



Australian Government
Australian Pesticides and
Veterinary Medicines Authority



PUBLIC RELEASE SUMMARY

on the evaluation of the new active *Aureobasidium pullulans* (strains DSM 14940 and DSM 14941) in the product Botector Fungicide

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Comments and enquiries regarding copyright:

Director Public Affairs and Communication

Australian Pesticides and Veterinary Medicines Authority

PO Box 6182

KINGSTON ACT 2604 Australia

Telephone: +61 2 6210 4988

Email: communications@apvma.gov.au

This publication is available from the APVMA website: www.apvma.gov.au.

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PREFACE

The Australian Pesticides and Veterinary Medicines Authority (APVMA) is the Australian Government regulator with responsibility for assessing and approving agricultural and veterinary chemical products prior to their sale and use in Australia.

In undertaking this task, the APVMA works in close cooperation with advisory agencies, including the Department of Environment and State Departments of Primary Industries.

The APVMA has a policy of encouraging transparency in its activities and seeking community involvement in decision making. Part of that process is the publication of Public Release Summaries for products containing new active constituents.

The information and technical data required by the APVMA to assess the safety of new chemical products, and the methods of assessment, must be consistent with accepted scientific principles and processes. Details are outlined on the [APVMA website](#).

This Public Release Summary is intended as a brief overview of the assessment that has been conducted by the APVMA and of the specialist advice received from its advisory agencies. It has been deliberately presented in a manner that is likely to be informative to the widest possible audience to encourage public comment.

About this document

This is a Public Release Summary.

It indicates that the APVMA is considering an application for registration of an agricultural or veterinary chemical. It provides a summary of the APVMA's assessment, which may include details of:

- the toxicology of both the active constituent and product
- the residues and trade assessment
- occupational exposure aspects
- environmental fate, toxicity, potential exposure and hazard
- efficacy and target crop or animal safety

Comment is sought from interested stakeholders on the information contained within this document.

Making a submission

In accordance with sections 12 and 13 of the Agvet Code, the APVMA invites any person to submit a relevant written submission as to whether the application for approval of the new active constituents and registration of Botector Fungicide should be granted. Submissions should relate only to matters that the APVMA is required, by legislation, to take into account in deciding whether to grant the application. These matters include aspects of public health, occupational health and safety, chemistry and manufacture, residues in food, environmental safety, trade, and efficacy and target crop or animal safety. Submissions should state the grounds on which they are based. Comments received that address issues outside the relevant matters cannot be considered by the APVMA.

Submissions must be received by the APVMA by close of business on 19 September 2017 and be directed to the contact listed below. All submissions to the APVMA will be acknowledged in writing via email or by post.

Relevant comments will be taken into account by the APVMA in deciding whether the product should be registered and in determining appropriate conditions of registration and product labelling.

When making a submission please include:

- contact name
- company or group name (if relevant)
- email or postal address (if available)
- the date you made the submission.

All personal information, and confidential information judged by the APVMA to be confidential commercial information (CCI)¹ contained in submissions will be treated confidentially.

Written submissions on the APVMA's proposal to grant the application for registration that relate to the grounds for registration should be addressed in writing to:

Case Management and Administration Unit
Australian Pesticides and Veterinary Medicines Authority
PO Box 6182
Kingston ACT 2604
Phone: +61 2 6210 4701
Fax: +61 2 6210 4721
Email: enquiries@apvma.gov.au

¹ A full definition of "confidential commercial information" is contained in the Agvet Code.

Further information

Further information can be obtained via the contact details provided above.

Further information on Public Release Summaries can be found on the APVMA website:

<http://www.apvma.gov.au>.

1 INTRODUCTION

1.1 Applicant

Nufarm Australia Limited.

1.2 Purpose of application

Nufarm Australia Limited has applied to the APVMA for registration of the new product Botector Fungicide containing 5×10^9 CFU/g (1.000 g/kg) of the new active constituent *Aureobasidium pullulans* (strains DSM 14940 and DSM 14941) as a wettable powder formulation.

This publication provides a summary of the information reviewed and an outline of the regulatory considerations for the proposed registration of Botector Fungicide, and approval of the new active constituent, *Aureobasidium pullulans* (strains DSM 14940 and DSM 14941).

1.3 Product claims and use pattern

Botector Fungicide is a biological fungicide intended for use as a preventative treatment in the control of botrytis bunch rot / grey mould (*Botrytis cinerea*) in grapes. It is applied at a rate of 100 g/100 L as a foliar spray into the bunch zone or the whole canopy from phenological stage EL25 (80% capfall / flower hoods fallen) to EL 37 (ripening).

The use of Botector Fungicide will be restricted to ground application, applied as a medium spray. Application can either be by dilute or concentrate spraying, in a minimum spray volume of 400 L/ha.

Up to 4 applications can be applied per season, as part of a botrytis bunch rot program. A withholding period is not required when used as directed.

1.4 Mode of action

The mode of action of *Aureobasidium pullulans* against *Botrytis cinerea* on grapes occurs through active competition for space and nutrients thereby excluding plant pathogens from infection. *Aureobasidium pullulans* is an antagonistic organism belonging to the class of Eu-ascomycetes and has no known sexual cycle. These microorganisms occur naturally in the environment.

Internationally, the Fungicide Resistance Action Committee (FRAC) has classified Botector Fungicide as "Not Classified". Due to the mode of action of *Aureobasidium pullulans* (competition in nutrition and space) there is no potential for traditional fungicide resistance development.

1.5 Overseas registrations

Botector Fungicide is at present registered for the control of *Botrytis cinerea* in grapevines in USA, Morocco, Switzerland, Canada (suppression), Germany and Spain. Botector Fungicide also has many overseas

provisional registrations for the control of *Botrytis cinerea* in grapevines including Austria, Hungary, Italy, Portugal, Slovakia, Greece and Slovenia.

