

# **GUIDELINES FOR THE REGISTRATION OF BIOLOGICAL AGRICULTURAL PRODUCTS**

**AUSTRALIAN PESTICIDES AND VETERINARY MEDICINES AUTHORITY**

**Canberra**

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## **1 INTRODUCTION**

### **1-1 Role of the APVMA**

The APVMA assesses and registers agricultural and veterinary chemical products. The work of the APVMA protects the health and safety of people, animals and the environment and enhances the domestic and export market potential of Australia's agricultural and animal industries.

### **1-2 Need for separate guidelines for biological agricultural products**

#### **1-2.1 Potential risks**

A number of products of biological origin fall into the *Agricultural and Veterinary Chemicals Code* (Agvet Code) definition of an agricultural chemical product and therefore require regulation by the APVMA. In many cases, biological products have different properties from conventional chemical products and therefore these separate guidelines and data requirements have been prepared to more appropriately address the potential risks posed by biological agricultural products.

Many biological pesticides have a narrow host range. They may target specific pests, exhibit limited nontarget effects and thus pose minimal adverse effects on humans and the environment. In the case of products that are degraded relatively readily in the environment, biological products may pose minimal long-term environmental effects. The APVMA recognises that some biological products, due to their inherently lower risk, may thus be more desirable than some synthetic pesticide chemicals. However, not all biological products are necessarily safer products and it is the responsibility of the APVMA to evaluate fully the risks associated with all products that fall under its jurisdiction.

#### **1-2.2 Existing data requirements**

Specific requirements for agricultural chemical products are set out in the APVMA's *AgManual: The Requirements Manual for Agricultural Chemicals* and the *Ag Requirements Series: Guidelines for Registering Agricultural Chemicals*. Some are not entirely appropriate or relevant to certain classes of biological products. It should be noted, however, that lessening of requirements does not eliminate the obligation to address safety issues and these guidelines should be read in conjunction with both the *Ag Manual* and the *Ag Requirements Series*.

These guidelines have therefore been developed specifically to simplify the registration process for biological agricultural products. The APVMA welcomes comment on the usefulness of this publication and suggestions for further improvement. Comments should be submitted to the Program Manager Pesticides, APVMA, PO Box E240, KINGSTON ACT 2604.

### **1-2.3 Flexibility and case-by-case approach**

The APVMA recognises the need for flexibility in determining the data requirements for biological products. These guidelines allow for full examination of any product that may give cause for concern, and products will be evaluated on a case-by-case basis where this is considered necessary.

Biological products are not always as efficacious as synthetic pesticides and it may be sometimes necessary to trade off efficacy against other factors, for example compatibility with organic farming systems or reduced environmental persistence.

These guidelines are to be considered as guidelines and not as absolute requirements. Where certain data are not considered necessary, relevant scientific arguments for their omission should be put forward.

### **1-3 Products covered by other legislation**

Some agricultural chemical products are also covered by other legislation. Applications for the following groups of products must also satisfy the requirements of the following legislation:

- classical biological control agents — *Quarantine Act 1908 (Cwlth)*, *Environment Protection and Biodiversity Conservation Act 1999 (Cwlth)*;
- genetically modified organisms — *Gene Technology Act 2000 (Cwlth)*; and
- imported biological agents — *Quarantine Act 1908 (Cwlth)* and *Environment Protection and Biodiversity Conservation Act 1999 (Cwlth)*.

The APVMA is required to consult with the Gene Technology Regulator on any application for registration or permit for a product that is, or contains, a genetically modified organism (GMO) or any product derived from a GMO. Further details on the role and function of the Gene Technology Regulator are available at [www.ogtr.gov.au](http://www.ogtr.gov.au)

Imported biological agents require a permit from the Australian Quarantine Inspection Service (AQIS) before they can be brought into Australia. Further information about the importation of biological products is available at <http://www.daff.gov.au/content/output.cfm?ObjectID=E1803CD4-D51B-4639-8E9649EC42F2E8A6>

## **2 WHAT ARE BIOLOGICAL AGRICULTURAL PRODUCTS?**

### **2-1 Definition**

A full definition of an agricultural chemical product is given in the *Agricultural and Veterinary Chemicals Code*.

## Guidelines for the Registration of Biological Agricultural Products

A biological agricultural chemical product is an agricultural chemical product where the active constituent comprises or is derived from a living organism (plant, animal, microorganism, etc), with or without modification. This includes many products that are commonly referred to as ‘botanicals’, ‘organics’ or ‘herbals’ (where the active constituent comprises an extract derived from an organism rather than a whole organism, it may be accompanied by unidentified components).

Applicants should check that their product is regarded by the APVMA as a biological product before adopting the biological products data requirements. Please seek advice from the Pesticides Program of APVMA if you are unsure about how your product will be considered.

There are four major groups of biological products:

- Group 1— biological chemicals (e.g. pheromones, hormones, growth regulators, enzymes and vitamins)
- Group 2 — extracts (e.g. plant extracts, oils)
- Group 3 — microbial agents (e.g. bacteria, fungi, viruses, protozoa)
- Group 4 — other living organisms (e.g. microscopic insects, plants and animals plus some organisms that have been genetically modified)

Each of these groups of biological products is described in detail in Section 3.

### **2-2 Products not regarded as biological agricultural chemical products**

#### **2-2.1 Products characterised as conventional agricultural chemical products**

A product where the active constituent is a biologically derived chemical that has direct toxicity to the target species and can be purified, fully identified and a residue detection method applied is not classed as a biological product. Examples include products based on nicotine, strychnine, rotenone and ivermectin. Data requirements for these products are the same as those for conventional agricultural chemical products.

#### **2-2.2 Specific exemptions**

Certain classes of product are specifically exempted from registration under Schedule 3 of the Agvet Code Regulations. These include soil ameliorants, fertilisers, some classes of pest management lures, domestic disinfectants, hay, silage or legume inoculants based on bacteria or enzymes, cut flower preservatives, predatory insects, predatory mites and macroscopic parasites. More detailed information about exemptions can be obtained from the Pesticides Program of the APVMA.

