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Proposed Registration Decision

PRD2020-01

# Beauveria bassiana strain GHA, Aprehend

*(publié aussi en français)*

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# Overview

## Proposed Registration Decision for *Beauveria bassiana* strain GHA

Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the [Pest Control Products Act](#), is proposing registration for the sale and use of *Beauveria bassiana* Technical and Aprehend, containing the technical grade active ingredient *Beauveria bassiana* strain GHA, to kill and control bed bugs indoors.

*Beauveria bassiana* strain GHA is currently registered to control whitefly, aphids and thrips in greenhouse ornamentals and vegetables. For details, see Proposed Registration Decision PRD2009-03, *Beauveria bassiana* strain GHA, and Registration Decision RD2009-13, *Beauveria bassiana* strain GHA.

An evaluation of available scientific information found that, under the approved conditions of use, the health and environmental risks and the value of the pest control products are acceptable.

This Overview describes the key points of the evaluation, while the Science Evaluation provides detailed technical information on the human health, environmental and value assessments of *Beauveria bassiana* strain GHA and Aprehend.

## What Does Health Canada Consider When Making a Registration Decision?

The key objective of the *Pest Control Products Act* is to prevent unacceptable risks to people and the environment from the use of pest control products. Health or environmental risk is considered acceptable<sup>1</sup> if there is reasonable certainty that no harm to human health, future generations or the environment will result from use or exposure to the product under its proposed conditions of registration. The Act also requires that products have value<sup>2</sup> when used according to the label directions. Conditions of registration may include special precautionary measures on the product label to further reduce risk.

To reach its decisions, the PMRA applies modern, rigorous risk-assessment methods and policies. These methods consider the unique characteristics of sensitive subpopulations in humans (for example, children) as well as organisms in the environment. These methods and policies also consider the nature of the effects observed and the uncertainties when predicting the impact of pesticides. For more information on how the Health Canada regulates pesticides, the assessment process and risk-reduction programs, please visit the [Pesticides](#) section of Canada.ca.

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<sup>1</sup> "Acceptable risks" as defined by subsection 2(2) of the *Pest Control Products Act*.

<sup>2</sup> "Value" as defined by subsection 2(1) of the *Pest Control Products Act*: "... the product's actual or potential contribution to pest management, taking into account its conditions or proposed conditions of registration, and includes the product's (a) efficacy; (b) effect on host organisms in connection with which it is intended to be used; and (c) health, safety and environmental benefits and social and economic impact."

Before making a final registration decision on *Beauveria bassiana* strain GHA and Aprehend, Health Canada's PMRA will consider any comments received from the public in response to this consultation document.<sup>3</sup> Health Canada will then publish a Registration Decision<sup>4</sup> on *Beauveria bassiana* strain GHA and Aprehend, which will include the decision, the reasons for it, a summary of comments received on the proposed registration decision and Health Canada's response to these comments.

For more details on the information presented in this Overview, please refer to the Science Evaluation of this consultation document.

## **What Is *Beauveria bassiana* strain GHA?**

*Beauveria bassiana* strain GHA is the active ingredient in the commercial class ready-to-use microbial product, Aprehend Insecticide, for indoor use to kill and control bed bugs. *Beauveria bassiana* strain GHA is a fungus that kills insects by infection and growth within the insect. It is active by contact.

## **Health Considerations**

### **Can Approved Uses of *Beauveria bassiana* strain GHA Affect Human Health?**

***Beauveria bassiana* strain GHA is unlikely to affect your health when Aprehend is used according to the label directions.**

Potential exposure to *B. bassiana* strain GHA may occur when handling and applying Aprehend. When assessing health risks, several key factors are considered:

- the microorganism's biological properties (for example, infection cycle);
- reports of any adverse incidents;
- its potential to cause disease or toxicity as determined in toxicological studies; and
- the level to which people may be exposed relative to exposures already encountered in nature to other isolates of this microorganism.

The levels used to assess risks are established to protect the most sensitive human population (for example, children and nursing mothers). As such, sex and gender are taken into account in the risk assessment. Only uses that are determined as having no health risks of concern are considered acceptable for registration.

Toxicology studies in laboratory animals describe potential health effects from large doses of exposure to a microorganism and identify any pathogenicity, infectivity and toxicity concerns. When Aprehend was tested on laboratory animals, there was low toxicity following oral, inhalation, and dermal exposures.

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<sup>3</sup> "Consultation statement" as required by subsection 28(2) of the *Pest Control Products Act*.

<sup>4</sup> "Decision statement" as required by subsection 28(5) of the *Pest Control Products Act*.

Aprehend was also slightly irritating to the skin and minimally irritating to the eyes. Aprehend was a dermal sensitizer. The microbial pest control agent, *B. bassiana* strain GHA, was not infectious or pathogenic following oral, pulmonary or intraperitoneal exposure routes.

### **Residues in Water and Food**

#### **Dietary risks from food and water are acceptable.**

Based on the lack of dietary exposure resulting from the proposed use of Aprehend, the health risks are acceptable for all segments of the population, including infants, children, adults and seniors.

