient to support the unconditional registration of this microbial pesticide for the proposed uses. The technical grade active ingredient (TGAI) was classified as Toxicity Category IV for acute oral toxicity, acute inhalation toxicity, acute dermal toxicity, primary dermal irritation, acute oral toxicity, and as Toxicity Category III for primary eye irritation.

The Agency accepted requests to waive acute oral toxicity/pathogenicity, acute dermal toxicity/pathogenicity, acute dermal toxicity/pathogenicity, acute pulmonary toxicity/pathogenicity, acute IV/IP toxicity/pathogenicity, dermal sensitization, reporting of hypersensitivity incidents, cell culture, and immune response studies. The rationale for granting waivers was based on the following: a) the low toxicity, infectivity and irritation potential was demonstrated by acute oral, acute dermal, acute eye, acute pulmonary, and acute injection toxicity/pathogenicity testing, plus a primary dermal irritation study; b) the

¹ The American Type Culture Collection (ATCC) acts as a central collection point for microorganisms.

inability of *P. oligandrum* to grow at normal mammalian body temperature and on animal tissue based culture media; c) a thorough literature review and characterization of the active ingredient showing that it is primarily a fungal parasite with ability to colonize plant tissue without harming the plant and no reports of toxins produced that affect mammalian health; and d) no documented reports of hypersensitivity incidents during production, testing and use of the active ingredient and end use products, some of which are used overseas in human pharmaceuticals for antifungal purposes directly applied to skin (i.e. foot soaks) or as mouthwash rinses [Table 3b and discussion in Section III.B.2].

Food Tolerances

For this section 3(c)(5) unconditional registration, a permanent tolerance exemption is being established in 40 CFR Part 180 for residues of *P. oligandrum* on all agricultural commodities when used/applied in accordance with label directions.

FQPA Considerations

The Agency has considered *P. oligandrum* in light of the safety factors identified in the Food Quality Protection Act (FQPA) of 1996 and has made a determination of reasonable certainty of no harm to the U.S. population in general, and to infants and children in particular. The ubiquitous occurrence of *P. oligandrum* suggests that humans are exposed to the microbe under natural conditions. Thus, application of *P. oligandrum* for agricultural purposes is not expected to increase exposure above normal background levels [Section III.B.3].

Toxicity endpoints which justify setting numerical tolerances for a pesticide product were not identified for *P. oligandrum*. Submitted studies indicate that the active ingredient demonstrates low acute oral toxicity potential (Toxicity Category IV), showing no incremental dietary risk [Section III.B.3]. In this assessment, no acute, subchronic, chronic, immune, endocrine, or non-dietary exposure issues were identified which may impose any incremental adverse effects on infants, children, and the general U.S. population. Based on the classification of Toxicity Category IV for acute oral toxicity effects, a safety factor is not required for residues of *P. oligandrum* DV 74 in food. Potential risks via exposure to drinking water or runoff are not expected, because the fungal agent does not thrive in aquatic environments [Section III.B.5].

The potential for aggregate non-occupational exposure is unlikely, because use sites identified for the subject active ingredient are agricultural and horticultural. If such exposure were to occur, risk concerns would be negligible, because the fungus is not considered a human pathogen and is minimally toxic to mammals.

Occupational and Residential Exposure and Risk

Potential worker and pesticide handler exposure to *P. oligandrum* is not expected to pose any undue risk. Appropriate Personal Protective Equipment (PPE) and a Restricted Entry Interval (REI) of four hours for agricultural applications is required to mitigate potential risks to workers. Residential exposure is not expected because the end use products will be used in agricultural settings. Risk to workers, pesticide

handlers, and residential communities are further reduced because the TGAI is minimally toxic and non-pathogenic to mammals.

Ecological and Environmental Exposure and Risks

The submitted non-target freshwater fish study, and accompanying waiver requests and justifications, fulfill the respective OPPTS data requirements for ecological assessment of microbial fungicide and are considered acceptable. No adverse effects to non-target populations of avian, freshwater fish, aquatic invertebrates, plants or their respective endangered taxa, are expected to result from intended uses of *P. oligandrum* end-use products.

In the unlikely event that some non-target organisms are affected during the commercial application of this product, such incidents should immediately be reported to the EPA, as required under FIFRA Section 6(a)(2), so that the Agency may take appropriate action.

Non-target toxicity tests were waived for wild mammal, avian oral toxicity/pathogenicity, avian inhalation toxicity/pathogenicity, freshwater aquatic invertebrate, estuarine and marine animal, non-target insect, honeybee, and non-target plants (section III.C.1.f.).

Data Gaps and Requirements/Labeling

There are no data deficiencies for *P. oligandrum*. However, if more extensive use patterns are sought for treatment of other agricultural terrestrial sites or crops, additional information and data may be required on a case-by-case basis.