#### **2-2.3 Plant growth-stimulating products**

Plant growth-stimulating products that are not for pest control or specific growth regulation are covered under State/Territory fertiliser regulations and do not require registration by the APVMA. However, products based on plant hormones do require registration.

## 2.4 Higher plants

Whilst higher plants are not registered as agricultural chemicals products by the APVMA, genes inserted in the genome of plants may require registration. Inserted genes that code for the production of pesticidal substances are considered to be a pesticide and require regulatory approval and registration of the gene in the plant (see Section 3-4). For example, the Ingard gene which expresses the CryIA(c) toxin of *Bacillus thuringiensis* in the cotton plant is registered as a biological agricultural chemical product.

Other genetically manipulated plants do not require registration, but may have implications that lead to consideration by the APVMA. For example, herbicide tolerant plants do not fall under the definition of an agricultural chemical product and therefore do not require a specific application to the APVMA. However, where the use pattern of a chemical product changes in association with a genetically modified crop plant, the APVMA will assess the new use pattern of the chemical. For example, glyphosate-tolerant soybeans could result in glyphosate use in that crop and would therefore require assessment as a major new use for a glyphosate product.

Similarly, the incorporation of genes that modify the physiology of a plant does not necessarily require regulation by the APVMA unless there are implications arising from the technology falling within the scope of APVMA functions.

## 2-3 Genetically modified products

Products from any of the groups listed above can consist of, or be derived from, naturally occurring organisms — those which are produced by traditional breeding techniques or modified by genetic engineering techniques.

Products based on GMOs will have an extra data requirement for information concerning the genetic manipulation. Details will be required about:

- the host organism;
- the donor organism;
- genetic engineering techniques used in the genetic modification;
- identity of the inserted or deleted gene segment (base sequence data or enzyme restriction map of the gene);
- information on the control region of the gene in question;
- description of the new traits or characteristics that are intended to be expressed;
- tests to evaluate genetic stability and exchange; and
- environmental expression and toxicology tests.

### **3 GROUPS OF BIOLOGICAL AGRICULTURAL PRODUCTS**

#### **3-1 Group 1 — biological chemicals**

Biologically derived chemicals with indirect toxicity or modifying effects in target species (i.e. a mode of action other than direct toxicity) comprise one major group of biological products. This group includes pheromones, hormones, growth regulators, enzymes and vitamins. The detailed data requirements for biologically derived agricultural chemicals are listed in Section 4.

##### **3-1.1 Semiochemicals**

Pheromones belong to the class of compounds known as semiochemicals. Semiochemicals are chemicals emitted by plants or animals that modify the behaviour of receptor organisms of like or different kinds of plants or animals. Use of semiochemicals usually result in less exposure to humans and the environment than conventional pesticides because of:

- very low application rates, or
- high volatility, or
- application in bait, trap or encapsulated formulation.

These factors, as well as their potential for low toxicity, will be taken into account in determining data requirements for individual products. The APVMA will decide on a case-by-case basis whether synthetically derived analogues that mimic naturally occurring pheromones could be considered as biological products for the purpose of determining data requirements.

##### **3-1.2 Hormones and growth regulators**

Hormones are biochemical agents that are synthesised in one part of an organism and transported to another part of the same organism where they have controlling, behavioural or regulating effects.

Plant hormones include the natural plant regulators, which are chemicals produced by plants that have inhibitory, stimulatory or other modifying effects on the same or other species of plants. Insect growth regulators are chemicals that have inhibitory, stimulatory or other modifying effects on the insect growth cycle.

##### **3-1.3 Enzymes and vitamins**

Enzymes are natural substances produced by all living cells. All living organisms depend on enzymes to regulate energy-releasing reactions, to synthesise the building blocks of cells and to regulate virtually all other physiological processes.

Enzymes are high molecular weight proteins composed of amino acids. They may also contain nonprotein parts such as carbohydrates, lipids, phosphate groups and metallic ions.

For the purposes of these guidelines, enzymes are defined as naturally occurring or genetically modified protein molecules that are the instruments for expression of gene action and that catalyse chemical reactions. This definition of 'proteins' includes

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peptides and amino acids but does not include toxic proteins such as endotoxins or exotoxins (to which normal agricultural chemical product data requirements apply).

The safety of enzyme products can be evaluated with respect to:

- potential risk to the environment in which the microorganisms and/or their products are released;
- possible health hazard for the staff working with the product; and
- safety of use on target plants.

Since enzymes are readily biodegradable, their environmental release is unlikely to cause any environmental problems. Furthermore, the containment of the production organism itself is controlled by the physical nature of the fermentation system and by the production organisms having been adapted to grow only under defined fermentation conditions.

Some occupational health risks may arise from the handling of enzyme preparations. Enzyme dusts may lead to respiratory allergies in susceptible individuals while certain proteases may cause irritation to the skin, eyes or mucous membranes. These risks can be avoided by protective measures and the use of specific formulations of the enzyme preparations.

To ensure human safety the microbial enzymes must be obtained from nonpathogenic and nontoxicogenic microorganisms grown on raw materials that do not contain components that might be hazardous to human health.

Safety to target plants must also be demonstrated in appropriate trials.

Products based on vitamins also require registration with the APVMA. Data requirements for vitamins are similar to those for synthetic agricultural chemical products, other than recognised human vitamins.

### **3-2 Group 2 — plant and other extracts**

The second major group of biological agricultural products includes unpurified or partially purified extracts derived from plants or other organisms including oils or other extracts. Plant oils that cannot be totally characterised are classed as biological products. Similarly, plant extracts where the level of purification is incomplete and the chemical composition of the active constituent cannot be fully characterised are classed as biological products. For example, natural 'pyrethrum' may consist of a chemical mixture of a number of related pyrethrins. 'Neem oil' may consist of a mixture of several different chemical entities and 'neem extract' similarly may consist of a mixture of chemical components, some characterised and others not characterised. Some of these compounds may be of biological (and/or toxicological) significance while other compounds may be considered as inert.

For detailed data requirements for plant and other extracts see Section 4.

### 3-2.1 Plant extracts

For this group of products, it may be difficult to characterise every constituent present, but applicants must provide as much information as possible.