### **Risks in Residential and Other Non-Occupational Environments**

#### **Estimated risk for non-occupational exposure is acceptable.**

Aprehend is proposed for use in residential and commercial structures to control and prevent bed bugs. The product label will include measures to reduce bystander and residential exposures, such as not allowing people or pets into treated areas until sprays have dried, the use of low pressure sprayers to reduce aerosols and preventing applications to non-target surfaces such as furniture or upholstery where prolonged contact with humans or pets will occur and food or food processing surfaces. Residential and non-occupational exposure to Aprehend is therefore expected to be low when label directions are observed. Consequently, the risk to residents and the general public is acceptable. Even in the event of exposure, risk to residents and the general population is acceptable since Aprehend is of low toxicity and there were no signs that *B. bassiana* strain GHA caused any disease in studies on laboratory animals.

### **Occupational Risks From Handling Aprehend**

#### **Occupational risks are not of concern when Aprehend is used according to label directions, which include protective measures.**

Workers handling Aprehend can come into direct contact with *B. bassiana* strain GHA on the skin, by inhalation, or in the eyes. To protect workers from exposure to Aprehend, the label states that workers must wear personal protective equipment, including waterproof gloves, long-sleeved shirt, long pants, goggles, a NIOSH-approved particulate filtering facepiece respirator, socks and shoes. If re-entry into treated areas is necessary before the sprays have dried, workers must wear waterproof gloves, long-sleeved shirt, long pants, a NIOSH-approved particulate filtering facepiece respirator, sock and shoes.

## **Environmental Considerations**

### **What Happens When *Beauveria bassiana* strain GHA Is Introduced Into the Environment?**

**Environmental risks are acceptable.**

The microbial pest control agent, *B. bassiana* strain GHA, is currently registered for use on greenhouse ornamentals and greenhouse food crops. The proposed use expansion of Aprehend to prevent and control bed bugs in residential and commercial structures is not expected to result in significant environmental exposure.

Based on a critical review of applicant-submitted data and information from public sources conducted during the initial registration of this microbial pest control agent, no significant effects to birds, wild mammals, fish, non-target insects, earthworms, soil microorganisms, or plants are expected when Aprehend is applied according to directions on the label.

## **Value Considerations**

### **What Is the Value of Aprehend?**

**Aprehend insecticide is a new commercial class product that kills and controls bed bugs indoors.**

Aprehend insecticide is applied as a barrier spray. When bed bugs cross the barrier they become infected and die. Aprehend Insecticide prevents re-infestation for up to three months and is effective against strains of bed bugs resistant to chemical insecticides. *Beauveria bassiana* strain GHA represents a new mode of action for use against bed bugs, which is important for resistance management.

## **Measures to Minimize Risk**

Labels of registered pesticide products include specific instructions for use. Directions include risk-reduction measures to protect human and environmental health. These directions must be followed by law.

### **Key Risk-Reduction Measures**

The key risk-reduction measures being proposed on the label of *Beauveria bassiana* Technical and Aprehend to address the potential risks identified in this assessment are as follows.

### **Human Health**

All microorganisms, including *B. bassiana* strain GHA, contain substances that are potential sensitizers and thus, sensitivity may possibly develop in individuals exposed to potentially large quantities of *B. bassiana* strain GHA. In turn, workers handling or applying Aprehend must wear waterproof gloves, goggles, long-sleeved shirt, long pants, socks with shoes, and a NIOSH-approved particulate filtering facepiece respirator.



People and pets will not be allowed to enter treated areas until sprays have dried. If re-entry into treated areas is required before the sprays have dried, workers must wear waterproof gloves, long-sleeved shirt, long pants, a NIOSH-approved particulate filtering facepiece respirator, socks and shoes.

The label will also instruct users to apply the product using a low pressure sprayer and prevent applications to non-target surfaces such as furniture or upholstery where prolonged contact with humans or pets will occur and to food or food processing surfaces.

### **Environment**

The end-use product label will include an environmental precaution statement that reduces contamination of aquatic systems from the use of Aprehend. The label will also include a statement alerting users that the end-use product contains petroleum distillates that are toxic to aquatic organisms.

### **Next Steps**

Before making a final registration decision on *Beauveria bassiana* strain GHA and Aprehend, Health Canada's PMRA will consider any comments received from the public in response to this consultation document. Health Canada will accept written comments on this proposal up to 45 days from the date of publication of this document.

Please forward all comments to Publications (contact information on the cover page of this document). Health Canada will then publish a Registration Decision, which will include its decision, the reasons for it, a summary of comments received on the proposed decision and Health Canada's response to these comments.

### **Other Information**

When the Health Canada makes its registration decision, it will publish a Registration Decision on *Beauveria bassiana* strain GHA and Aprehend (based on the Science Evaluation of this consultation document). In addition, the test data referenced in this consultation document will be available for public inspection, upon application, in the PMRA's Reading Room (located in Ottawa).