II. OVERVIEW

A. Product Overview

Biological Name:	<i>Pythium oligandrum</i> DV 74
ATCC Number:	38472
Trade/Other Names:	Technical DV 74 and Polyversum®
OPP Chemical Code:	028816
Basic Manufacturer:	Biopreparaty Co. Ltd. Tylisovska 1 Prague 6, Czech Republic

B. Use Profile

Type of Pesticide:	Fungal hyperparasite and plant growth regulator
Use Sites:	Technical DV 74: Manufacturing use only End-use Product: Fruiting vegetables, leafy vegetables, cucurbit vegetables, legume crops, root crops, grain and forage crops, vine crops, tropical crops, ornamental trees and shrubs, bedding plants, and turf grass.
Target Pests:	Plant pathogenic species of <i>Alternaria</i> , <i>Ascochyta</i> , <i>Botrytis cinerea</i> , <i>Fusarium</i> , <i>Peronosplasmopara.</i> , <i>Phoma.</i> , <i>Phytophthora infestans</i> , <i>Plasmopara viticola</i> , <i>Puccinia</i> , <i>Pythium.</i> , <i>Rhizoctonia solani</i> , <i>Sclerotinia sclerotiorum</i> , <i>Unicula necator</i> , and <i>Verticillium</i> species.
Formulation Types:	Powder
Method/Rate of Application:	The end-use product should be applied before planting and in early stages of plant growth and may be reapplied at 14-day intervals, or as needed, throughout the growing season. The end-use product comes in a powder form that should be diluted with water for all uses except seed dressing.

C. Estimated Usage

An estimate of usage, based on existing commercial use patterns of similar products, cannot be made since these are the first pesticide registrations containing *P. oligandrum* DV 74 as the active ingredient.

D. Data Requirements

Data and accompanying information, submitted under section 3(c)(5) of FIFRA in support of this unconditional registration, have been reviewed by the BPPD. Product identity and analysis data, as well as documents submitted for acute mammalian toxicity and ecological effects, meet the requirements set forth

for the proposed use patterns. If label instructions are followed, the Agency foresees no unreasonable adverse effects to human health and the environment from use of *P. oligandrum*.

E. Regulatory History

1. Experimental Use and Temporary Tolerance Exemption

No EUPs or temporary tolerance exemptions have been issued for *P. oligandrum*.

2. Section 3 Registration and Exemption from Tolerance

On November 15, 2004, Biopreparaty Co. Ltd, Tylišovska 1, Prague 6, Czech Republic, submitted to EPA an application to register the active ingredient *P. oligandrum* DV 74. When the application package for the new active ingredient was deemed complete, receipt of the application was published in the Federal Register [FR: May 27, 2005, Vol. 70, No. 102, pp. 30723-30725]. The Agency received no comments on the FR announcement.

Concomitant with the application for the Section 3(c) registration, the registrant filed a petition (PP 0F6191) requesting a permanent exemption from the requirement of a tolerance for the active ingredient, *P. oligandrum* DV 74, on all agricultural commodities. A notice of filing of this petition was published in the Federal Register [FR: May 25, 2005, Vol. 70, No. 100, pp. 30105-30109]. An exemption from the requirement of a tolerance for residues of *P. oligandrum* on all agricultural commodities is being processed in connection with this petition and the final rule will be published in the Federal Register (40 CFR Part 180), concurrent with the unconditional registration.

III. RISK ASSESSMENT

A. Physical and Chemical Properties Assessment

The data submitted in support of product identity requirements for *Pythium oligandrum* DV 74 (hereafter referred to as *P. oligandrum*) are sufficient for the proposed use patterns of the microbial pesticide.

Table 1: Product identity and manufacturing process for *P. oligandrum*.

Data Requirement	Guideline	Classification	MRID #
Product identity	885.1100* 151-20**	Acceptable	464107-01
Manufacturing process	885.1200 151-21	Acceptable	464107-01
Discussion of formation of unintentional ingredients	885.1300 151-22	Acceptable	464107-01
Analysis of samples	885.1400 151-23	Acceptable	464107-01
Certification of limits	885.1500 151-25	Acceptable	464107-01
Enforcement analytical method	830.1800 151-25	Acceptable	464107-01
Physical and chemical properties	151-26	Acceptable	464109-01 467542-01 467542-02

*OPPTS Microbial pesticide test guidelines

**Microbial pesticide test guidelines identified in the code of federal regulations.

1. Product Identity and Mode of Action (MRID 464107-01; OPPTS Gdln. 885.1100, 885.1200, 885.1300, 885.1400, 885.1500, 151-10)

The manufacturing use product Technical DV 74 contains 5% *P. oligandrum*, the active ingredient in this product and one gram of the technical product contains not less than 1×10^6 cfu/g. *P. oligandrum*.

Pythium oligandrum is commonly found in soil and in or on plants and the species' spiny oospores serve to differentiate it from other fungal oospores (*i.e.* *Pythium* spp.). Published scientific literature, submitted studies, and other data support the hypothesis that *P. oligandrum* is not a pathogen per se, but acts as a hyperparasite of other fungi. It exhibits limited growth on plant-based media, and no growth on animal

tissue-based media. In addition, growth capability tapers off as temperature approaches normal human body temperature of 37°C.

P. oligandrum is registered and marketed in the Czech Republic, Poland, Slovakia, Austria, Germany, and the United Arab Emirates. In Europe, *P. oligandrum* (brand name: BioRepel Fungus) is marketed to control mildew and mold on walls, masonry, and other hard surfaces in buildings and is the active ingredient in a variety of over the counter products (footbath, fingernail treatment preparation, mouthwash, bath additive, and skin cream).

There are no impurities of toxicological significance associated with *P. oligandrum* and human/animal pathogens are not expected due to sterile manufacturing processes (BPPD Reviews dated February 22, 2006 and December 12, 2006).