In cases where biologically derived chemicals are poorly characterised and the purity and amounts of contaminants are unavailable, Part 2 (Chemistry and Manufacture) of the application must include all known details of the composition of the active ingredient and the formulated product.

Applicants should apply to the APVMA for active constituent approval exemption when the active constituent cannot be isolated and purified. In this situation, quality control of the product is very important. Applicants must demonstrate adequate batch analysis and process control and confirm that they can produce a consistent product that meets product specifications.

Additionally, the composition of the material used in the toxicology and other studies must be clearly identified and must conform closely to the declared composition of the extract to be used in the manufactured product.

Product labels must carry an active constituent statement that specifies the identity and concentration of the active constituent present. Applicants should propose a suitable active constituent statement for inclusion on their product label.

An expiry date is a requirement for all biological products. Data in support of a suitable shelf-life are particularly important with plant extracts.

### 3-2.2 Essential oils

Essential oils are the plant oils responsible for the odours of many aromatic plants. They consist of mostly terpenoids, but also include aliphatic and aromatic esters, phenolics and substituted benzene hydrocarbons. They may include:

- flavour and fragrance materials that are not steam distilled; and
- fragrances, flavour concentrates and perfumes.

Some synthetic substances that are not found in nature have at times been regarded as essential oils. The APVMA would consider these to be conventional chemical products to which the data requirements for an agricultural chemical product would apply.

Active approval exemption has been granted for a number of essential oils. Essential oils have traditionally been used in insect repellent and medicinal products over a long period of time — in some cases despite a lack of toxicology data. In some cases, a well-documented history of the safe use of such a substance can support its approval in an agricultural chemical product.

However, it should be recognised that some essential oils are intrinsically quite toxic, so that mere characterisation as an essential oil should not be presumed to equate with low toxicity. Some essential oils are scheduled poisons.

### **3-2.3 Food products**

Extracts that are prepared from products generally regarded as human foods (e.g. garlic, chilli, vegetables etc) may be exempted from full data requirements when they are used in concentrations similar to those of the food product. Thus, a garlic or cabbage extract at physiological concentration may be considered to be of little health concern.

Purified and concentrated extracts from a food product, on the other hand, may pose risks that would necessitate a fuller data package; for example, a concentrated garlic or chilli extract may require detailed toxicological and occupational health and safety evaluation.

### **3-2.4 Other extracts derived from organisms**

Other extracts derived from organisms will be considered on a case-by-case basis depending on the nature of the extract.

## **3-3 Group 3 — microbial agents**

The products referred to as microbial agents include (but are not limited to) naturally occurring or genetically modified microorganisms, including bacteria, fungi, viruses, protozoa, microscopic nematodes or other microbial organisms. Macroscopic organisms can also be biological agricultural products, but macroscopic predators and parasites, including entomopathogenic nematodes, are excluded (see Section 2-2.2).

Microbial pest control agents may survive and reproduce in the environment, and may infect other living organisms. Thus, the basic testing requirements are designed specifically to detect the potential to exhibit any of these characteristics. Requirements for further testing emphasise exposure or environmental expression in addition to expanded testing of infectivity and pathogenicity.

For detailed data requirements for microbial agents, see Section 5.

### **3-3.1 Microbial pesticides (viable)**

The data requirements for microbial pesticides are designed to give basic hazard and exposure information for the microorganism. If the microbial pesticide under consideration is taxonomically similar to a clinically or agriculturally significant microorganism, its properties and effects should be examined in greater detail than suggested by the tests generally required.

The overall level of risk posed by a microbial pesticide used in agriculture is related to the possible hazards associated with the organism and the degree of exposure to humans and the environment. Potential hazards of microbial agents include toxin production, pathogenicity/infectivity, host range expansion and competition with existing microbial flora. Exposure factors include survival of the organism, replication in the environment, dissemination, persistence and horizontal gene transfer. Unreasonable risks include adverse effects on humans, commercially/economically important species, ecologically important plant and animal species and endangered plant and animal species. The origin of the microbial

organism is also important, with organisms from overseas countries requiring closer scrutiny than Australian indigenous organisms.

### **3-3.2 Microbial pesticides (nonviable)**

Microbial pesticides that have been rendered nonviable may be subject to special testing requirements depending on the specific characteristics of the microorganism.

### **3-3.3 Genetically modified microbial pesticides**

Genetically modified microbial pesticides will be subject to additional data or information requirements on a case-by-case basis depending on the particular microorganism, its parent microorganism, the proposed pesticide use pattern, and the manner and extent to which the organism has been genetically modified. Additional requirements may include information on the genetic engineering techniques used, the identity of the inserted or deleted gene segment (base sequence data or enzyme restriction map of the gene), and the control region of the gene in question.

Descriptions of the 'new' traits or characteristics that are intended to be expressed, tests to evaluate genetic stability and exchange, and/or selected environmental expression and toxicology tests may also be required. Each new isolate of a microbial pesticide will generally be considered to be a new active constituent. If a subject isolate is sufficiently similar to a previously registered isolate, a case can be made for reduced data.

Major concerns for microbial pesticide control agents are pathogenicity of the microbial pest control agent and of microbial contaminants; infectivity/unusual persistence of the microbial pest control agent and of microbial contaminants; or toxicity of the microbial pest control agent, microbial contaminants and preparation by-products.

Applicants should propose an active constituent statement for microbial products that specifies the identity and proportion of the organism present in the product.

## **3-4 Group 4 — other living organisms**

Predatory insects, predatory mites and macroscopic parasites are specifically excluded from the definition of an 'agricultural chemical product'. Other living organisms that may require evaluation by APVMA are mainly plants that have been modified by genetic manipulation to incorporate a gene that encodes for pesticidal activity or pest resistance.

Plants used as biological control agents are not considered to require registration. Thus, chrysanthemum plants that produce pyrethrins are not regulated by the APVMA. However, substances that are extracted from plants and used as pesticides (plant extracts) do require registration (see Group 2, Section 3-1).

This distinction is reasonable in light of the potential for increased and unique exposures due to large-scale application of extracted chemicals to plants that do not naturally produce them. The use of extracted chemicals as insecticides can involve exposure to the pesticide over large areas, whereas the exposure associated with chemicals contained in living plants would not be expected to reach such proportions.