In addition, Botector Fungicide is registered in the USA for the control of *Botrytis cinerea* in tomatoes; Anthracnose, *Botrytis cinerea*, Phomopsis sp. and Rhizopus Fruit Rot in berries, and Blossom blight and Brown rot in almonds and stone fruit, and in Spain for the control of *Botrytis cinerea* in strawberry and tomatoes.

2 CHEMISTRY AND MANUFACTURE

2.1 Active constituent

The active constituents *Aureobasidium pullulans* strain DSM 14940 and strain DSM 14941 are biological fungicides that protect grapes from infections with grey mould (*Botrytis cinerea*). *Aureobasidium pullulans* strain DSM 14940 and strain DSM 14941 are not listed in Food and Agriculture Organisation of the United Nations (FAO) specifications.

The active constituent *Aureobasidium pullulans* strain DSM 14940 and strain DSM 14941 have the following characteristics:

COMMON NAME:	<i>Aureobasidium pullulans</i> strain DSM 14940 <i>Aureobasidium pullulans</i> strain DSM 14941
SPECIES NAME:	<i>Aureobasidium pullulans</i> (var. pullulans)
GENUS:	<i>Aureobasidium</i>
FAMILY:	<i>Dothioraceae</i>
ORDER:	<i>Dothideales</i>
CLASS:	<i>Euscomycetes / Dothideomycetes</i>
PHYLUM:	Ascomycota
KINGDOM:	FUNGI
CAS NUMBER:	67891-88-7 (for both strains DSM 14940 and DSM 14941)
BRIEF DESCRIPTION:	Strains <i>A. pullulans</i> DSM 14940 and 14941 were isolated in 1989 at the University of Konstanz from an apple plantation ('Golden Delicious').

Aureobasidium pullulans strain DSM 14940 and strain DSM 14941 have the following physiochemical properties:

PHYSICAL FORM:	Granule
COLOUR:	Off-white to light pink
ODOUR:	Similar to bread
IGNITION TEMPERATURE (°C)	Product is not flammable
DANGER OF EXPLOSION:	Product does not present an explosion hazard
SOLUBILITY/MISCIBILITY WITH WATER:	Dispersible
ORIGIN AND NATURAL OCCURRENCE:	Species <i>A. pullulans</i> is a ubiquitous, globally distributed saprophytic yeast-like fungus (yeast, feeding from plant exudates and dead plant tissues, on a multitude of substrates. It can be readily isolated all over the world from the phylloplane, plant residues, vegetables ripe for harvesting, soil, wood, air, bark, roots, marsh, marine sediments, estuarine, waters, skin, nails, stone, and glass. <i>A. pullulans</i> is one of the most common epiphytes on plant surfaces and leaves
MODE OF ACTION:	Provides competition for nutrients and space
HOST SPECIFICITY:	Not applicable, ubiquitous saprophytic phylloplane microorganism
LIFE CYCLE:	Complex polymorphic life cycle consisting of various unicellular forms and a filamentous mycelium. Individual hyphae produce blastospores and chlamydo-spores. No sexual reproduction stage is known
INFECTIVITY, DISPERSAL AND COLONISATION ABILITY:	Neither strain replicates at or above 35°C and are therefore not infective to humans
RELATIONSHIP TO KNOWN PLANT, ANIMAL OR HUMAN PATHOGENS:	No relationships known
GENETIC STABILITY:	Stable genotype maintained through standard procedures (stock cultures), mutation rates above the background levels are not expected
PRODUCTION OF RELEVANT METABOLITES/TOXINS:	No indications for production of toxins or toxic metabolites

The APVMA has evaluated the chemistry aspects of *Aureobasidium pullulans* strain DSM 14940 and strain DSM 14941 (identification, manufacturing process, quality control procedures, batch analysis results and analytical methods) and found them to be acceptable.

Based on a review of the data provided by the applicant, the APVMA is satisfied that the chemistry and manufacturing details of *Aureobasidium pullulans* strain DSM 14940 and strain DSM 14941 are acceptable.

2.2 Formulated product

The product Botector Fungicide will be manufactured overseas and imported into Australia in 400 g - 5 kg high density polyethylene (HDPE) containers.

Botector Fungicide is a biological plant protection product proposed for use as a treatment for grey mould (*Botrytis cinerea*) in grape production. Botector Fungicide contains yeast-like fungi, *Aureobasidium pullulans* strains DSM 14940 and DSM 14941 as the active constituent.

The APVMA has reviewed the chemistry and manufacturing aspects of Botector Fungicide and found them to be acceptable.

BOTECTOR FUNGICIDE

DISTINGUISHING NAME:	Botector Fungicide
FORMULATION TYPE:	Wettable Powder (WP)
ACTIVE CONSTITUENT CONCENTRATION:	<i>Aureobasidium pullulans</i> (strains DSM 14940 and DSM 14941) (5 x 10 ⁹ CFU /g)

PHYSICAL AND CHEMICAL PROPERTIES OF THE FORMULATED PRODUCT

PHYSICAL FORM:	Granule
COLOUR:	Off white to light pink
ODOUR:	Similar to bread
PH (10 G/L) AT 20°C:	6.6
SOLUBILITY/MISCIBILITY WITH WATER:	Dispersible
PACK SIZES AND MATERIALS:	400 g, 1.2 kg, 2 kg, 2.5 kg and 5 kg high density polyethylene (HDPE) containers
PRODUCT STABILITY	Stable under refrigerated storage (≤ 8 °C) for up to 24 months in the commercial packaging material. Stability is reduced at higher temperatures.

2.3 Recommendations

Based on a review of the chemistry and manufacturing details provided by the applicant, the registration of Botector Fungicide is supported from a chemistry perspective.

3 TOXICOLOGICAL ASSESSMENT

3.1 Evaluation of toxicology

The product Botector Fungicide contains two new active constituents, *Aureobasidium pullulans* - strains DSM 14940 and DSM 14941, which are fungi that act as biological control agents. The following summary focuses on the toxicity of the two fungal strains with additional information on the toxicity of Botector Fungicide.