2. Physical and Chemical Properties Assessment (MRIDs 464109-01, 467542-01, 467542-02; OPPTS Gdln. 830.6302, 830.6303, 830.7000, 830.7300, 830.6320, 830.6317, 151-17)

The manufacturing use product is a whitish powder with a bulk density of 90 g/L and a pH of 5.5-6.5. Data requirements (40 CFR Part §158.740(a)) for melting point, boiling point, solubility, vapor pressure, dissociation constant, octanol/water partition coefficient, stability, oxidizing or reducing potential, flammability/flash point, explodability, viscosity, miscibility, and dielectric breakdown voltage were waived due to the nature of the microbial pesticide (BPPD Review – February 22, 2006).

B. Human Health Assessment

Submitted mammalian toxicology studies are sufficient to support the unconditional registration of *P. oligandrum* DV 74 for the proposed use patterns.

1. Toxicological Hazard Assessment

Summaries of acute toxicology studies (Table 2) are discussed below.

Table 2: Tier I – Microbial pesticides toxicology data requirements for *P. oligandrum*.

Data Requirement	Guideline	Classification	Toxicity Category	Test Substance	Results Summary	MRID #
Acute oral toxicity	885.3050* 152-30**	Acceptable waiver rationale	IV	N/A	N/A	464109-03 464107-02 469901-01
Acute dermal toxicity	885.3100 152-31	Acceptable	IV	Technical DV 74	A 14-day acute dermal toxicity study showed that the LC ₅₀ for rats was > 5000 mg test material/kg body weight.	464109-04 464107-02
Acute inhalation toxicity	152-32	Acceptable	IV	<i>P. oligandrum</i> DV 74 [†]	A 4-hour acute inhalation study showed that the acute inhalation LC ₅₀ for rats was > 5 mg/L test material.	464109-05 464107-02
Acute pulmonary toxicity/pathogenicity	885.3150 152-32	Acceptable waiver rationale	IV	N/A	N/A	N/A
Acute injection toxicity/pathogenicity	885.3200 152-33	Acceptable (acute injection toxicity) Acceptable waiver rationale (infectivity testing).	Not toxic or pathogenic	<i>P. oligandrum</i> DV 74	The test material does not appear to be toxic or pathogenic to rats when dosed at 2.9x10 ⁴ oospores/animal.	465823-01 467542-01 464109-10 469901-01
Primary dermal irritation	870.2500 152-34	Acceptable	IV	Technical DV 74 [‡]	A 24 hour dermal irritation study showed that the test substance was non-irritating.	464605-02 464107-02
Acute eye irritation	870.2400 152-35	Acceptable	III	Technical DV 74	A 24 hour eye irritation study showed that the test substance was non-irritating.	464109-06
Skin sensitization	152-36	Supplemental	N/A	N/A	Incidents must be reported post-registration.	464109-10
Immune response	870.2500 152-38	Acceptable waiver rationale	N/A	N/A	N/A	464109-10
Cell culture	885.3500	N/A	N/A	N/A	Not required because the active ingredient is not a virus.	N/A
Pathogen and infectivity	Non-guideline	Acceptable	N/A	<i>P. oligandrum</i> DV 74	The test material exhibits limited growth on plant-based media, and no growth on animal tissue-based media.	469901-01

*OPPTS Microbial pesticide test guidelines

**Microbial pesticide test guidelines identified in the code of federal regulations.

[†] *P. oligandrum* DV 74 is the active ingredient (a.i.).

[‡] Technical DV 74 a manufacturing use product that contains 5% *P. oligandrum*.

a. Acute Oral Toxicity (MRIDs 464109-03, 464107-02, 464109-10 and 469901-01; OPPTS Gdln. 885.3050, 152-30)

The applicant submitted two oral studies (completed in 1979 and 1981) which used test substances that had been lyophilized and, in one case, sterilized. Although no adverse effects were noted in these studies, they were not done according to either EPA or OECD guidelines and did not adequately answer the questions posed by the data requirement. Consequently, EPA determined that the studies did not meet the requirement for dietary hazard assessment. In a subsequent acute oral toxicity study, ten mice (five males, five females) were given a total dose of 5000 mg/kg Technical DV 74. No adverse effects were seen during the 14-day observation period that followed dosing. Consequently, the test substance was rated toxicity category IV (BPPD reviews- February 22, 2006, December 12, 2006, and March 7, 2007).

b. Acute Dermal Toxicity (MRID 464109-04, 464107-02; OPPTS Gdln. 870.1200, 152-31)

In a 14-day acute dermal toxicity study, the dermal LD₅₀ for rats was greater than 5000 mg/kg body wt. Technical DV 74. Consequently, the test substance was rated toxicity category IV (MRID 464605-02) (BPPD Review – February 22, 2006).

c. Acute Inhalation Toxicity (MRID 464109-05; OPPTS Gdln. 870.1300, 152-32)

In a 4-hour acute inhalation toxicity study using rats, no mortality or adverse effects, and no gross abnormalities resulted from a limit dose (5 mg/L) of *P. oligandrum* DV 74. Although the MMD was 7.45 µm, approximately 68 % of the particles were ≤3.75 µm. The acute inhalation LC₅₀ for males, females, and combined was > 5 mg/L for a 4-hour exposure. Consequently, the test substance is classified as toxicity category IV (BPPD Review February 22, 2006).

d. Acute Pulmonary Toxicity/Pathogenicity-Waiver Granted (MRID 464109-10; OPPTS Gdln. 885.3150, 152-32)