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Plants that have a naturally evolved resistance (for example, herbicide resistance or insect resistance) do not require registration with the APVMA, nor do plants that have been conventionally bred to have, say, increased resistance to insect attack.

Genetic manipulation technology has opened the possibility of novel pesticides being produced within a plant by introduced genes not normally found in that plant. These pesticidal substances require regulation by the APVMA due to their potential impact on human health and safety or the environment.

There are a number of substances produced in plants that enable plants to resist pest attack and disease. These substances include both those pesticidal substances that would be considered normally a component of a plant and those that would be considered new to a plant. Examples of plant pesticides that would be considered normally a component of a plant are phytoalexins (plant-produced substances that act against phytopathogenic microorganisms). An example of a plant pesticide that would not be considered normally a component of a plant is the insecticidal delta-endotoxin that is produced in the bacterium *Bacillus thuringiensis* (Bt).

Where a resistance gene that produces a pesticidal substance (toxin or enzyme) is transferred from one species of plant to another one where that gene does not occur naturally, application must be made to the APVMA.

Genetically modified plants with genes for herbicide tolerance will not themselves require registration, but applicants should check on APVMA requirements relating to herbicide use before release of seeds or plants.

A proposed new use pattern for a chemical to be used on a genetically modified plant will require a label change application for the relevant chemical product as discussed above.

For detailed data requirements for other living organisms, see Section 5.

## **4 DATA REQUIREMENTS FOR GROUPS 1 AND 2**

Applications for registration of agricultural products containing biologically derived chemicals should follow the overall outline set out in the APVMA's *Ag Requirements Series: Guidelines for Registering Agricultural Chemicals*. Modifications and/or additions should be made to every part of the application, as indicated below.

### **PART 1 Application overview**

The overview should be prepared according to the format for Part 1 in the *Ag Requirements Series*.

Extra sections should be added as follows:

- biological properties of active constituent
  - natural occurrence and distribution in Australia of the source organism

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- natural occurrence of the chemical or, if synthesised, relationship to the form occurring in an organism
- mode of action
- specificity of action
- likely biological effects arising from use
- biological properties of the formulated product (if different from above)

### **PART 2 Chemistry, manufacture and biological properties**

Biologically derived chemicals are often poorly characterised and the purity and amounts of contaminants are unavailable. It is imperative that the Chemistry Part of the application include all known details of the composition of the active ingredient and the formulated product.

These notes should be read in conjunction with the detailed discussion in the *Ag Requirements Series, Part 2 (Chemistry and Manufacture)*.

In some cases, active constituent approval is not required for products where the active constituent is a biological chemical. Applicants must apply for active constituent exemption in such cases. The following classes of biological chemicals are likely to be considered for exemption:

- food quality ingredients of agricultural products (e.g. fruit drying oils);
- commonly recognised food sources or components, such as plant extracts (e.g. garlic extract, orange oil);
- pesticides from natural sources such as pyrethrum extract or neem oil; and
- pheromones, natural insect or plant growth regulators, which are used at very low concentration and dissipate rapidly.

Where a active constituent application is required, it must include the information given below. If any particular section of the following list of data requirements is not considered relevant to a particular active constituent, the applicant should provide a reason for its exclusion.

#### **Active constituent**

##### *Active constituent identification*

- common name
- chemical name (IUPAC)
- CAS registry number
- common or distinguishing name
- chemical formula, molecular structure and molecular weight where appropriate
- chemical and physical properties
- stability

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### *Active constituent approval or standard*

- active constituent approval number, application form, or application for exemption
- compendial or manufacturer's standard (where appropriate)

### *Manufacturer details*

- name of manufacturer
- address (street and postal)

### *Manufacturing plant details*

- name
- address (street and postal)
- letter of confirmation of source where applicant is not the manufacturer

### *Manufacturing process*

- quality control during manufacture
- declaration of composition of active constituent/manufacturing concentrate (in the case of crude extracts please provide as much information as possible)
- process chemistry/production method (purification processes and resultant yields should be fully described)
- if the product of a GMO, describe the genetic manipulation method, together with a detailed description of the donor organism or the gene isolated from it, the vector and the recipient organism

### *Analytical methods*

- active constituent
- impurities
- toxic impurities (including discussion of unintentional ingredients/microcontaminants)

*Batch analyses* (normal number required is five)

### *Packaging*

*Provision of analytical reference materials to Curator of Standards* (Australian Government Analytical Laboratory)

### *Biological properties*

- natural occurrence and distribution in Australia of source organism
- natural occurrence of the chemical or, if synthesised, relationship to the form occurring in an organism. For GMOs, include information about the source gene(s)
- mode of action
- specificity of action
- likely biological effects arising from use
- effect of storage and other conditions on biological activity.

## **Product**

The following information must be included in Part 2 (Chemistry and Manufacture) of the application for registration of the product. If any particular section of the following list of data requirements is not considered relevant to a particular product, the applicant should provide a reason for its exclusion.

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### *Product identification*

- distinguishing name
- formulation type
- active constituent(s) and concentration

### *Formulation composition*

### *Chemical and physical properties*

### *Formulator*

- name
- address (street and postal)

### *Formulation plant*

- name
- address (street and postal)

### *Formulation process*

### *Quality control in product formulation*

### *Analytical methods*

- active constituent in the formulation (if different from above)

### *Storage stability*

- storage conditions
- proposed shelf-life
- toxic products/degradation products

### *Allowable variations*

### *Packaging*

### *Biological properties (where different from active constituent)*

- describe any biological properties of the formulated product that differ from the active constituent (e.g. binding to substrates)

## **PART 3 Toxicology**

The composition of the material used in the toxicology studies must be clearly identified and must conform closely to the declared composition. Further details of study types may be obtained from Part 3 (Toxicology) of the *Ag Requirements Series*.

The toxicology data requirements in this guideline are based on current approaches to hazard assessment. As new areas of concern arise, further testing may be expected. If a particular study is not submitted, a statement indicating why the study is not considered necessary should be provided.