A range of toxicity studies have been conducted in laboratory animals mostly with *A. pullulans* - strain DSM 14941, which are also relevant for the highly similar strain DSM 14940. In interpreting the data, it should be noted that toxicity tests generally use doses that are high compared with likely human exposures. The use of high doses increases the likelihood that potentially significant toxic effects will be identified.

Findings of adverse effects in any one species do not necessarily indicate such effects might be generated in humans. From a conservative risk assessment perspective, however, adverse findings in animal species are assumed to represent potential effects in humans, unless convincing evidence of species specificity is available.

Where possible, considerations of the species specific mechanisms of adverse reactions weigh heavily in the extrapolation of animal data to likely human hazard. Equally, consideration of the risks to human health must take into account the likely human exposure levels compared with those, usually many times higher, which produce effects in animal studies. Toxicity tests should also indicate dose levels at which the specific toxic effects are unlikely to occur.

Microbiological properties

A. pullulans is a saprophytic fungus (feeding on dead and decaying organic matter) ubiquitous in the environment, readily isolated from a wide range of food, soil, decaying vegetation, wood, air, shower curtains and other damp surfaces. For example, on apple leaves the background level of the organism is approximately 10^4 to 10^5 Colony Forming Units (CFU – i.e., viable organisms) per gram dry weight.

A. pullulans is commercially used for the production of pullulan, a linear homopolysaccharide of glucose (α -(1→6) maltotriose) and has, together with its derivatives, a range of uses in foods, pharmaceuticals, manufacturing, and electronics, such as underivatized films which readily dissolve in water, used as edible food coatings. *A. pullulans* - strains DSM 14940 and DSM 14941 are nearly identical genetically requiring advanced molecular biology techniques for a definitive differentiation from each.

Infectivity and pathogenicity

Strains similar to *A. pullulans* strains DSM 14940 and DSM 14941 are ubiquitous and therefore human exposure to these organisms is unavoidable. *A. pullulans* strains DSM 14940 and DSM 14941 were not infectious, toxic or pathogenic when administered to rats by the oral (4×10^8 CFU), subcutaneous (10^7 CFU), or intratracheal routes (0.8×10^8 CFU) and viable organisms did not persist at the site of administration or migrate to other tissues. When isolated from human clinical specimens *A. pullulans* is generally considered to be a laboratory contaminant, but under specific circumstances where the patient is debilitated or immune-

suppressed some strains of this organism have infrequently been identified as pathogens. Pathogenic strains, where investigated, are able to grow at, or close to, body temperatures whereas strains isolated from the environment are generally unable to grow or survive at temperatures above 30 - 35°C, as has been shown to be the case for the two strains in Botector Fungicide. No skin or pulmonary sensitisation or allergenic response of, or clinical findings in, any of the production or agricultural workers handling the fungus or Botector Fungicide have been observed.

Toxicity of *Aureobasidium pullulans* strains DSM 14940 and DSM 14941

The acute oral and dermal toxicities of *A. pullulans* strain DSM 14941 in rats are low (oral LD₅₀ > 2000 mg/kg bw; dermal LD₅₀ > 2000 mg/kg bw), as is its acute inhalational toxicity (LC₅₀ of ~6.9 x 10⁸ blastospores /m³). Studies in rabbits show *A. pullulans* strains DSM 14941 is not irritating to the skin and eyes. It is a moderate skin sensitiser in Guinea pigs but is not genotoxic and production cultures of *A. pullulans* strains DSM 14940 and DSM 14941 do not contain antimicrobials or toxic metabolites.

Toxicity of Botector Fungicide

Studies with a formulation that is very similar to Botector Fungicide show it is likely to have low acute oral and dermal toxicity in rats (LD₅₀ > 2000 mg/kg bw, > 6 x 10⁹ CFU /kg) and low inhalational toxicity (LC₅₀ > 1.5 x 10⁹ CFU /m³), is not a skin or eye irritant in rabbits but a moderate skin sensitiser in Guinea pigs. The formulation was not genotoxic, infectious or pathogenic (other than eliciting a normal immune response).

3.2 Public Health Standards

Poisons scheduling of *A. pullulans* strains DSM 14940 and DSM 14941

On 29 June 2017, the Scheduling Delegate published a [final decision](#) to create a new Appendix B entry for *A. pullulans* strains DSM 14940 and DSM 14941 in the Poisons Standard. Substances listed in Appendix B have been considered to be exempt from scheduling requirements. The decision will become effective as of 1 October 2017. The strains were placed in Appendix B because they are not considered acutely toxic, although they can induce skin and respiratory sensitisation in laboratory animal tests. However, there are no known reports of occupational sensitisation despite industrial and farm use internationally, and the risk of sensitisation to *A. pullulans* can be mitigated through personal protective equipment controlled through APVMA labelling. Further, the strains were not considered mutagenic, pathogenic or infective and do not produce toxins.

Acceptable Daily Intake (ADI) and Acute Reference Dose (ARfD)

Aureobasidium pullulans strains DSM 14940 and DSM 14941 are common environmental organisms normally present on fruit and vegetables. The organisms are not infective or pathogenic and were not toxic at limit doses in acute toxicity tests, consequently the establishment of an Acceptable Daily Intake (ADI), or of an Acute Reference Dose (ARfD), is not required.

4 RESIDUES ASSESSMENT

4.1 Metabolism

No metabolism studies are available for *Aureobasidium pullulans* DSM 14940 and DSM 14941 in target plants or animals. However, these are naturally occurring organisms which were not infectious, toxic or pathogenic when administered to rats. No kinetics and metabolism data are required for this microbial product.