In a 4-hour acute inhalation toxicity study using rats, a limit dose (5 mg/L) of *P. oligandrum* DV 74 produced no mortality or adverse effects, and no gross abnormalities were seen at necropsy 14 days later. Although the MMD was 7.45 µm, approximately 68 % of the particles were ≤3.75 µm. The acute inhalation LC₅₀ for males, females, and combined was > 5 mg/L for a 4-hour exposure. Consequently, the test substance is classified as toxicity category IV (BPPD Review February 22, 2006). Infectivity testing was waived for this study based on the results of the growth temperature study which showed no growth on plant-based growth media at or above 37° C, and no growth at any temperature on animal tissue-based growth media (see section III.B.1.k. below).

e. Acute Injection Toxicity/Pathogenicity (MRIDs 465823-01, 467542-01, 464109-10, and 469901-01; OPPTS Gdln. 885.3200, 152-33)

An acute injection toxicity/pathogenicity study was conducted using rats. Storage stability data showed that following 9 months of storage, 80.5% of oospores were viable after 120 hours incubation. Based on the submitted data, *Pythium oligandrum* DV 74 does not appear toxic or pathogenic to rats when dosed at 2.9×10^4 oospores/animal. However, since no attempts were made to isolate viable organisms prior to testing, infectivity cannot be assessed in the present study. Infectivity testing was waived based on the results of the growth temperature study which showed no growth on plant-based growth media at or above 37° C, and no growth at any temperature on animal tissue-based growth media (see section III.B.1.k. below).

f. Primary Dermal Irritation (MRID 464605-02 and 464107-02; OPPTS Gdln.152-34, 870.2500)

The registrant submitted an acute dermal irritation study that used rabbits. Very slight erythema was noted on 3/3 rabbits one hour after patch removal with clearance on two rabbits by 24 hours and on one rabbit by 48 hours. The primary irritation index was 0.3. Technical DV 74 was essentially nonirritating, so the test substance was rated toxicity category IV (BPPD Review February 22, 2006).

g. Acute Eye Irritation (MRID 464109-06; OPPTS Gdln. 870.2400, 152-35)

The registrant conducted an acute eye irritation study using rabbits. No corneal opacity or iritis was noted on any rabbit during the study. Positive conjunctival irritation (score 2) was noted on 2 rabbits 1 hour after test material instillation with resolution by 48 hours. The maximum average score was 6.7 at 24 hours after Technical DV 74 instillation. The test substance was rated toxicity category III (BPPD Review February 22, 2006).

h. Skin sensitization-Waiver Granted (MRID 464109-10; OPPTS Gdln. 870.2600, 152-36)

See conclusions discussed in III.B.1.b and III.B.1.j. *Pythium oligandrum* DV 74 is the active ingredient in various over the counter products sold in Europe, including a mouthwash, a bath additive and a skin cream (the registrant did not state the percent active ingredient in these products). These products have been on the market in parts of the EU since 1999, with no reported adverse effects. The lack of any reported sensitization effects from repeated dermal exposure via consumer products containing the active ingredient suggests that *P. oligandrum* is not a dermal sensitizer. Additionally, the agricultural use label requires that applicators and handlers wear a long-sleeved shirt and long pants, waterproof gloves, and shoes plus socks.

i. Immune Response-Waiver Granted (MRID 464109-10; OPPTS Gdln. 880.3800, 152-38)

See conclusions discussed in III.B.1.a and waiver justification provided in III.B.1.h.

j. Cell Culture (MRID 464109-10; OPPTS Gdln. 885.3500)

Since *Pythium oligandrum* is not a virus, this study is not required.

k. Pathogenicity and Infectivity (MRID 469901-01 and 02; OPPTS Gdln. N/A)

Pythium oligandrum DV 74 is primarily a fungal hyperparasite that exhibits limited growth on plant-based media, and no growth on animal tissue-based media. In addition, growth capability tapers off as temperature approaches normal human body temperature of 37°C and there is no growth at or above this temperature, even on plant based media. Consequently, it is unlikely that infectivity in animal testing would occur, or that there would be a feasible way to demonstrate clearance in animal models; therefore, infectivity testing in the 885 series guidelines would not be possible. This information supports waivers for infectivity testing in the acute oral, acute dermal, acute inhalation, and injection exposure studies.

m. Subchronic, Chronic Toxicity and Oncogenicity

Based on the data generated in accordance with Tier I data requirements (40 CFR Part §158.740(c)), Tier II tests (Guidelines 152B-40 through 152B-49), which include acute oral, acute inhalation, subchronic oral, acute intraperitoneal/intracerebral, primary dermal, primary eye, immune response, teratogenicity, virulence enhancement, and mammalian mutagenicity, were not required. Tier III tests (Guidelines 152-50 through 53), which include chronic testing, oncogenicity testing, mutagenicity, and teratogenicity, were also not required.

n. Effects on the Endocrine System

EPA is required under section 408(p) of the FFDCA, as amended by FQPA, to develop a screening program to determine whether certain substances (including all pesticide active and other ingredients) "may have an effect in humans that is similar to an effect produced by a naturally-occurring estrogen, or other such endocrine effects as the Administrator may designate." *Pythium oligandrum* is not a known endocrine disruptor nor is it related to any class of known endocrine disruptors. Consequently, endocrine-related concerns did not adversely impact the Agency's safety finding for *P. oligandrum*.