### **Primary toxicology data**

#### *Active constituent*

- acute oral toxicity
- acute dermal toxicity
- acute inhalation toxicity
- genotoxicity

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- short-term studies (route depending on likely source/s of human exposure)

### *Product*

- acute oral toxicity
- acute dermal toxicity
- acute inhalation toxicity
- eye irritation
- skin irritation
- skin sensitisation

### **Supplementary toxicological studies (active constituent)**

When other potential hazards are indicated by the results from the above studies or through other means (such as information on class effects), appropriate supplementary data may be required as follows:

- subchronic toxicity studies by an appropriate route;
- developmental studies;
- reproduction studies;
- chronic toxicity/oncogenicity studies;
- human exposure data;
- additional genotoxicity studies; and
- other studies to determine special forms of toxicity.

## **PART 4 Metabolism and kinetics**

Biochemical pesticides that may require metabolic/kinetic studies are those where:

- the active constituents have been identified; and/or
- the concentration of the product, when applied following the recommended use pattern, results in levels that can be differentiated from background levels.

An additional section should be added to include tests to show that minor contaminating biological substances/organisms are not biomagnified in the field.

Details of study types in each section may be obtained from the *Ag Requirements Series*, Part 4 (Metabolism and Kinetics).

## **PART 5 Residues**

Residue studies are usually not required for biologically derived chemicals. The applicant should request an exemption from the need for a maximum residue limit (MRL) and provide reasoned scientific argument for the exemption together with information on potential hazard and exposure where applicable. Scientific argument against the need for residue data and requests for exemption from the need for an MRL will be considered on a case-by-case basis. 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 are otherwise of no toxicological significance, are generally considered not to require MRLs.

## Guidelines for the Registration of Biological Agricultural Products

If the product is exempt overseas from the need for MRLs or tolerances, this information should be provided in the application. The information should include detail of the reasons for the exemption.

If residue studies data are required in Part 5 of the application, the data should be set out as described in the *Ag Requirements Series*, Part 5A (Residues) and the following additional data should be include:

- analytical method
  - analytical methodologies are to be provided for the active constituent(s)
  - complete descriptions of detection, identification and quantification techniques
  - details of specificity, sensitivity and reliability of the detection techniques
- fate of residues during storage, processing and cooking
  - information should be provided on the effect on food quality

### **Applicant's proposed entry in the *MRL Standard***

It is particularly important with biological products to address the question of residue definition for inclusion in the APVMA's *MRL Standard: Maximum Residue Limits in Food and Animal Feedstuffs*.

## **PART 6 Occupational health and safety**

The occupational health and safety (OHS) data requirements are based on the toxicity of the biological chemical and the potential for occupational exposure. Biological activity of the biological product in humans is an important consideration for occupational health. Biologically derived chemicals such as semiochemicals and hormones, which have acute as well as chronic health effects, may also require comprehensive OHS data.

Where information is not available or the requirements are not considered relevant, the reasons should be provided by the applicant. Each case will be treated on its merits.

### **Occupational exposure data**

Applicants should address all potential occupational exposure to biological products within Australia, including manufacturing/laboratory procedures, formulation, packaging, transport, handling, use and disposal. Exposure arising from products that have been treated with the biologically derived chemicals should be addressed (e.g. during harvesting or processing).

Information should also be provided on the use pattern, application equipment and methods, application rates, frequency of application and the most common routes of exposure.

For each of the work categories, the approximate number of workers who have the potential for exposure/infection, the nature of the work carried out and the maximum

## Guidelines for the Registration of Biological Agricultural Products

duration of exposure (in hours per day and days per year) should be provided. Measures to prevent worker exposure should be provided. Precautions for handling the product should include details of precautions to be taken at each stage of product handling (e.g. in the preparation of bacterial culture).

### **Health surveillance and health conditions contraindicating work with biologicals**

Medical examination of workers before work placement in addition to routine health surveillance for workers should be considered where relevant. Details of the examination and clinical tests performed before placement and for routine health surveillance should be provided. The examination should include serological testing to set a baseline for immunological parameters. A routine preplacement examination should be able to detect immunocompromised workers, and workers with a history of hypersensitivity disorders. Where relevant, methods for biological and atmospheric monitoring should be included. Details on sampling techniques and sampling equipment and a brief description of the analytical method(s) used should be provided.

Workers with health conditions, such as asthma, or a history of allergy, may not be suited to work with some biological products. Details should be provided on health conditions that are absolute contraindications, and conditions that require extra precautions during handling.

### **Follow-up information**

Follow-up information on workers is required and should include any symptoms, signs and results of tests, where required.

For further details, refer to the *Ag Requirements Series*, Part 6 (Occupational Health and Safety) Section 6.5.

### **Information provision**

*Label and material safety data sheets (MSDS)*

Refer to the *Ag Requirements Series*, Part 6 (Occupational Health and Safety).

*Education and training*

Biological products may provide a special class of hazard and workers need to be trained in handling them in addition to the education and training on other chemical and physical hazards at the workplace. For further details, refer to the *Ag Requirements Series*, Part 6 (Occupational Health and Safety).

## **PART 7 Environmental studies**

Data requirements are the same as those for conventional agricultural and veterinary products, and the applicant should consult Part 7 (Environment) of the *Ag Requirements Series* (and should include a table of contents and summary as Section 7.1 and Section 7.2, respectively).

## Guidelines for the Registration of Biological Agricultural Products

As noted in this document, the environmental requirements for registration of biological agricultural products are flexible in order to allow for the differing degrees and nature of environmental exposure that arise from their use.

Applicants are advised to submit as complete an account as possible on what is already known of effects on the environment arising from the use or natural occurrence of the chemical. This should take the form of a review of existing knowledge describing likely effects on the environment and living organisms, as well as the fate in soil and water and the potential for accumulation.

The relevant studies should then be appended in the format detailed in *Ag Requirements Series*, Part 7 (Environment). The Department of the Environment and Heritage is prepared to be flexible in its data requirements (e.g. less data might be required for a chemical that was very specific to, say, Lepidoptera), but data or scientific argument is required to support the claim.

The following two hypothetical examples may help applicants understand the Department of the Environment and Heritage's approach.