4.2 Residues in food and animal feeds

Botector Fungicide is intended for use as a fungicide for the prevention of *Botrytis cinerea* infection of grapes. *Aureobasidium pullulans* is ubiquitous and the APVMA toxicology assessment for the product concluded that given the absence of toxicity, infectivity or pathogenicity demonstrated in the submitted studies the establishment of either an ADI or ARfD is not required. In the USA, *Aureobasidium pullulans* strains DSM 14940 and DSM 14941 are exempt from requirement of a tolerance in or on all food commodities when used in accordance with label directions and good agricultural practices. In the EU no MRL is required for use of *Aureobasidium pullulans* strains DSM 14940 and DSM 14941 on grapes (table and wine grapes). A Table 5 entry is appropriate to cover the proposed use of *Aureobasidium pullulans* strains DSM 14940 and DSM 14941 on grapes. [Note: Table 5 lists uses of substances where MRLs are not necessary. MRLs are not necessary in situations where residues do not or should not occur in foods or animal feeds; or where the residues are identical to or indistinguishable from natural food components; or otherwise are of no toxicological significance].

4.3 Residues in animal commodities

Grape pomace from wine or juice production from treated crops may be fed to livestock. Treated vineyards may be grazed by cattle or sheep. A grazing withholding period or restriction has not been proposed and is not considered necessary from a residues perspective given the organisms are naturally occurring and are not infectious, toxic or pathogenic.

4.4 Dietary risk assessment

A Table 5 entry to the MRL Standard has been recommended to cover the proposed use. The APVMA toxicology assessment concluded that health based guidance values were not necessary. It is not necessary to undertake a dietary risk assessment.

4.5 Recommendations

The following amendments to the APVMA MRL Standard are required for the current application:

Table 5:

SUBSTANCE	USE
ADD: <i>Aureobasidium pullulans</i> strains DSM 14940 and DSM 14941	When used on grapes

5 ASSESSMENT OF OVERSEAS TRADE ASPECTS OF RESIDUES IN FOOD

Aureobasidium pullulans is ubiquitous in the environment. Detectable pesticide residues are not expected to be found in grapes as a result of the proposed use. Given that the proposed use involves a naturally occurring organism the risk to trade with respect to residues is low.

6 OCCUPATIONAL HEALTH AND SAFETY ASSESSMENT

6.1 Use pattern

Botector Fungicide is a preventative treatment to inhibit growth of *Botrytis cinerea* applied as a foliar spray up to 4 times during the summer growing season. On larger vineyards where treatment of the vineyard may require a number of days of spraying, exposure across the summer growing season may be moderately frequent across the critical growth period. The product (wetable powder) is diluted at the rate of 100 g to 100 L of water and applied to grapes by airblast sprayer at a maximum rate of 1 kg/ha. Botector Fungicide will be available in pack sizes of 400 g, 1.2 kg, 2 kg, 2.5 kg, and 5 kg.

6.2 Occupational exposure

Users may be potentially exposed to Botector Fungicide during mixing/loading, spray application and clean-up operations. The principal route of exposure is likely to be dermal with some potential for inhalation of dust and spray mist. Inhalation of dust during mixing is likely to be somewhat reduced by the granular nature of the product. Eye contact may be possible through transfer from the hands or contact with dust.

Likely post-application activities may include irrigation, scouting, weed control, pruning and harvesting. Given the nature of the post-application activities typically performed (for example, scouting treated areas), dermal contact with treated surfaces is possible, as well as inhalation of dislodged material that has dried on the treated crop. While the degree of exposure will be related to the time of re-entry and the duration of the activities, the potential risk due to exposure resulting from post-application work is not a concern, regardless of the type and duration of the activity. Primarily, *A. pullulans* occurs naturally on a range of fruit and vegetables, in the environment and in the home. The naturally occurring density of the organism on apple leaves for example is $10^4 - 10^5$ CFU /g dry weight. Human exposure to the organism is therefore ubiquitous and unavoidable, and for workers, exposure to *A. pullulans* in a treated area will be broadly similar to that in untreated areas. However, a small number of workers may be sensitive to the increased numbers of *A. pullulans* and show signs of dermal and pulmonary sensitisation/inflammation reactions.

6.3 Public exposure

This product is intended for professional use only.

Exposure of the public at some distance from the point of application of *A. pullulans* in Botector Fungicide is likely to be minimal and the levels of *A. pullulans* is predicted to be similar to background environmental levels. Given this low potential for exposure, and that the strains of *A. pullulans* in Botector Fungicide are not infective or pathogenic, no risk to the public is identifiable.

6.4 Recommendations for safe use

Overall, dermal and pulmonary sensitisation/inflammation are the principal hazards likely to be associated with use of Botector Fungicide for workers. However, the potential for occupational exposure will be minimized and the subsequent risk considered acceptable, when workers follow the First Aid Instructions

and Safety Directions on the product label. In particular, the requirement for Personal Protective Equipment (PPE) will reduce exposure to potentially high levels of *A. pullulans* to acceptable levels.

First aid instructions

If poisoning occurs contact a doctor or Poisons Information Centre. Phone Australia 131126.

Safety directions

Harmful if Inhaled. Do not inhale dust. Repeated exposure may cause allergic disorders. Sensitive workers should wear protective clothing. When opening the container and preparing the spray wear cotton overalls buttoned to the neck and wrist, a washable hat, disposable gloves and disposable dust face mask covering mouth and nose. When using the prepared spray wear cotton overalls buttoned to the neck and wrist and a washable hat. Wash hands after use. After each day's use wash contaminated clothing.

6.5 Conclusions

The approval of the new biological active constituents *Aureobasidium pullulans* - strains DSM 14940 and DSM 14941 for agricultural use, and the registration of Botector Fungicide (containing 5×10^9 CFU /g) is supported for professional use.