2. Dietary Exposure Assessment

a. Food Clearances/Tolerances

This is the first proposed Section 3(c)(5) unconditional registration of *P. oligandrum*. There is low potential for toxicity and a demonstrated lack of adverse effects from oral, inhalation, dermal, and injection studies; only slight eye irritation was noted from this product. Infectivity and clearance of this organism were not tested, however it was shown that growth at body temperature and on animal tissues was highly unlikely. *Pythium oligandrum* DV 74 is a fungal hyperparasite with limited ability to grow on some plant tissues, though it is not a plant pathogen. The active ingredient is used as a dermally applied anti-fungal agent and in a mouthwash rinse in some European countries – without reports of adverse effects. There is a reasonable certainty that no harm is likely to result from exposure to the active ingredient. This includes all anticipated dietary exposures for which there is reliable information. As such, an exemption from the requirement of a food tolerance for residues of *P. oligandrum* DV 74 is being established concomitant with the unconditional registration (40 CFR Part 180).

b. Dietary Risk Characterization

Residues of *P. oligandrum* may be present on agricultural commodities. Negligible to no risk is expected for the general population, including infants and children, because *P. oligandrum* demonstrated no pathogenicity or oral toxicity at the maximum doses tested (BPPD Review – December 12, 2006).

c. Drinking Water Risk Characterization

Pythium oligandrum does not thrive in aquatic environments and there are no aquatic use sites for the pesticide. Accordingly, application of this pesticide to approved use sites is not expected to increase drinking water exposure to *P. oligandrum*. Furthermore, any material that is consumed through drinking water would pose negligible to no risk for the general population, including infants and children, due to the pesticide's low toxicity classification.

d. Acute and Chronic Dietary Risks for Sensitive Subpopulations Particularly Infants and Children

There is a reasonable certainty that no harm to the U.S. population, including infants and children, will result from aggregate exposure to residues of *P. oligandrum* due to its use as a microbial pest control agent. This includes all anticipated dietary exposures and all other exposures for which there is reliable information. *Pythium oligandrum* is minimally toxic, non-pathogenic, and non-infective to mammals. Accordingly, exempting *P. oligandrum* from the requirement of a tolerance is considered safe and poses no significant risks.

e. Determination of Safety for U.S. Population, Infants and Children

See section III.B.2.e above. Further, FFDC section 408(b)(2)(C) provides that EPA shall apply an additional tenfold margin of exposure (safety) for infants and children in the case of threshold

effects to account for prenatal and postnatal toxicity and the completeness of the database on toxicity and exposure, unless EPA determines that a different margin of exposure (safety) will be safe for infants and children. Margins of exposure (safety), which often are referred to as uncertainty factors, are incorporated into EPA risk assessment either directly or through the use of a margin of exposure analysis or by using uncertainty (safety) factors in calculating a dose level that poses no appreciable risk. Actual exposures to adults and children through diet are expected to be several orders of magnitude less than the doses used in the toxicity and pathogenicity tests referenced in Section III above. Thus, the Agency has determined that an additional margin of safety for infants and children is unnecessary.

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

The potential for aggregate exposure should be adequately mitigated if label instructions are followed.

i. Dermal

Dermal exposure is limited by use of the required PPE and REI in occupational settings, and residential users are advised to avoid skin contact and to wash any exposed skin or clothing (see Section III.B.1 above).

ii. Oral

Oral exposure would occur primarily from eating treated produce. However, negligible to no risk is expected, because *P. oligandrum* demonstrated no pathogenicity or toxicity potential at the maximum doses tested. Based on the acute oral toxicity study, the pesticide is classified as Toxicity Category IV for oral exposure (see Section III.B.1 above).

iii. Inhalation

The greatest likelihood of inhalation exposure would occur in an occupational setting, among mixers/loaders and applicators. However, as demonstrated in the acute pulmonary toxicity/pathogenicity test, *P. oligandrum* is not infective, pathogenic, or toxic to mammals. Despite the benign nature of the active ingredient, the agency requires that all workers exposed to microbial pesticides must wear a dust/mist filtering respirator. As such, the risks anticipated for inhalation exposure are considered minimal.

g. Cumulative Effects

Section 408(b)(2)(D)(v) of the FFDCFA requires the Agency to consider the cumulative effect of exposure to *P. oligandrum* and to other substances that have a common mechanism of toxicity. These considerations include the possible cumulative effects of such residues on infants and children. *Pythium oligandrum* is not toxic or pathogenic to mammals, and only minimally irritating in an eye exposure study. Consequently, no cumulative effects from the residues of this product with other related microbial pesticides are anticipated (see Section III.B.1 above).

3. Occupational and Residential Risk Characterization

a. Non-occupational Residential, School and Day Care Exposure, and Risk Characterization

Pythium oligandrum will be applied to agricultural fields, turf and professional landscapes, and in home gardens. Although some applications may be made near residential areas, no harm would be expected to result from exposure to *P. oligandrum* due to its low toxicity classification (see Section III.B.1 above).

b. Occupational Exposure and Risk

Potential worker and pesticide handler exposure to *P. oligandrum* is not expected to pose any undue risk. Appropriate Personal Protective Equipment (PPE) and a Restricted Entry Interval (REI) of four hours are required to mitigate any potential risks to workers and pesticide handlers. PPE for workers and handlers consists of long-sleeved shirt, long pants, shoes, socks, waterproof gloves, and a filtering respirator. To perform post-application activities, early entry workers must wear coveralls in addition to the PPE described above.