## Science Evaluation

### *Beauveria bassiana* strain GHA and Aprehend

#### 1.0 The Active Ingredient, Its Properties and Uses

##### 1.1 Identity of the Active Ingredient

<b>Active microorganisms</b>	<i>Beauveria bassiana</i> strain GHA
<b>Function</b>	Biological insecticide to control bed bugs
<b>Binomial names</b>	<i>Beauveria bassiana</i> strain GHA
<b>Taxonomic designation<sup>5</sup></b>	
<b>Kingdom</b>	Fungi
<b>Phylum</b>	Ascomycota
<b>Class</b>	Sordariomycetes
<b>Order</b>	Hypocreales
<b>Family</b>	Cordycipitaceae
<b>Genus</b>	<i>Beauveria</i>
<b>Species</b>	<i>bassiana</i>
<b>Strain</b>	GHA
<b>Patent Status information</b>	No Canadian patent status information was provided.
<b>Minimum purity of active</b>	Technical grade active ingredient (TGAI): $1.4 \times 10^{14}$ conidia/kg End-Use Product (EP): $2.2 \times 10^9$ viable spores/mL
<b>Identity of relevant impurities of toxicological, environmental and/or significance.</b>	The technical grade active ingredient and end-use product do not contain any impurities or micro contaminants known to be Toxic Substances Management Policy (TSMP) Track 1 substances. The product must meet microbiological contaminants release standards. Beauvericin, a secondary metabolite of <i>B. bassiana</i> strain GHA, has been identified in the technical product. Each production lot is monitored for the presence of this metabolite.

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<sup>5</sup> National Center for Biotechnology Information - Taxonomy Browser  
(<https://www.ncbi.nlm.nih.gov/Taxonomy/Browser/wwwtax.cgi?id=101201>)

## 1.2 Physical and Chemical Properties of the Active Ingredient and End-Use Product

### Technical Product—*Beauveria bassiana* Technical

Property	Result
Colour	Off-white (near Pantone #12-0808)
Odour	Slightly musty
Physical State	Fine powder
Guarantee	$1.4 \times 10^{14}$ conidia/kg
Density	$0.183 \pm 0.12$ g/cm <sup>3</sup>
Storage Stability	Dry place at -20°C
Flammability	N/A
Explosibility	Non-explosive
pH	5.8

### End-Use Product—Aprehend

Property	Result
Physical state	Liquid
Corrosion characteristics	No observation of corrosion or impact to packaging integrity was observed during a one-year storage stability study at room temperature.
Viscosity	6.076 mm <sup>2</sup> /s (cSt)
Density	0.8027 g/cm <sup>3</sup>
Flammability	Flash point = 91°C

## 1.3 Directions for Use

Aprehend contains the entomopathogenic fungus *Beauveria bassiana* strain GHA at a guarantee of  $2.2 \times 10^9$  spores/mL to kill and control bed bugs indoors (for example, offices, apartments, houses, bed frames, chairs, baseboards, shelves, couches and modes of transportation) at a rate of 15 mL/15 m (5 cm wide barrier) with a residual effect of up to 3 months.

## 1.4 Mode of Action

*Beauveria bassiana* strain GHA belongs to Insecticide Resistance Action Committee Mode of Action Group UNF (Fungal agents of unknown or uncertain mode of action). It is an entomopathogenic fungus, which causes disease in insects. When spores of the fungus come into contact with the cuticle of a host, they germinate and grow hyphae into the body of the host eventually killing the host. It is active by contact.

## **2.0 Methods of Analysis**

### **2.1 Methods for Identification of the Microorganisms**

Refer to PRD2009-03, *Beauveria bassiana* strain GHA.

### **2.2 Methods for Establishment of Purity of Seed Stock**

Refer to PRD2009-03, *Beauveria bassiana* strain GHA.

### **2.3 Methods to Define the Content of the Microorganism in the Manufactured Material Used for the Production of Formulated Products**

The guarantees of *Beauveria bassiana* Technical and Aprehend are expressed in units of viable spores/kg and viable spores/mL, respectively. The method for determining the guarantee was fully described and representative batch data were submitted in support of Aprehend.

### **2.4 Methods to Determine and Quantify Residues (Viable or Non-viable) of the Active Microorganism and Relevant Metabolites**

Refer to PRD2009-03, *Beauveria bassiana* strain GHA.

### **2.5 Methods for Determination of Relevant Impurities in the Manufactured Material**

For details on the technical grade active ingredient, refer to PRD2009-03, *Beauveria bassiana* strain GHA.

The absence of human pathogens and below-threshold levels of contaminating microorganisms were shown in the microbial screening of batches of Aprehend.

### **2.6 Methods to Determine Storage Stability, Shelf-life of the Microorganism**

Storage stability data were provided for Aprehend. Results support a storage period of 12 months at 25°C.

## **3.0 Impact on Human and Animal Health**

### **3.1 Toxicity and Infectivity Summary**

#### **3.1.1 Testing**

The PMRA conducted a detailed review of the toxicological studies submitted in support of the new end-use product and the proposed use expansion of *B. bassiana* strain GHA. The studies submitted to fulfil the requirements for the health hazard assessment of the new end-use product, Aprehend, included acute oral, acute inhalation, acute dermal, dermal irritation, eye irritation and dermal sensitization studies.