7 ENVIRONMENTAL ASSESSMENT

7.1 Introduction

Botector Fungicide protects grapevines from the causal organism botrytis bunch rot (or grey mould) *Botrytis cinerea*. The active constituents of Botector Fungicide are two strains (DSM 14940 and DSM 14941) of *Aureobasidium pullulans* at 5×10^9 CFU /g. *A. pullulans* is a Eu-ascomycete with asexual, yeast-like reproducing cells (blastospores) that is ubiquitous in the environment and naturally occurs on plant surfaces. *A. pullulans* is a saprophytic, epiphytic and, in the case of *Botrytis cinerea*, antagonistic microorganism. It competes with the pathogen for living space and nutrients due to its rapid proliferation rate. The applicant has submitted both strain-specific and not strain-specific information investigating the *A. pullulans* distribution, persistence and survival in the environment. DSM 14940 and DSM 14941 are closely related strains and, for this reason, the environmental assessment is congruent to both strains.

7.2 Environment Fate and Behaviour

The fate and behaviour of the microorganism in the environment will be dependent upon a range of factors, including competition with other microorganisms (parasites/predators of fungi), soil parameters (pH, moisture, clay content) and agricultural practices such as tillage. With four possible applications per season, initial population levels may increase substantially.

The predicted environmental concentrations of both strains in soil and water after a single foliar application were calculated to be 6.7×10^3 CFU /g and 3.3×10^6 CFU /L, respectively, and after four applications (assuming no decline) 2.68×10^4 CFU /g and 1.3×10^7 CFU /L. These figures were calculated assuming that neither of these fungal strains occurs in the Australian environment. *A. pullulans* is not regarded as a soil microorganism, its natural levels in soil being very low (100 CFU/kg). It is likely that any fall of fungi from foliar application to soil will rapidly decline in number to the endogenous level in that medium.

A. pullulans could be potentially spread by the movement of surface water, particularly rainfall, floods, spray drift and run-off. The fungus can survive and reproduce in water environments to a limited extent. However, such an environment is not regarded as being optimal for its survival, a crucial reason being that it is usually poor in organic carbon. One study concluded that the half-life for *A. pullulans* in natural freshwater is less than 2 days.

The dispersal of the fungus in air will be enhanced by its production of large quantities of yeast-like propagules. However, the sticky and slimy nature of the fungus means that spores are not readily airborne. The proposed use of Botector Fungicide is not expected to result in elevated levels of *A. pullulans* spores in the air.

7.3 Environmental Effects

Biological pesticides can have direct and indirect adverse effects on non-target organisms, primarily through the production of toxic secondary metabolites or pathogenesis.

The mode of action for suppression of botrytis bunch rot by these strains of *A. pullulans* is likely by antagonistic action on *Botrytis cinerea*, including competition for nutrients and space with the pathogen when both are present on a plant. Fungal metabolites with potential antagonistic properties include hydrolytic enzymes, secreted proteins and anti-microbial compounds. In addition, the promotion of cell division by *A. pullulans* may impede penetration of a pathogen.

A discussion of potential effects on non-target-organisms is included in the risk assessment below. The risk assessment evaluated the potential adverse effects of *A. pullulans* to non-target organisms.

Terrestrial vertebrates

LD₅₀ acute oral toxicity and intraperitoneal/subcutaneous values are both >2000 mg/kg bw with no signs of infectivity or pathogenicity in the submitted studies. On the basis of USEPA toxicity rankings, this classifies the fungal active constituents as 'practically non-toxic'.

An oral pathogenicity and toxicity study on Japanese quail recorded no mortality or toxic symptoms amongst the birds, and a LD₅₀ > 2000 mg/kg bw, which on the basis of USEPA toxicity rankings makes the active constituent only 'slightly toxic' to these animals. Consultation of publicly available literature failed to find any reference that specifically associated the fungus (despite its abundance in the environment) with toxicity or pathogenicity in birds, amphibians or reptiles.

Considering the lack of toxicity, infectivity or pathogenicity at environmentally relevant rates, the risks to terrestrial vertebrates are considered to be acceptable.

Aquatic organisms

A study with rainbow trout indicated no mortality after exposure to *A. pullulans*, and there was no evidence that the fungus had any pathogenic effects on the fish. The most sensitive endpoints are EC₅₀/LC₅₀ and NOEC values > 100 mg/L. On the basis of USEPA toxicity rankings, the active constituents are 'practically non-toxic' to aquatic organisms. Consultation of publicly available literature failed to find any evidence that recorded toxic or pathogenic effects of *A. pullulans* on any aquatic organism, including phytopathogenic properties against aquatic plants. Considering the lack of toxicity, infectivity or pathogenicity at environmentally relevant rates, the risks to aquatic organisms are considered to be acceptable.

Bees and other non-target arthropods

A 30 day oral toxicity test on bees, which was terminated at day 22 due to mortality in the control group exceeding 20%, recorded no significant differences in mortality between the control and test treatments, no unusual behavioural effects amongst the insects, and a LC₅₀ > 200 µg/bee. On the basis of the USEPA toxicity rankings, the active constituents are 'practically non-toxic' to bees. No reference could be found in publicly available literature recording *A. pullulans* with toxicity or pathogenicity in these organisms.

A single arthropod study, concerning the predatory mite *Typhlodromos pyri*, showed no significant difference between the test item and the control at the highest dose of 3.82 x 10¹³ CFU/ha. No reference could be found in publicly available literature recording *A. pullulans* with toxicity or pathogenicity in these organisms.

Considering the lack of toxicity, infectivity or pathogenicity at environmentally relevant rates, the risks to bees and other non-target arthropods are considered to be acceptable.

Soil organisms

An acute toxicity study demonstrated that *A. pullulans* was not associated with mortality in earthworms at concentrations up to 1000 mg/kg soil. In an avoidance test, there was no evidence that the worms avoided the fungus. On the basis of USEPA toxicity rankings, the fungus is 'very slightly toxic' to earthworms. Earthworms appear to be extremely resistant to pathogens, there being no recorded microbial pathogen of these organisms that has detrimental effects on their growth and survival.