The primary routes of exposure for mixer/loaders and applicators would be dermal and/or inhalation exposure. The acute pulmonary toxicity/pathogenicity study submitted in support of the registration demonstrated that *P. oligandrum* is minimally toxic and non-pathogenic. As such, the risks anticipated for occupational exposure are considered minimal (Section III.B.1 above).

C. Environmental Assessment

1. Ecological Effects Hazard Assessment

Below is a summary of the ecological effects database evaluated in support of this action (Table 3). A determination of reasonable certainty that no incremental irreversible adverse effects to wild mammals, avian species, insects including beneficial insects, freshwater fish, aquatic invertebrates, estuarine and marine animals or to the vast majority of plant species will result from the intended applications to outdoor terrestrial environments. The database consists of acceptable waiver requests supported by scientific rationale and submitted data that support the conclusion that there are no incremental irreversible hazards to non-target organisms as a result of intended uses of *P. oligandrum*.

Table 3: Tier I – Microbial pesticides non-target organism data requirements for *P. oligandrum*.

Data Requirement	Guideline	Classification	Test Substance	Results Summary	MRID #
Avian oral	885.4050* 154-16**	Acceptable waiver rationale	N/A	N/A	464109-10
Avian injection	885.4100 154-17	Acceptable waiver rationale	N/A	N/A	464109-10
Wild mammal	885.4150 154-18	Acceptable waiver rationale	N/A	N/A	464109-03 464109-05 464109-10
Freshwater fish	885.4200 154-19	Supplemental Acceptable waiver rationale	<i>P. oligandrum</i> DV 74 [†]	In a 4-day study, no adverse effects were noted following a single dose of 100 ppm test substance.	464109-09 464109-10
Freshwater aquatic invertebrate	885.4240 154-20	Acceptable waiver rationale	N/A	N/A	464109-10
Estuarine and marine animal	885.4280 154-21	Acceptable waiver rationale	N/A	N/A	464109-10
Non-target plant	885.4300 154-22	Acceptable waiver rationale	N/A	N/A	464109-10
Non-target insect testing	885.4340 154-23	Acceptable waiver rationale	N/A	N/A	464109-10
Honey bee testing	885.4380 154-24	Acceptable waiver rationale	N/A	N/A	464109-10

*OPPTS Microbial pesticide test guidelines

**Microbial pesticide test guidelines identified in the code of federal regulations.

[†] *P. oligandrum* DV 74 is the active ingredient (a.i.).

a. Avian Oral-Waiver Granted (MRID 464109-10; OPPTS Gdln. 885.4050, 154-16)

Pythium oligandrum occurs naturally in the U.S. in a variety of soil types, under a wide range of environmental conditions (Ribiero and Butler, 1992) and is often associated with other mycoparasites and fungi (Foley and Deacon, 1985). Environmental levels of *P. oligandrum* could temporarily increase as a result of intended applications to seeds, foliage or soil; however these population "spikes" are expected to decrease to naturally-occurring levels, because of low survival capability in the absence of sufficient nutrients (McQuilken et al., 1992). *Pythium oligandrum* binds to and penetrates the hyphae of several plant-pathogenic fungi and has been shown to stimulate host plant resistance mechanisms to parasitic infection. The disease resistance mode of action functions by producing a small proteinaceous molecule that serves as a biochemical signal in the plant. The mycoparasitic action and stimulation of plant resistance are both associated with positive effects on plant health and viability, and no adverse effects were found when a growing plant was treated with extract. A search of the AGRICOLA, TOXLINE and NLM PubMed databases indicated that the active ingredient is not known to have toxic or pathogenic effects on the referenced non-target organisms. (BPPD Review – February 24, 2006).

b. Avian Injection-Waiver Granted (MRID 464109-10; OPPTS Gdln. 885.4100, 154-17)

See section III.C.1.a above for waiver justification.

c. Wild Mammal (MRIDs 464109-03, 464109-05, and 464109-10; OPPTS Gdln. 885.4150, 154-18)

In an acute oral toxicity study, ten mice (five males, five females) were given a total dose of 5000 mg/kg Technical DV 74. No adverse effects were seen during the 14 day observation period that followed dosing. The test substance was rated toxicity category IV (see section III.B.1.a). See section III.C.1.a above for additional justification.

d. Freshwater Fish (MRID 451664-10; OPPTS Gdln. 885.4200, 154-19)

In a static acute toxicity test (limit test), guppies (*Poecilia reticulata*) were exposed to an extract of *Pythium oligandrum* at a dose of 100 mg active ingredient per liter of test solution and monitored for 96 hours. No mortality or changes in morphology or behavior were observed in either the test or control guppies. (BPPD Review – December 1, 2005). See section III.C.1.a above for additional justification.

e. Freshwater Aquatic Invertebrate-Waiver Granted (MRID 464109-10; OPPTS Gdln. 885.4240, 154-20)

See section III.C.1.a above for waiver justification. Furthermore, in a non-GLP contact and feeding study, no adverse effects were noted in honeybees after dosing for a 48-hr observation period. (BPPD Review – February 24, 2006).

f. Estuarine/Marine Organisms-Waiver Granted (MRID 464109-10; OPPTS Gdln. 885.4280, 154-21)

See section III.C.1.a above for waiver justification.

g. Nontarget Plant-Waiver Granted (MRID 464109-10; OPPTS Gdln. 885.4300, 154-22)