### *Example for Group 1 — an insect growth regulator*

A new product, NoMolt, contains a new insect growth regulator — a protein of plant origin but able to be isolated in pure form. NoMolt was proposed for use for the control of aphids and white fly on tomatoes and cucurbits in glasshouses. An assessment indicated that it was readily degraded in soil and water. The toxicity reflected its mode of action and was most pronounced for certain sucking insects.

Table 7-3 in Part 7 of the *Ag Requirements Series* indicates that glasshouse crops are considered to reflect localised use with confinement by the glasshouse, but would generally require the base set in Tables 7-1 and 7-2 of Part 7 of the *Ag Requirements Series* as well as 7.1.6(b)–(d), 7.1.7(a) and 7.1.8(b) of Table 7.1. That is, besides the base set covering the assessment of the extent of and potential for environmental exposure, physicochemical degradation and biodegradation, data would be required for biodegradation, field dissipation (soils only) and accumulation (soils only).

In the above example for NoMolt, the applicant would be able to argue that, as the active constituent, a protein, readily degraded to constituent amino acids, it was not likely to be mobile and leach to groundwater, or accumulate in soils. Therefore, data for 7.1.6(b)–(d), 7.1.7(a) and 7.1.8(b) of Table 7-1 would not be necessary.

For a persistent chemical, however, field dissipation and accumulation studies would be essential, particularly if exposure is high. In this case, the scale of field use (i.e. glasshouse versus broad acre) could not be used to justify omission of such data (see the *Ag Requirements Series*, Part 7 (Environment) for more details).

### *Example for Group 2 — a plant extract*

The product Riddoff contains the active constituent disbug2 which, although characterised, is extracted from a plant. The applicant, A Riddell & Co., is able to control the manufacturing process so that the purity of disbug2 is at a level of 25±1% in the manufacturing concentrate, but with other compounds that appear to be inactive.

## Guidelines for the Registration of Biological Agricultural Products

Another company, GEE Puzzled Pty Ltd, has submitted another product, Destruct-a-pest, which also contains disbug2, again extracted from plants but using another process. However, in this case the process is not well characterised and results in a final product in which disbug2 is at a level of 0.5–5%.

Both applicants were able to submit scientific literature that indicated the fate and effects of disbug2. A Riddell & Co were able to submit data that demonstrated that their purified active would break down through abiotic (principally photolysis) and biotic processes. The effects studies indicated that disbug2 was highly to very highly toxic to several aquatic invertebrates, while only moderately to highly toxic to fish. They showed only slight toxicity to other taxa considered (which included mammals, birds and plants).

GEE Puzzled Pty Ltd, however, presented data in which it was obvious that their process resulted in an active constituent in which the active disbug2 was quite variable (from 0.5% to 5%). There also appeared to be a range of compounds in their active, some with similar structures to disbug2. The company provided only limited fate and effects data, with the source of the active unclear (i.e. it was unclear whether the studies were performed with the same active to be used in the product). From the range of results varying from slightly to highly toxic, it was impossible to predict the true toxicity of the poorly characterised active.

Of the above information given by the two companies, the data for the active provided by GEE Puzzled Pty Ltd would be unsatisfactory whilst that from A Riddell & Co would be satisfactory. The Department of the Environment and Heritage would need to have data indicating the variability of the active constituent to be used in Destruct-a-pest with respect to fate and effects because of the active constituent's variable nature (with respect to the level of disbug2, as well as the other compounds). That is, while not all components might be identified or characterised, the Department of the Environment and Heritage would have to be convinced that the mixture could be obtained reproducibly and that the transport, fate and effects of the active could be adequately predicted from the supplied data.

### **PART 8      Efficacy and safety**

Efficacy and safety data requirements for biologically derived chemicals are similar to those for conventional agricultural products and applicants are referred to the *Ag Requirements Series*, Part 8 (Efficacy and Safety).

In some cases, a lower level of efficacy may be accepted for a product that has advantages in reduced hazard to humans or the environment. The applicant must provide evidence in support of any claimed reduced hazard to enable a risk analysis to be carried out by the APVMA.

## 5 DATA REQUIREMENTS FOR GROUPS 3 AND 4

Because microbial pest control agents represent a diverse range of microorganisms, not all studies or data requirements may be appropriate for a specific microorganism. Applicants should consider the unique characteristics of their proposed microorganism when addressing specific data requirements and protocols, and are encouraged to consult the Pesticides Program of APVMA before testing begins. In addition, exemptions from certain data requirements will be considered when accompanied by a sound scientific rationale.

In most cases, active constituent approval is not required for products where the active constituent is an organism. Applicants must apply for active constituent exemption in such cases. It should be noted, however, that active constituent approval is required for products based on the bacterium *Bacillus thuringiensis* (Bt) and an application is required for each new source of Bt.

Before consulting the APVMA, applicants should familiarise themselves with these guidelines and be prepared to provide information and propose studies deemed appropriate to address the APVMA requirements.

An agricultural chemical product containing organisms is defined in the Agvet Code Regulations as a 'date-controlled product'. A date-controlled product must have an expiry date on the label and the product cannot be supplied after the expiry date.

### PART 1 Application overview

The overview should be prepared as indicated in the *Ag Requirements Series*, Part 1 (Application Overview).

Replace the section on Chemistry and Manufacture of this overview with the following:

#### **Biology and manufacture**

##### *Active agent identification*

- approved common name and scientific name
- distinguishing name
- full taxonomic description (including strain and serotype)
- manufacturer's code number(s) and/or synonym(s) (if applicable)
- physical properties, including state and stage of the organism (e.g. spores, mycelium, larvae etc).

##### *Active agent approval or standard*

- active agent approval or standard
- active constituent approval number, application form or application for exemption (most microbial agents will be exempted from requirement for active constituent approval).

## Guidelines for the Registration of Biological Agricultural Products

### *Manufacture*

- name of manufacturer
- address (street and postal) of manufacturer
- name and address of manufacturing plant (if different)

### *Biological properties of the active agent*

- provide a summary of the biology of the organism

### *Product characterisation (if different from active agent)*

- distinguishing name
- formulation type
- active agent level and concentration
- formulation composition
- physical properties
- storage stability
- proposed shelf-life
- toxic products

### *Product formulation*

- name and address of formulator
- name and address of formulation plant
- summary of formulation process

### *Biological properties of product (if different from active agent)*

- provide a summary of the biological properties of the product

## **PART 2 Chemistry, manufacture and biological properties**

These guidelines should be read in conjunction with the *Ag Requirements Series*, Part 2 (Chemistry and Manufacture).