In the acute oral toxicity study, three fasted, young adult, Sprague Dawley-derived female rats were given a single oral (gavage) dose of undiluted Aprehend ( $3.825 \times 10^9$  conidia/mL) at a limit dose of 5000 mg/kg body weight (bw). The animals were then observed for a period of up to 14 days. There were no mortalities and all animals appeared active and healthy throughout the study period. One female rat lost weight from Day 7 to 14, however, the two remaining animals gained body weight over the 14-day observation period. At necropsy, no gross abnormalities were noted for any of the animals.

In the acute inhalation toxicity study, a group of young adult, Sprague Dawley-derived albino rats (5/sex) were exposed by the inhalation route to undiluted Aprehend ( $3.825 \times 10^9$  conidia/mL) for 4 hours and 4 minutes to nose only at a concentration of 5.11 mg/L. Animals then were observed for 14 days. There were no mortalities noted throughout the study. However, irregular respiration (10/10) and ano-genital staining (1/10) were noted on Days 0–3. Also, all but one animal exhibited weight loss between Days 1 and 3; but gained weight by Day 14. At necropsy, no gross abnormalities were noted for any of the animals at the conclusion of the 14-day observation period.

In the acute dermal toxicity study, a group of young adult Sprague Dawley-derived albino rats (5/sex) were dermally exposed to undiluted Aprehend ( $3.825 \times 10^9$  conidia/mL) at a dose of 5000 mg/kg bw for 24 hours to an area of approximately 10% of the body surface. Following exposure, the animals were observed for a period of 14 days. There were no mortalities and no clinical signs of toxicity apart from the dermal irritation (erythema, desquamation and/or mild eschar) noted in 9/10 animals between Days 1 and 14. Although two females lost weight by Day 7, all animals gained body weight over the 14-day observation period. No gross abnormalities were noted for any of the animals when necropsied at the conclusion of the 14-day observation period.

In the dermal irritation study, young adult New Zealand white rabbit (3 females) were dermally exposed to 0.5 mL of undiluted Aprehend ( $3.825 \times 10^9$  conidia/mL) for 4 hours to an area 6 cm<sup>2</sup>. Animals then were observed for 7 days. Irritation was scored by the method of Draize. Within 30–60 minutes of patch removal, all three treated animals exhibited very slight to well defined erythema and two treated sites exhibited very slight to slight edema. The overall incidence and severity of irritation decreased gradually with time. Desquamation was noted at two dose sites at the 72-hour timepoint. All animals were free of skin irritation by Day 7. The calculated Maximum Irritation Score (MIS) and Maximum Average Score (MAS) values were 2.3 at the 30–60-minute timepoint and 1.2 at the 24-, 48- and 72-hour timepoints, respectively.

In the eye irritation study, an aliquot (0.1 mL) of undiluted Aprehend ( $3.825 \times 10^9$  conidia/mL) was instilled into the conjunctival sac of the right eye of three female New Zealand white rabbits. The upper and lower lids were then gently held together for about one second before releasing to minimize loss of the test substance. Animals then were observed for 72 hours. Irritation was scored by the method of Draize. One hour after test material instillation, minimal conjunctivitis was noted for two treated eyes, which cleared by 24 hours. The reported MIS was 2/110 at the 1-hour timepoint. The calculated MAS was 0/110 at the 24-, 48- and 72-hour timepoints.

In the skin sensitization study with Aprehend ( $3.825 \times 10^9$  conidia/mL) in acetone/olive oil (4:1), young adult CBA/J mice (5 females/group) were tested by local lymph node assay. On Days 1, 2 and 3, aliquots (25  $\mu$ L) of the vehicle (negative control), 25% w/w  $\alpha$ -hexylcinnamaldehyde (positive control) and the test material, Aprehend (25%, 50 and 100%) in acetone/olive oil was applied to the dorsum of both ears of each mouse. On Day 6 of the study, an aliquot (250  $\mu$ L) of sterile phosphate buffered saline containing 20  $\mu$ Ci of 3H-methyl thymidine was injected intravenously via the tail vein of each mouse. Approximately five hours after the injection, all animals were euthanized and the draining auricular lymph nodes were excised and assessed. There were no mortalities or clinical signs noted throughout testing.

Dermal treatments with Aprehend resulted in increasing dermal reactions by Day 3, including slight to well defined erythema, slight edema and desquamation. The calculated stimulation indices for 25%, 50% and 100% Aprehend were 6.52, 5.77 and 5.27, respectively. The stimulation index for the positive control was 4.94.

No new information or data were submitted in support of the technical grade active ingredient, *Beauveria bassiana* Technical. Instead, the registrant of the technical grade active ingredient cited existing data evaluated in support of the initial registration, including acute oral toxicity and infectivity, acute pulmonary toxicity, infectivity, acute intraperitoneal infectivity, acute dermal toxicity, and eye irritation studies. For details on these studies, see PRD2009-03, *Beauveria bassiana* strain GHA.