Pythium oligandrum occurs naturally in a variety of soil types and, based on October 2004 searches of the AGRICOLA, TOXLINE, and NLM PubMed databases, has not been reported as toxic or pathogenic to nontarget terrestrial plants. The mode of action is associated with biocontrol mechanisms which stimulate plant resistance to fungal pathogens and mycoparasites. Environmental levels of *P. oligandrum* could temporarily increase as a result of intended applications; however these population increases are considered temporary and the ACTIVE INGREDIENT is not expected to proliferate in the absence of sufficient nutrients (McQuilken et al., 1992) (BPPD Review – February 24, 2006).

h. Non-target Insects-Waiver Granted (MRID 464109-10; OPPTS Gdln. 885.4340, 154-23)

See section III.C.1.a above for waiver justification. Furthermore, in a non-GLP contact and feeding study, no adverse effects were noted in honeybees after dosing for a 48-hr observation period (BPPD Review – February 24, 2006).

i. Honeybees-Waiver Granted (MRID 464109-10; OPPTS 885.4380, 154-24)

See section III.C.1.a above for waiver justification. Furthermore, in a non-GLP contact and feeding study, no adverse effects were noted in honeybees after dosing for a 48-hr observation period (BPPD Review – February 24, 2006).

**2. Environmental Fate, Ecological Exposure, and Environmental Expression Risk
Characterization**

Pythium oligandrum occurs naturally and is commonly isolated from a wide range of soil types in the U.S., and is often associated with other fungal and plant species. Although several species of *Pythium* are well-known plant pathogens (e.g., *P. ultimum*), causing seedling diseases on a variety of plants, *P. oligandrum* is not amongst the plant-pathogenic Pythiaceae. The type strain (*Pythium oligandrum* ATCC 38472) is manufactured in Czechoslovakia under several trade names (e.g., Polyversum®) and is registered and marketed widely in Europe and the United Arab Emirates. The requests to waive non-target organism studies are based on the rationale that the active ingredient occurs naturally in a variety of soil types and has not been reported toxic nor pathogenic to the OPPTS- referenced nontarget organisms in a literature search of AGRICOLA, TOXLINE and NLM PubMed databases, encompassing a period of 20+ years of study on *P. oligandrum*. Environmental levels of *P. oligandrum* could temporarily increase as a result of intended applications to crop seeds, foliage or soil, however these temporary population "spikes" would likely decrease to naturally-occurring levels.

The reported biological effects include mycoparasitism of several fungi (including several causing severe plant diseases) and stimulation of plant resistance mechanisms to fungal infection in plants. The mycoparasitic mode of action is initiated by a specific affinity for the cells of the fungus, followed by binding to the host hyphae and local penetration. The (plant) disease resistance mode of action is by production of a small proteinaceous molecule that serves as a biochemical signal in the plant.

These modes of action are host-specific and restricted to fungal species; and are not associated with adverse effects in nontarget insects (including honeybees), avian species, aquatic flora and fauna, humans, or other mammals. Both the mycoparasitic action and stimulation of plant disease resistance are associated with positive effects on plant health and viability, and no adverse effects were found when a growing plant was treated with extract.

The ecological data (as summarized in section III.C.1 above) support a conclusion that no incremental irreversible hazards to non-target organisms or to the environment are expected as a result of intended uses of *P. oligandrum*. These data and information support labeled outdoor terrestrial uses; accordingly, OPPTS Tier I testing for ecological effects or environmental expression is not required. In the unlikely event that some non-target organisms are affected during the commercial application of this product, such incidents should be immediately reported to the EPA as required under FIFRA Section 6(a)(2) so that the Agency may take appropriate action. The end-use product(s) is(are) intended for outdoor terrestrial applications as a seed dressing, a pre-plant soil or soak, irrigation, or overhead spray or root drench, as needed.

3. Endangered Species Assessment

An environmental risk assessment was performed on non-target birds, wild mammals, plants, freshwater fish, aquatic invertebrates, estuarine and marine animals, honeybees and non-target insects using information submitted by Technology Sciences Group on behalf of Biopreparaty, Inc and relevant bibliography from the open literature. The submitted information and data from the open literature regarding product identity, ecology and characterization support a risk characterization and a conclusion of a reasonable certainty that there are no incremental irreversible hazards to non-target organisms, including endangered and threatened species, as a result of the intended uses of products containing *P. oligandrum*.

This opinion is based on a general rationale pertaining to the biology and ecology of the active ingredient, restricted host range to various genera of fungi (including plant pathogens) and the biological control mechanisms as a mycoparasite and inducer of plant disease resistance mechanisms from the open literature. *Pythium oligandrum* is widespread in soils and in root zones of plants; and has been studied for nearly 30 years without evidence of toxicity or pathogenicity to non-target plants.

Sufficient information and published data from the open literature were summarized in a scientific rationale to justify waiving several Tier I non-target organism tests (avian, wild mammal, aquatic invertebrates, estuarine/marine organisms and insects). Non-target wild mammal and estuarine/marine organism testing are conditional requirements (CR) for terrestrial food use patterns (40 CFR 158.740(d)).

Requests to waive wild mammal toxicity/pathogenicity studies were reviewed and determined acceptable based on associative rationale substantiating a reasonable certainty that no irreversible effects to wild mammals will result from intended applications of the active ingredient. In addition, direct testing of rodent species for human health assessment purposes did not reveal any hazards. A determination of reasonable certainty was made that no incremental irreversible hazards will occur to avian species, freshwater fish, aquatic invertebrates, insects (including honeybees) or estuarine and marine animals and plants from the intended application method and the fate of the active ingredient.