The following information must be included in Part 2 (Chemistry and Manufacture) of the application for registration of the product. If any particular section is not relevant to a particular product, the applicant should provide a reason for its exclusion.

### **Active agent**

#### *Active agent identification*

- scientific and common name
- manufacturer's code number(s) and/or synonym(s) (if applicable)
- identification of active organism (e.g. genus, species, strain, type) — include relevant taxonomic methods (e.g. phenotypic, biochemical, genetic, molecular) and relationship to organisms which are important in agriculture is also relevant
- physical description of the organism including physical state and stage of the organism (e.g. spores, mycelium, larvae)

## Guidelines for the Registration of Biological Agricultural Products

### *Active agent approval or standard*

- active constituent approval number, application form, or application for exemption
- compendial or manufacturer's standard (where appropriate)

### *Producer details*

- name
- address (street and postal)

### *Production plant details*

- name
- address (street and postal)

### *Production process*

- source of active organism and all other biological media
- brief description of growth media, fermentation processes etc
- if the organism is a GMO, description of the method that was used, together with a detailed description of the donor organism or the gene isolated from it, the vector and the recipient organism

### *Quality control in production*

#### *Analytical methods*

- active agent
- contaminants (chemical and/or microbiological)
- methods to verify genetic integrity (if a GMO).

#### *Batch analyses*

- potency assay, no organisms/mL etc (where relevant)

#### *Tests showing absence of contaminating organisms, chemicals or toxins*

#### *Packaging*

#### *Evidence of provision of analytical reference materials to Curator of Standards*

#### *Biological properties*

- geographic origin and natural occurrence of the organism in Australia
- history of the organism and its uses
- life cycle and growth characteristics of the organism
- specificity, host range and indication of whether the agent is closely related to a crop pathogen or to a pathogen of a vertebrate species or a nontarget invertebrate species
- pathogenicity or antagonism to target host species
- pathogenicity/infectivity in humans
- site of infection, mode of action and of entry into host
- infective dose level and indication of numbers of organisms to be used or released

## Guidelines for the Registration of Biological Agricultural Products

- transmissibility and persistence of the organism under different climatic conditions
- genetic stability of the agent under environmental conditions of proposed use (GMOs only)
- likely biological effects arising from use

### **Product** (if different from active agent)

#### *Product identification*

- distinguishing name of product
- formulation type
- name and concentration of active agents

#### *Formulation composition*

- composition/specifications of other constituents

#### *Physical properties (where applicable)*

#### *Effect of storage and other conditions on biological activity*

#### *Formulator*

- name
- address (street and postal)

#### *Formulation plant*

- name
- address (street and postal)

#### *Formulation process*

- quality control in product formulation
- analytical method for active agent in the formulation (if different from above)

#### *Storage stability*

- storage conditions
- proposed shelf-life

#### *Allowable variations*

#### *Biological properties (where different from active constituent)*

Please describe any properties of the formulated product that differ from the active organism, including those that are designed to reduce hazards (e.g. encapsulation of spores, binding to substrates).

## **PART 3 Toxicology**

The data requirements in this guideline are based on current approaches to hazard assessment. As new areas of concern arise, further testing may be expected. Further details of study types may be obtained from the *Ag Requirements Series, Part 3 (Toxicology)*.

If a particular study is not submitted, a statement indicating why the study is not considered necessary should be provided.

### **Microbial agents**

For microbial agents, it should be established that the active agent is not a known pathogen of humans or other mammals and that the preparation does not contain such pathogens or mutants as contaminants, as determined by acceptable test(s).

### **Primary toxicology data**

#### *Active agent*

- acute infectivity: intravenous (for bacteria and viruses); intraperitoneal (for fungi and protozoa); and intracerebral (for neurotropic agents) — these are single studies with a single high dose of active ingredient injected
- acute oral toxicity/infectivity
- acute dermal toxicity/infectivity
- acute inhalation toxicity/infectivity
- eye irritation/infectivity
- skin irritation
- hypersensitivity/allergy incident reports
- genotoxicity on appropriate extracts
- short-term studies (route depending on likely source(s) of human exposure)

#### *Product*

- acute oral toxicity/infectivity
- acute dermal toxicity/infectivity
- acute inhalation toxicity/infectivity
- eye irritation
- skin irritation
- skin sensitisation

### **Supplementary toxicological data**

Further studies may be required, depending on indications of toxin production, significant signs of infectivity or unusual persistence of the microbial pesticide. For example:

- subchronic toxicity studies
- developmental studies
- reproduction studies
- immunotoxicity studies (for viruses)
- additional genotoxicity studies

## **Other living organisms**

### **Nematodes and other microscopic parasites**

#### *Active agent*

- acute oral toxicity/infectivity
- acute dermal toxicity/infectivity
- acute inhalation toxicity/infectivity
- eye irritation/infectivity
- hypersensitivity/allergy incident reports

### **Insects/macrosopic parasites, plants and animals**

Submission of toxicological data has generally been waived for this category. It should be noted, however, that toxicological data on any specific product may be required if deemed necessary for proper evaluation, particularly when significant risk concerns are identified.

## **PART 4 Metabolism and kinetics**

In general, kinetic and metabolism data are not relevant for microbial agents and other living organisms unless the organism produces a mammalian toxin.

If the organism produces, or is suspected of producing, a toxin or toxic metabolite, then these should be identified, and also isolated if possible. Toxins or toxic metabolites may be subject to the complete requirements outlined in the *Ag Requirements Series*, Part 4 (Metabolism and Kinetics).

## **PART 5 Residues**

Residue data are generally not necessary for microbial agents. The applicant should request an exemption from the need for an MRL and provide reasoned scientific argument for the exemption. The APVMA will consider such an exemption on a case-by-case basis. 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 are otherwise of no toxicological significance are generally considered as not requiring MRLs.

If the product is exempt from the need for MRLs or tolerances overseas, this information should be provided in the application. The information should include detail of the reasons for the exemption.