### **3.1.2 Additional Information**

No additional information or data were submitted in support of the new end-use product and the proposed use expansion of *B. bassiana* strain GHA. During initial registration, a survey of published literature was conducted and this survey revealed some cases of human infection in immunocompromised individuals from *B. bassiana*. The cases included reports of deep tissue infection, pulmonary mycosis, empyema and corneal keratitis. The PMRA concluded that cases of systemic infection were rare given the ubiquitous nature of *B. bassiana* as a common soil microorganism. *Beauveria bassiana* does not generally infect healthy individuals, and available antifungal therapies offer an effective treatment. Cases of corneal keratitis caused by *B. bassiana* occurred following traumatic eye injury or surgery, and the prognosis for recovery is excellent with appropriate therapeutic treatments.

A new search of published scientific literature was conducted in the PUBMED database (<https://www.ncbi.nlm.nih.gov/pubmed>) using the keywords “*Beauveria bassiana* infection” to identify new reports of infections. This search identified a newer case of corneal keratitis following a surgical procedure that was successfully treated with appropriate therapies. The search also identified three cases of contact lens-associated keratitis caused by *B. bassiana*. These cases were also successfully treated with appropriate therapeutic treatments. In another case of corneal keratitis in aphakic bullous keratopathy, the infectious agent was found to be resistant to standard topical treatment. The infection was eventually successfully treated, however, a penetrating keratoplasty was required. The PMRA concludes that cases of systemic infection remain rare given the ubiquitous nature of *B. bassiana*.

### **3.1.3 Incident Reports Related to Human and Animal Health**

As of July 29, 2019, no human or domestic animal incident reports involving *Beauveria bassiana* strain GHA, nor its related strains, have been reported to the PMRA.

### **3.1.4 Hazard Analysis**

The available data package in support of the new end-use product, Aprehend, and the proposed use expansion of *B. bassiana* strain GHA was reviewed from the viewpoint of human health and safety and was determined to be acceptable.

Based on all the available information in support of initial registration, the technical grade active ingredient, *Beauveria bassiana* Technical, was considered to be of low toxicity by the oral and pulmonary routes, and was not pathogenic or infective by the oral, pulmonary and intraperitoneal routes. In irritation studies, the technical grade active ingredient was considered mildly irritating to the eyes. Also, the MPCA was considered to be a potential sensitizer.

Based on the studies provided in support of Aprehend, the end-use product is of low toxicity by the oral, inhalation, and dermal routes. Aprehend is also slightly irritating to the skin, minimally irritating to the eyes and is a dermal sensitizer. Consequently, the hazard statement “POTENTIAL SENSITIZER” is required on the principal display panel of the end-use product label. The statement, “May cause sensitization. Avoid contact with skin and clothing. Avoid inhaling/breathing mist.” is also required on the secondary panel of the label under the “PRECAUTIONS” section. The statement, “Avoid contact with eyes.” is also recommended as an additional precaution against accidental exposure based on the reported corneal infections in published scientific literature.

## **3.2 Occupational, Residential and Bystander Risk Assessment**

### **3.2.1 Occupational Exposure and Risk**

When handled according to the label instructions, the potential for dermal, eye and inhalation exposure for workers exists, with the primary exposure route being dermal. Since unbroken skin is a natural barrier to microbial invasion of the human body, dermal absorption could occur only if the skin were cut, if the microbe was a pathogen equipped with mechanisms for entry through or infection of the skin, or if metabolites were produced that could be dermally absorbed. *Beauveria bassiana* has not been identified as a dermal wound pathogen, there is no indication that it could penetrate intact skin of healthy individuals, and does not contain any known toxic secondary metabolites. Furthermore, toxicity testing with Aprehend showed no toxicity via the oral, inhalation and dermal routes; and it was slightly irritating to the skin, minimally irritating to the eyes, and a dermal sensitizer. Testing with the technical grade active ingredient showed no signs of infectivity or pathogenicity via the oral, pulmonary or intraperitoneal injection routes (see PRD2009-03, *Beauveria bassiana* strain GHA).

Although Aprehend was of low dermal and inhalation toxicity, the PMRA assumes that all microorganisms contain substances that can elicit positive hypersensitivity reactions, regardless

of the outcome of sensitization testing. Also, there were reports of corneal keratitis identified in published scientific literature. Consequently, risk mitigation measures, such as personal protective equipment, including waterproof gloves, goggles, long-sleeved shirt, long pants, a NIOSH-approved particulate filtering facepiece respirator, socks and shoes are required to minimize exposure and protect commercial applicators and mixer/loaders that are likely to be exposed. In addition, unprotected workers and users are not allowed to enter areas where Aprehend has been applied until sprays are dried.

Overall, occupational risks to workers are acceptable when the precautionary statements on the label are followed, which include personal protective equipment (PPE).