The active ingredient's modes of action are fungal host-specific and likely induce plant disease resistance mechanisms; furthermore, these biological control mechanisms are not associated with adverse effects in nontarget insects (including honeybees), avian species, aquatic flora and fauna, humans, or other mammals.

This analysis supports a no "may effect" opinion to federally listed threatened and endangered species from the intended applications as a fungicide to control fungal root diseases and induce plant resistance mechanisms on various terrestrial food and ornamental crops applications.

IV. RISK MANAGEMENT AND REGISTRATION DECISION

A. Determination of Eligibility

Section 3(c)(5) of FIFRA provides for the registration of a new active ingredient if it is determined that: a) its composition is such as to warrant the proposed claims for it; b) its labeling and other materials required to be submitted comply with the requirements of FIFRA; c) it will perform its intended function without unreasonable adverse effects on the environment; and d) when used in accordance with widespread and commonly recognized practice, it will not generally cause unreasonable adverse effects on the environment.

To satisfy Criterion “A” above, *P. oligandrum* DV 74 has well known properties. The Agency has no knowledge that would contradict the claims made on the label of this product and the active ingredient is not expected to cause unreasonable adverse effects when used according to label instructions. Criterion “B” is satisfied by the current label and by the data presented in this document. It is believed that this new pesticidal active ingredient will not cause any unreasonable adverse effects, and is likely to provide protection as claimed, satisfying Criterion “C”. Criterion “D” is satisfied in that *P. oligandrum* is not expected to cause unreasonable adverse effects when used according to label instructions. Therefore, *P. oligandrum* DV 74 is eligible for registration.

B. Regulatory Position

1. Unconditional Registration

The data requirements are fulfilled. Consequently, BPPD recommends unconditional registration of products that contain *P. oligandrum* DV 74 as a new active ingredient.

2. Tolerances for Food Uses and /or Exemption

EPA received a pesticide petition (PP 4F6877) from Biopreparaty Co. Ltd., which proposed [pursuant to section 408(d) of the Federal Food, Drug and Cosmetic Act, 21 U.S.C. section 346a(d)] to amend 40 CFR Part 180 by establishing an exemption from the requirement of a tolerance for residues of the microbial pesticide, *P. oligandrum* DV 74, on growing crops.

EPA is issuing a notice establishing an exemption from the requirement of a tolerance for residues of *P. oligandrum* in or on all food commodities (40 CFR Part 180).

3. CODEX Harmonization

There are no Codex harmonization considerations since there is no Codex Maximum Residue Limits set for food use of this active ingredient.

4. Risk Mitigation

There is minimal or negligible potential risk to non-target organisms (plants and wildlife), and to ground and surface water contamination through the proposed use of products containing *P. oligandrum* as discussed in this document. No mitigation measures are required at this time for dietary risk, including risk due to exposure via drinking water. Appropriate PPE is required for pesticide handlers. These include long-sleeved shirt, long pants, shoes plus socks, and a dust/mist filtering respirator. The product label will also bear environmental hazards text to mitigate any potential risk as determined by reviewed data and use sites.

C. Labeling

The labels and labeling of all products must comply with EPA's current regulations and requirements as specified in 40 CFR Part 156.10 and other applicable notices, such as, and including the WPS labeling. *Pythium oligandrum* products with commercial use sites are subject to the Worker Protection Standard. Because of the low toxicity of *P. oligandrum*, the Restricted Entry Interval (REI) for greenhouse foliar applications within the scope of WPS is 4 hours. For use as a soil amendment (incorporation into soil mixes), the REI is 0 hours due to the low likelihood of contact with treatment residues. Precautionary statements and personal protective equipment (PPE), as specified below, are required based on the acute toxicity categories of this organism.

Handlers (including mixer/loaders and applicators) applying this product must wear long-sleeved shirt, long pants, shoes plus socks, and a dust/mist filtering respirator meeting NIOSH standards of at least N-95, R-95, or P-95 (DHHS 1987 and 2004). Post application agricultural workers and early-entry workers must wear coveralls in addition to the PPE above when entering treated areas during the REI period of four hours.

Labels for registered products containing the active ingredient *Pythium oligandrum* are available at <http://ppis.ceris.purdue.edu/htbin/epachem.com>. The PC code for this active ingredient is 028816. Labels for all products produced by Biopreparaty Co. Ltd. are available at <http://oaspub.epa.gov/pestlabl/ppls.home>. The relevant company number is 81606.

V. ACTIONS REQUIRED BY REGISTRANTS

Reports of incidents of adverse effects to humans or domestic animals are required under FIFRA, Section 6(a)(2) and incidents of hypersensitivity under 40 CFR Part 158.690(c), data requirement reference number 152-16. Before releasing these products for shipment, the registrant is required to provide appropriate labels and other Agency requirements as discussed in this Biopesticide Registration Action Document.

VI. BIBLIOGRAPHY

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- 469901-02 J. Kratochvilova (2006). *Pythium oligandrum* DV 74: Growth in Various Temperatures on Potato Extract and Sheep's Blood Agar. Received 22-Nov-06.
- 469901-03 A. Roberts (2006). Supplemental Product Chemistry for Technical DV 74. Received 22-Nov-06.

B. Federal Register Publications

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C. BPPD Data Evaluation Records/Reviews

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D. Other Publications

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