A. pullulans is to be used as an agent to control the spread of *Botrytis cinerea* on grapevines. As such the fungus is expected to have adverse effects upon the target microorganism, and very likely other foliar microorganisms. It is expected that it may have minor effects on the survival and numbers of endogenous soil and foliar microorganisms, but any effect will most likely be transient and is unlikely to lead to a significant adverse indirect effect upon other aspects of an ecosystem, including non-target organisms of other taxa (e.g. plants, higher animals) that may be dependent upon microorganisms for food.

Based on the above considerations, the risks to soil organisms are considered to be acceptable.

Non-target terrestrial plants

A. pullulans is commonly found on vegetables, both before harvest and after they enter commerce, and fruit. Therefore, the fungus normally exists on the surface of common foods without causing any significant adverse effects. Review of publicly available literature failed to find any evidence that the fungus is linked to any significant adverse effects on plants. No endpoints are available for terrestrial plants. Based on these considerations, the risk to non-target terrestrial plants is considered to be acceptable.

7.4 Risk Assessment

Botector Fungicide is to be applied by ground spray at a maximum application rate of 1 kg/ha (5×10^{12} CFU/ha) with up to four applications performed per season.

The environmental risk assessment was based on the submitted data and review of publicly available literature. The risks of the proposed use of Botector Fungicide to terrestrial vertebrates, bees, arthropods, nematodes, earthworms, microorganisms, plants, and aquatic organisms were determined to be acceptable.

7.5 Conclusions

Consequently, the APVMA is satisfied that the proposed use of this product is unlikely to have an unintended effect that is harmful to animals, plants or things or the environment.

8 EFFICACY AND SAFETY ASSESSMENT

8.1 Proposed product use pattern

Botector Fungicide is a biological fungicide intended for use as a preventative treatment in the control of botrytis bunch rot / grey mould (*Botrytis cinerea*) in grapes. It is applied at a rate of 100 g/100L as a foliar spray into the bunch zone or the whole canopy from phenological stage EL25 (80% capfall / flower hoods fallen) to EL 37 (ripening).

The use of Botector Fungicide will be restricted to ground application, applied as a medium spray. Application can either be by dilute or concentrate spraying, in a minimum spray volume of 400 L/ha.

Up to 4 applications can be applied per season, as part of a botrytis bunch rot program. A copy of the proposed label is included in Section 9 - Labelling Requirements.

8.2 Summary of evaluation of efficacy and crop safety

The results of 15 crop safety and 14 efficacy trials have been provided with this application using Botector Fungicide in solo and mixed treatments applied in spray programs on 10 different grape cultivars for the preventative management of Botrytis bunch rot. A total of 13 field trials were conducted in Australia (Vic x5, WA x5, SA x2 and Qld x1) with two trials conducted overseas in Spain and Portugal.

All field trials were undertaken in commercial vineyards in Australia and overseas using spraying equipment representative of standard commercial application equipment. Overseas trials were carried out in Spain and Portugal grown under similar climatic conditions representative of production areas in Australia.

All trials were generally consistent in their methodology and assessments were carried out for the presence of phytotoxicity and droplet residues for crop safety and percent bunch disease incidence and bunch damage severity on a predetermined sample sizes of grape clusters. All efficacy trials were replicated and compared against an industry standard fungicide treatment and an untreated control and statistically tested for significant differences of the treatment means following good agriculture research practice.

Efficacy

Fourteen trials were submitted to support the efficacy of Botector Fungicide for the control of *Botrytis cinerea* in grapes.

Three trial reports did not show significant reductions in efficacy to reduce disease incidence and damage severity when compared to the untreated control. There were also several Australian trial reports demonstrating mixed efficacy results in reducing the level of disease damage severity and sometimes disease incidence.

Several trials (Australia, Spain and Portugal); however, did show significant reductions in disease incidence and damage severity when compared to the untreated control and standard fungicide treatments. For example one trial conducted near Loxton, South Australia demonstrated Botrytis bunch rot developed on

67% of the untreated bunches with a severity of 19%. Botector Fungicide at label rates and after 4 applications reduced both disease incidence (35.3%) and severity (8.6%) when compared to the untreated control.

Further support from a trial conducted on Botrytis bunch rot development in grapevines near San Cristovo in Spain also demonstrated good control after treatment with Botector Fungicide. Untreated controls recorded an incidence of 11% at 22 days after treatment 2 (22 DAT-2) and 18.5% at 14 days after treatment 4 (14 DAT-4), with damage severity in the untreated control reaching 0.74% and 1.4%, 22 DAT-2 and 14 DAT-4, respectively. Treatment with BOTECTOR at label rates reduced disease incidence to 6.5% and disease severity to 0.37% 14 DAT-4.

Whilst some of the trials did indicate variable efficacy after application of Botector Fungicide, label claims advise the user to apply Botector Fungicide as a preventative treatment within the recommended growth stages and that monitoring conditions in the vineyard suitable for botrytis activity can help select the ideal preventative timing for use of Botector Fungicide to minimise performance variability.

Crop Safety

Crop safety observations from fifteen field trials in grapevines were included in this submission for both wine grapes and table grapes. Botector Fungicide at 50 g, 100 g and 200 g/100 L were evaluated with 3 – 5 applications occurring from flowering, bunch closure, berry ripening and pre-harvest. No symptoms of phytotoxicity were visible to grapes after multiple applications in any of the fifteen trials.

Resistance management

The mode of action of *Aureobasidium pullulans* against *Botrytis cinerea* on grapes occurs through active competition for space and nutrients thereby excluding plant pathogens from infection.

Internationally, FRAC has classified Botector Fungicide as “Not Classified”. Due to the mode of action of *Aureobasidium pullulans* (competition in nutrition and space) there is no potential for traditional fungicide resistance development.

8.3 Conclusions

Trial data support that Botector Fungicide will provide acceptable control against *Botrytis cinerea* on grapes when used as directed. Acceptable crop safety is expected when the product is used as directed. The directions for use are appropriate and consistent with fungicide use in commercial agriculture in Australia.

The application for registration of Botector Fungicide is supported on efficacy and crop safety grounds when used in accordance with label directions.