### **3.2.2 Residential and Bystander Exposure and Risk**

The use of Aprehend to prevent and control bed bugs inside residential and commercial structures, including modes of transport, may result in bystander and residential exposure. Aprehend is of low toxicity and there were no signs that the MPCA, *B. bassiana* strain GHA, caused any disease in studies on laboratory animals. Also, people and pets will not be allowed into treated areas until sprays have dried. In addition, label instructions that require low pressure sprayers to reduce aerosols and prevent applications to non-target surfaces such as furniture or upholstery with prolonged human contact and food or food processing surfaces will ensure that exposure to humans and companion animals in residential areas is low. Consequently, the health risks to bystanders and individuals in residential areas are considered acceptable.

### **3.3 Dietary Exposure and Risk Assessment**

The proposed use of Aprehend to prevent and control bed bugs inside residential and commercial structures, including modes of transport, excludes application to food or feed crops. Also, dietary exposure from drinking is not expected. Consequently, there is no health risk from dietary exposure for the general population, including infants and children, or animals. Furthermore, *B. bassiana* strain GHA demonstrated no pathogenicity or infectivity in Tier I acute oral, pulmonary (intratracheal) and intraperitoneal injection studies (see PRD2009-03, *Beauveria bassiana* strain GHA); and no acute toxicity was observed for Aprehend.

### **3.4 Cumulative Assessment**

The *Pest Control Products Act* requires that the PMRA consider the cumulative exposure to pesticides with a common mechanism of toxicity. In its assessment of common mechanism of toxicity, the PMRA considers both the taxonomy of MPCAs and the production of any potentially toxic metabolites. For the current evaluation, the PMRA has determined that *B. bassiana* strain GHA shares a common mechanism of toxicity with the MPCAs; *B. bassiana* strain HF23, *B. bassiana* strain ANT-03, and *B. bassiana* strain PPRI 5339. The potential health risks from cumulative exposure of *B. bassiana* strain GHA and these other MPCAs are acceptable when used as labelled given their low toxicity and pathogenicity.



## 4.0 Impact on the Environment

No new environmental data or information were provided in support of the new end-use product, Aprehend, and the proposed use expansion of *B. bassiana* strain GHA. Instead, the registrant of the technical grade active ingredient cited existing data evaluated in support of the initial registration. For additional information on the environmental fate of *B. bassiana* strain GHA and its effects on non-target organisms, see PRD2009-03, *Beauveria bassiana* strain GHA.

The proposed use of Aprehend is limited to indoor residential and commercial structures (including modes of transport). Environmental exposure resulting from these proposed uses is expected to be very low.

### 4.1 Incident Reports related to the Environment

As of 29 July 2019, no environmental incident reports involving *Beauveria bassiana* strain GHA, nor its related strains, have been reported to the PMRA.

## 5.0 Value

The results from laboratory efficacy trials demonstrated control of bed bugs on treated surfaces, including residual control of up to three months. *Beauveria bassiana* strain GHA represents a new mode of action for use against bed bugs. A rate of 15 mL/15 m (5 cm wide barrier), with a residual effect of up to 3 months, was supported for use indoors. Resistance is not expected to develop based on the mode of action of the active ingredient.

## 6.0 Pest Control Product Policy Considerations

### 6.1 Toxic Substances Management Policy Considerations

The Toxic Substances Management Policy (TSMP) is a federal government policy developed to provide direction on the management of substances of concern that are released into the environment. The TSMP calls for the virtual elimination of Track 1 substances, such as, those that meet all four criteria outlined in the policy: persistent (in air, soil, water and/or sediment), bio-accumulative, primarily a result of human activity and toxic as defined by the *Canadian Environmental Protection Act*. The *Pest Control Products Act* requires that the TSMP be given effect in evaluating the risks of a product.

During the review process, *Beauveria bassiana* Technical and Aprehend were assessed in accordance with the PMRA Regulatory Directive DIR99-03<sup>6</sup> and evaluated against the Track 1 criteria. *Beauveria bassiana* Technical and Aprehend do not meet the Track 1 criteria because the active ingredients are biological organisms and hence are not subject to the criteria used to define persistence, bioaccumulation and toxicity properties of chemical control products.

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<sup>6</sup> DIR99-03, The Pest Management Regulatory Agency's Strategy for Implementing the *Toxic Substances Management Policy*

## 6.2 Formulants and Contaminants of Health or Environmental Concern

During the review process, contaminants in the technical as well as formulants and contaminants in the end-use products are compared against the *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern*.<sup>7</sup>

The list is used as described in the PMRA Notice of Intent NOI2005-01<sup>8</sup> and is based on existing policies and regulations including: DIR99-03; and DIR2006-02<sup>9</sup> and taking into consideration the Ozone-depleting Substance Regulations, 1998, of the *Canadian Environmental Protection Act* (substances designated under the Montreal Protocol). The PMRA has reached the following conclusions:

- Technical grade *Beauveria bassiana* Technical and its end-use product, Aprehend, do not contain any formulants or contaminants identified in the *List of Pest Control Product Formulants of Health or Environmental Concern*.

The use of formulants in registered pest control products is assessed on an ongoing basis through the PMRA formulant initiatives and Regulatory Directive DIR2006-02.

## 7.0 Summary

### 7.1 Methods for Analysis of the Microorganism as Manufactured

The product characterization data submitted in support of Aprehend and the product characterization data previously submitted for the initial registration of *Beauveria bassiana* Technical were adequate to assess their potential human health and environmental risks for the proposed use expansion of *B. bassiana* strain GHA. The technical grade active ingredient was previously characterized and the specifications of the new end-use product were supported by the analyses of a sufficient number of batches. All batches of technical grade active ingredient must conform to the limits set out in the OECD issue paper on microbial contaminants for microbial pest control products [ENV/JM/MONO(2011)43]. Storage stability data for the end-use product were sufficient to support a shelf life of one year when stored at 25°C. For additional information on the technical grade active ingredient, refer to PRD2009-03, *Beauveria bassiana* strain GHA.

### 7.2 Human Health and Safety

The previously-submitted acute toxicity/infectivity studies in support of the technical grade active ingredient and newly-submitted end-use product studies in support of Aprehend were determined to be acceptable. Based on all the available information, the end-use product is of low toxicity when administered via oral, inhalation and dermal routes.

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<sup>7</sup> SI/2005-114

<sup>8</sup> NOI2005-01, *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern*

<sup>9</sup> DIR2006-02, *Formulants Policy and Implementation Guidance Document*.

The end-use product is also slightly irritating to the skin, minimally irritating to the eyes and a dermal sensitizer. The MPCA is also considered to be a potential sensitizer and it was not infective via the oral, pulmonary and intraperitoneal routes of exposure.

When handled according to the label instructions, the potential for dermal, inhalation and eye exposure for workers exist, with the primary source of exposure to workers being exposure to the skin. Respiratory and dermal sensitivity could possibly develop upon repeated exposure to the product, since all microorganisms, including *B. bassiana* strain GHA, contain substances that are potential sensitizers. Therefore, anyone handling or applying Aprehend must wear waterproof gloves, goggles, a long-sleeved shirt, long pants, NIOSH-approved particulate filtering facepiece respirator with any N, R, or P filter, socks and shoes. In addition, to minimize postapplication exposure, workers entering areas treated with Aprehend must wear the above personal protective equipment until sprays have dried. Precautionary statements (for example, wearing of personal protective equipment) on the end-use product label aimed at mitigating exposure are considered adequate to protect individuals from risk due to occupational exposure.

Aprehend is proposed for use in commercial and residential areas. People and pets will not be allowed into treated areas until sprays are dried. Also, the label instructions requiring low pressure sprayers, and preventing applications to non-target surfaces such as furniture or upholstery with prolonged human contact and food or food processing surfaces will ensure minimal exposure to humans and companion animals. Furthermore, the proposed use pattern excludes application to food or feed crops, and no dietary exposure from drinking water is expected. The health risk to the general population, including infants and children, as a result of residential and bystander exposures and/or chronic dietary exposure is acceptable due to the low exposure and the low toxicity/pathogenicity profile for Aprehend. The specification of a maximum residue limit (MRL) under the *Pest Control Products Act* is not required for *B. bassiana* strain GHA.

### **7.3 Environmental Risk**

The previously-submitted scientific studies and rationales in support of *Beauveria bassiana* Technical were determined to be acceptable. The use of Aprehend inside commercial and residential areas is not expected to pose a risk to non-target organisms when the directions for use on the label are followed. While Aprehend contains petroleum distillates that are toxic to aquatic organisms, environmental exposure to this end-use product is expected to be negligible given that the proposed new use of Aprehend is limited to indoor commercial and residential areas.

As a general precaution, the Aprehend label will direct users to avoid contaminating surface water by disposal of equipment wash waters. The label will also include a statement alerting users that the end-use product contains petroleum distillates that are toxic to aquatic organisms.

## 7.4 Value

The submitted value information supports the use of Aprehend to kill and control bed bugs indoors when applied at a rate of 15 mL/15 m (5 cm wide barrier). Aprehend would provide a new mode of action for this use, which is important to resistance management.

## 8.0 Proposed Regulatory Decision

Health Canada's PMRA, under the authority of the *Pest Control Products Act*, is proposing registration for the sale and use of *Beauveria bassiana* Technical and Aprehend, containing the technical grade active ingredient *Beauveria bassiana* strain GHA, to kill and control bed bugs indoors.

An evaluation of available scientific information found that, under the approved conditions of use, the health and environmental risks and the value of the pest control products are acceptable.