9 LABELLING REQUIREMENTS



KEEP OUT OF REACH OF CHILDREN
READ SAFETY DIRECTIONS BEFORE OPENING OR USING

Botector®

Fungicide

ACTIVE CONSTITUENT:
5 x 10⁹ CFU/g (1.000 g/kg) *Aureobasidium pullulans* (strains DSM 14940 and DSM 14941)

A biological fungicide to protect grapes from infections by botrytis bunch rot / grey mould (*Botrytis cinerea*) as per the Directions for Use Table.

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Contents: 400 g
1.2 kg
2 kg
2.5 kg
5 kg

APVMA Approval No.: 82495/105881

nufarm.com.au

DIRECTIONS FOR USE

RESTRAINTS:

DO NOT apply during the hottest part of the day when temperatures exceed 25°C.

DO NOT apply if it is likely to rain before the spray is dry.

CROP	PEST	RATE	WHP	CRITICAL COMMENTS
Grapes	Botrytis Bunch Rot / Grey Mould (<i>Botrytis cinerea</i>)	100 g / 100 L (minimum rate: 400 g/ha, maximum rate: 1 kg/ha)	Not required when used as directed	Botector should be applied as a preventative treatment within the recommended growth stages. Apply as part of a botrytis bunch rot program, using up to 4 applications, particularly when weather conditions favour disease infection. Application should ensure penetration of canopy and thorough even coverage of flowers/bunches, from growth stages EL 25-37.

NOT TO BE USED FOR ANY PURPOSE, OR IN ANY MANNER, CONTRARY TO THIS LABEL UNLESS AUTHORISED UNDER APPROPRIATE LEGISLATION.

WITHHOLDING PERIOD: NOT REQUIRED WHEN USED AS DIRECTED.

GENERAL INSTRUCTIONS

Botector should be applied preventatively within the recommended growth stages.

The product competes for space and nutrients with the pathogen.

Botector colonises entry points on the flowers or developing bunches that are present at the time of application, competing with the pathogen for space and nutrients.

Botector is not mobile on plant surfaces and as such will not colonise fresh entry points created after the application has occurred.

Botector will not be effective in controlling latent or active infection that has occurred prior to application, but can help reduce secondary spread through protection of uninfected bunches.

Botrytis can be active at different stages in the growing season within the vineyard and this must be taken into account when planning preventative programs. Monitoring conditions in the vineyard that are suitable for botrytis activity can help to select ideal preventative timings for Botector use to minimise performance variability.

Colonisation of Botector at entry points can be affected by various factors including poor spray coverage, high temperatures, heavy rainfall events with 24 hours of application or the presence of chloride levels within spray water.

Always consider crop stage, environmental conditions and application guidelines when using Botector to maximise performance.

MIXING

Ensure the spray tank is thoroughly cleaned out prior to mixing, as residues of incompatible products in the tank can affect the viability of Botector.

Partly fill the spray tank with water and add the required amount of product while agitating. If required, add compatible products and agitate thoroughly. Continue agitation as filling of the tank is completed. Ensure the temperature of the tank mixture is below 25°C.

Agitate mixture before and during application. Use the spray mixture within 8 hours of preparation.

APPLICATION

Botector must be applied when the temperature is below 25°C, preferably under slow drying conditions.

Depending on weather conditions, *Botrytis* infection starts during the flowering period or later, and continues throughout the vegetation period.

Therefore, to ensure consistent protection against *Botrytis* infection, applications as a foliar spray into the bunch zone or the whole canopy at the following stages are recommended:

EL	Phenological Stage
25	80% of flower hoods fallen
31	Beginning of bunch closure
35	Start of berry softening
37	During ripening

Botector is not mobile within the canopy so coverage is critical. Apply sufficient water to wet all surfaces up to the point of run-off. Apply using MEDIUM spray droplets. Air-blast sprayers are recommended for application to vines with very dense foliage.

Botector can be applied up to the date of harvest

DILUTE SPRAYING

Use a sprayer designed to apply high volumes of water up to the point of run-off and matched to the crop being sprayed. Set up and operate the sprayer to achieve even coverage throughout the crop canopy. Apply sufficient water to cover the crop up to the point of run-off. Avoid excessive run-off. The required water volume may be determined by applying different test volumes, using different settings on the sprayer, from industry guidelines or expert advice. Add the amount of product specified in the Directions for Use table for each 100L of water. The required dilute spray volume will change and the sprayer set up and operation may also need to be changed, as the crop grows.

CONCENTRATE SPRAYING

Use a sprayer designed and set up for concentrate spraying (i.e. a sprayer which applies water volumes less than those required to reach the point of run-off) and matched to the crop being sprayed. Set up and operate the sprayer to achieve even coverage throughout the crop canopy using a minimum water volume of 400 L. Determine an appropriate dilute spray volume (See Dilute Spraying above) for the crop canopy. This is needed to calculate the concentrate mixing rate. Do NOT concentrate more than 2X. The mixing rate for concentrate can then be calculated in the following way:

EXAMPLE ONLY

1. Dilute spray volume as determined above: For example 800 L/ha
2. Your chosen concentrate spray volume: For example 400 L/ha
3. The concentration factor in this example is: 2X (i.e. 800 L ÷ 400 L = 2)
4. If label rate is 100 g/100 L, so the concentrate rate becomes 2 x 100, i.e. 200 g/100 L of concentrate spray.

The chosen spray volume (minimum 400 L), amount of product per 100 L of water, and the sprayer set up and operation may need to be changed as the crop grows. For further information on concentrate spraying, users are advised to consult relevant industry guidelines, undertake appropriate competency training and follow Industry Best Practices.

APPLICATION BY GROUND-RIG

Apply as a MEDIUM spray in a minimum of 400 litres of water per hectare. Air assisted sprayers are recommended for use on vines with dense foliage/canopy to achieve thorough coverage of flowers/bunches.

Avoid application in very windy conditions or when the temperature and humidity cause rapid drying.

COMPATIBILITY

Botector is compatible with a variety of commercially available fungicides, insecticides and adjuvants.

Ensure a 3 day interval is adhered to both pre and post the Botector application when using a non-compatible product.

Contact your Nufarm representative for compatibility details.

PROTECTION OF CROPS, NATIVE AND OTHER NONTARGET PLANTS

DO NOT apply under weather conditions, or from spraying equipment, that may cause spray to drift onto nearby susceptible plants/crops, cropping lands or pastures.

PROTECTION OF WILDLIFE, FISH, CRUSTACEANS AND ENVIRONMENT

DO NOT contaminate streams, rivers or waterways with the chemical or used containers.

STORAGE AND DISPOSAL

Store in the closed, original container in a dry, cool, well-ventilated area out of direct sunlight. Store (refrigerated) at less than 8°C. DO NOT freeze.

Triple-rinse containers before disposal. Add rinsings to spray tank. DO NOT dispose of undiluted chemicals on-site. If recycling, replace cap and return clean containers to recycler or designated collection point. If not recycling, break, crush, or puncture and deliver empty packaging to an approved waste management facility. If an approved waste management facility is not available, bury the empty packaging 500 mm below the surface in a disposal pit specifically marked and set up for this purpose clear of waterways, desirable vegetation and tree roots in compliance with relevant local, state or territory government regulations. DO NOT burn empty containers or product.

SAFETY DIRECTIONS

Harmful if inhaled. Do not inhale dust. Repeated exposure may cause allergic disorders. Sensitive workers should wear protective clothing. When opening the container and preparing the spray wear cotton overalls buttoned to the neck and wrist, a washable hat, disposable gloves and disposable dust face mask covering mouth and nose. When using the prepared spray wear cotton overalls buttoned to the neck and wrist and a washable hat. Wash hands after use. After each day's use wash contaminated clothing.

FIRST AID

If poisoning occurs, contact a doctor or Poisons Information Centre. Phone Australia 131126

SAFETY DATA SHEET

For further information refer to the Safety Data Sheet (SDS), which can be obtained from your supplier or from the Nufarm website – www.nufarm.com.au

In case of emergency: Phone 1800 033 498 Ask for shift supervisor. Toll free 24 hours.

CONDITIONS OF SALE

"Any provisions or rights under the Competition and Consumer Act 2010 or relevant state legislation which cannot be excluded by those statutes or by law are not intended to be excluded by these conditions of sale. Subject to the foregoing, all warranties, conditions, rights and remedies, expressed or implied under common law, statute or otherwise, in relation to the sale, supply, use or application of this product, are excluded.

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Nufarm Australia Limited
ACN 004 377 780
103-105 Pipe Road,
Laverton North Victoria 3026
Tel: (03) 9282 1000
Fax: (03) 9282 1001

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ABBREVIATIONS

ac	active constituent
ADI	Acceptable Daily Intake (for humans)
ai	active ingredient
ARfD	Acute Reference Dose
bw	bodyweight
°C	Degrees Celsius
CFU	Colony Forming Units
d	day
DAT	Days After Treatment
DofE	Department of Environment
DT ₅₀	Time taken for 50% of the concentration to dissipate
EC ₅₀	concentration at which 50% of the test population are immobilised
EI	Export Interval
ESI	Export Slaughter Interval
EUP	End Use Product
Fo	original parent generation
FRAC	Fungicide Resistance Action Committee
g	gram
GAP	Good Agricultural Practice
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GVP	Good Veterinary Practice
h	hour
ha	hectare
HDPE	High Density Polyethylene
HPLC	High Pressure Liquid Chromatography or High Performance Liquid Chromatography

ip	intraperitoneal
IPM	Integrated Pest Management
in vitro	outside the living body and in an artificial environment
in vivo	inside the living body of a plant or animal
kg	kilogram
K _{oc}	Organic carbon partitioning coefficient
L	Litre
LC ₅₀	concentration that kills 50% of the test population of organisms
LD ₅₀	dosage of chemical that kills 50% of the test population of organisms
mg	milligram
mL	millilitre
MoA	Mode of Action
MRL	Maximum Residue Limit
MSDS	Material Safety Data Sheet
ng	nanogram
NOEC/NOEL	No Observable Effect Concentration Level
OC	Organic Carbon
OM	Organic Matter
po	oral
ppb	parts per billion
PPE	Personal Protective Equipment
ppm	parts per million
s	second
sc	subcutaneous
SDS	Safety Data Sheet
SUSMP	Standard for the Uniform Scheduling of Medicines and Poisons
TGA	Therapeutic Goods Administration

TGAC	Technical grade active constituent
T-Value	A value used to determine the First Aid Instructions for chemical products that contain two or more poisons
µg	microgram
WHP	Withholding Period
WP	Wettable Powder

GLOSSARY

Active constituent	The substance that is primarily responsible for the effect produced by a chemical product
Acute	Having rapid onset and of short duration.
Carcinogenicity	The ability to cause cancer
Chronic	Of long duration
Codex MRL	Internationally published standard maximum residue limit
Desorption	Removal of a material from or through a surface
Efficacy	Production of the desired effect
Formulation	A combination of both active and inactive constituents to form the end use product
Genotoxicity	The ability to damage genetic material
Hydrophobic	repels water
Leaching	Removal of a compound by use of a solvent
Log Pow	Log to base 10 of octanol water partitioning co-efficient, synonym KOW
Metabolism	The chemical processes that maintain living organisms
Photodegradation	Breakdown of chemicals due to the action of light
Photolysis	Breakdown of chemicals due to the action of light
Subcutaneous	Under the skin
Toxicokinetics	The study of the movement of toxins through the body
Toxicology	The study of the nature and effects of poisons
Ubiquitous	Present, appearing or found everywhere

REFERENCES

National Occupational Health and Safety Commission (2004). *NOHSC Approved Criteria for Classifying Hazardous Substances*.

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