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## List of Abbreviations

°C	degree(s) Celsius
ADI	acceptable daily intake
ARfD	acute reference dose
bw	body weight
cm	centimetre(s)
cSt	centistoke(s)
EP	end-use product
g	gram(s)
kg	kilogram(s)
L	litre(s)
LC <sub>50</sub>	median lethal concentration
LD <sub>50</sub>	median lethal dose
LOC	level of concern
MAS	maximum average score
MCC	maximum challenge concentration
MIS	maximum irritation score
m	metre(s)
mL	millilitre(s)
mm	millimetre(s)
MPCA	microbial pest control agent
OECD	Organization for Economic Co-operation and Development
PMRA	Pest Management Regulatory Agency
RQ	risk quotient
s	second(s)
TSMP	Toxic Substances Management Policy
μCi	microcurie(s)
μL	microliter(s)

## Appendix I Tables and Figures

**Table 1 Toxicity Profile of Aprehend Containing *Beauveria bassiana* strain GHA**

(Effects are known or assumed to occur in both sexes unless otherwise noted; in such cases, sex-specific effects are separated by semi-colons)

Study Type/Animal/PMRA #	Study Results
Acute oral toxicity Rat, Sprague-Dawley (♀) PMRA # 2927373	LD <sub>50</sub> ♀ > 5000 mg/kg bw  Low toxicity
Acute dermal toxicity Rat, Sprague-Dawley PMRA # 2927370	LD <sub>50</sub> ♂♀ > 5000 mg/kg bw  Low toxicity
Acute inhalation toxicity Rat, Sprague-Dawley PMRA # 2927374	LC <sub>50</sub> ♂♀ > 5.11 mg/L  Low toxicity
Eye irritation Rabbit, New Zealand White (♀) PMRA # 2927372	MAS <sup>a</sup> = 0/110 (at 24, 48 and 72 hours) MIS <sup>b</sup> = 2.3/110 (at 1 hour)  Minimally irritating
Skin Irritation Rabbit, New Zealand White (♀) PMRA # 2927371	MAS <sup>a</sup> = 1.2/8 (at 24, 48 and 72 hours) MIS <sup>b</sup> = 2.67/8 (at 30–60 minutes)  Slightly irritating
Dermal sensitization (Local lymph node assay) Mouse, CBA/J PMRA # 2927375	Positive  Dermal sensitizer

<sup>a</sup> MAS = Maximum Average Score for 24, 48, and 72 hours

<sup>b</sup> MIS = Maximum Irritation Score (mean)

## References

### A. List of Studies/Information Submitted by Registrant

PMRA           References  
Document  
Number

#### 1.0 Product Characterization and Analysis

2927363       2018, Product Profile and Proposed Use Patterns, DACO: M1.2  
2927364       2018, International Regulatory Status, DACO: M1.3  
2927365       2018, Product Characterization, DACO: M2.1, M2.2, M2.3, M2.4, M2.5, M2.6,  
M2.7.1, M2.7.2 CBI  
2927366       2018, Cross Reference to Technical Active PCP 29319, DACO: M2.10.1,  
M2.10.2, M2.10.3, M2.9.2, M2.9.3 CBI  
2927367       2015, Stability of Aprehend EP during long-term storage in HDPE bottles,  
DACO: M2.11 CBI  
2927368       2016, Product Chemistry for Aprehend with Confidential Attachment, DACO:  
M2.12, M2.8, M2.9.1 CBI

#### 2.0 Human And Animal Health

2927369       2018, Cross reference to technical, PCP 29319, DACO: M4.2.2, M4.2.3, M4.3.2,  
M4.3.3, M4.6, M4.8  
2927370       2014, Aprehend: Acute Dermal Toxicity in Rats, DACO: M4.4  
2927371       2014, Aprehend: Primary Skin Irritation in Rabbits, DACO: M4.5.2  
2927372       2014, Aprehend: Primary Eye Irritation in Rabbits, DACO: M4.9  
2927373       2014, Aprehend: Acute Oral Toxicity Up and Down Procedure in Rats, DACO:  
M4.9  
2927374       2014, Aprehend: Acute Inhalation Toxicity in Rats, DACO: M4.9  
2927375       2014, Aprehend: Local Lymph Node Assay (LLNA) in Mice, DACO: M4.9  
2927376       2018, Toxicology Study Summaries, DACO: M4.1, M4.2.1, M4.3.1, M4.5.1

#### 3.0 Environment

None

#### 4.0 Value

2927377       2015, Aprehend: Direct contact effect on bed bugs, DACO: 10.2.3.2(C)  
2927378       2015, Aprehend: Evaluation of residual activity, DACO: 10.2.3.2(C)  
2927379       2014, Aprehend: Efficacy of spray formulation on chemical resistant bed bugs,  
DACO: 10.2.3.2(C)  
2927380       2015, Comparative efficacy of Aprehend and Suspend SC on susceptible and  
pyrethroid resistant bed bugs, DACO: 10.2.3.2(C)

- 2927381 2015, Aprehend: Relative humidity requirements for mycosis of bed bug cadavers, DACO: 10.2.3.2(C)
- 2927382 2015, Aprehend: Efficacy of different barrier widths, DACO: 10.2.3.2(C)
- 2927383 2016, Evaluation for potential repellency of Aprehend to bed bugs, DACO: 10.2.3.2(C)
- 2927384 2018, Summaries of Value, DACO: 10.1,10.2.1,10.2.3,10.2.3.1,10.3.1