## **PART 6 Occupational health and safety**

The OHS data requirements are based on the toxicity of the biological product and the potential for occupational exposure. Biological activity of the biological product in humans is an important consideration for occupational health.

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Where information is not available or the requirements are not relevant, the reasons for this should be given. Each case will be treated on its merits.

### **Occupational exposure data**

Applicants should address all potential occupational exposure to biological products within Australia, including manufacturing/laboratory procedures, formulation, packaging, transport, handling, use and disposal. Exposure arising from products that have been treated with the microbial product (e.g. during harvesting or processing of crops) should be addressed.

Information should also be provided on the use pattern, application equipment and methods, application rates, frequency of application and the most common routes of exposure. Consideration should also be given to other chemical and physical hazards related to handling the biological product at the workplace (e.g. liquid nitrogen). While the microbial agent itself may not be toxic when grown in pure culture, the culture components and fermentation byproducts may be. In this case, exposure information should include the potential for exposure to the end-use product and, where relevant, for each of the components.

For each of the work categories, the approximate number of workers who have potential for exposure/infection, the nature of the work carried out and the maximum duration of exposure (in hours per day and days per year) should be provided. Measures to prevent worker exposure should be provided. Precautions for handling should include details of precautions to be taken at each stage of product handling (e.g. in the preparation of bacterial culture). Some microbial agents may release toxins on the crop after application. In these situations exposure estimates for workers handling the crops should be provided and re-entry restrictions should be considered.

Some microbial agents may be toxic by routes other than oral, dermal or inhalational (e.g. intraperitoneal or intracerebral injection). The exposure data requirements in these cases will be based on the risk of contracting infection in the normal occupational use rather than the hazard of the microbial by nonoccupational exposure routes.

For some microbial agents (or other living organisms), the capacity to multiply within a suitable host/nontarget organism (e.g. humans) is of concern. If it is established that the microbe has a potential for multiplication, potential long-term effects of the microbial exposure should be considered.

### **Health surveillance and health conditions contraindicating work with biologicals**

Medical examination of workers before work placement in addition to routine health surveillance for workers should be considered where relevant. Details of the examination and clinical tests performed before placement and for routine health surveillance should be provided. The examination should include serological testing to set a baseline for immunological parameters. A routine preplacement examination should be able to detect immunocompromised workers, and workers with a history of hypersensitivity disorders. Where relevant, methods for biological and atmospheric monitoring should be included. Details on sampling techniques and sampling

## Guidelines for the Registration of Biological Agricultural Products

equipment and a brief description of the analytical method(s) used should be provided.

Workers with health conditions, such as asthma, or a history of allergy, may not be suited to work with some biological products. Details should be provided on health conditions that are absolute contraindications, and conditions that require extra precautions during handling.

### **Follow-up information**

Follow-up information is required to be provided on workers, including any symptoms, signs and results of tests where required. For further details, refer to the *Ag Requirements Series*, Part 6 (Occupational Health and Safety).

### **Information provision**

#### *Label and MSDS*

Refer to the *Ag Requirements Series*, Part 6 (Occupational Health and Safety).

#### *Education and training*

Biological products are a special class of hazard and workers need to be trained in handling them in addition to the education and training on other chemical and physical hazards at the workplace. For further details, refer to the *Ag Requirements Series*, Part 6 (Occupational Health and Safety).

## **PART 7 Environmental studies**

### **Format**

The following format should be followed when preparing Part 7 of the submission:

- 7.1 Table of contents
- 7.2 Summary
- 7.3 Review of current knowledge
- 7.4 Chemical and biological properties of the active agent (refer to Part 2 of this section)
- 7.5 Fate and behaviour in the environment
- 7.6 Environmental toxicology and pathogenicity/infectivity studies to nontarget organisms
- 7.7 Environmental hazard assessment

### **Review of current knowledge**

For Section 7.3 (see also Part 2 of this section), applicants should submit a review of current knowledge on:

- systematic position of the agent/organism, and the extent to which the systematics of the group to which it belongs is characterised;

## Guidelines for the Registration of Biological Agricultural Products

- natural occurrence, distribution, habitat and ecological role of the agent/organism and its close relatives in Australia;
- target species occurrence, distribution and ecological role in Australia;
- target species predators, parasites and competitors;
- host range;
- infectivity and pathogenicity to nontarget organisms;
- environmental fate, including exposure routes, and ability to survive and persist in the environment; and
- direct and indirect environmental effects of release and use of the agent/organism, including effects on natural ecosystems.

### **Overview of issues to be considered**

Table 5.1 gives an indication of some issues that need to be considered by the applicant and the sections of the environment submission where information on each should be included. Further details are provided in the Explanatory notes sections below.

**Table 5-1: Environmental studies issues to be considered in Part 7 of submission**

<b>Key issues</b>	<b>Examples</b>	<b>Include in Section</b>
Purity, consistency and strain stability	The organism might have closely allied forms that may produce exotoxins (e.g. Bt)	7.4
Population dynamics of the agent/organism	This might include describing the organism's life history and its preferred habitats and conditions etc	7.5
Method of disruption to the target organism	Bt, for example, disrupts gut tissues, causing septicaemia	7.5
Ability to survive in a niche or host after release to the environment	Some organisms may have very specific requirements for survival (e.g. obligative anaerobes c.f. facultative anaerobes)	7.5
Pathogenicity and infectivity to nontarget organisms	Some organisms might be shown to be quite specific from laboratory screening data and literature references	7.6
Potential (directly or indirectly) for disrupting natural ecosystem dynamics	Some conclusion may be made from the above information, or there may be some field data available	7.6 and 7.7
Potential (directly or indirectly) for adversely affecting environmentally significant biota	Some conclusion may be made from the above information, or there may be some field data available	7.6 and 7.7
<b>Other issues</b>		
Environmental impacts of the presence of any contaminating organisms	Some organisms or their products (e.g. exotoxins) may contaminate the end-use product, potentially causing an uncharacterised harm	7.4
Hypersensitivity of nontarget organisms	While the control organism might be very efficacious, some nontarget organisms may be much more sensitive to it	7.6
Potential for the agent/organism to initiate severe local tissue damage through the immunological consequences of exposure	Again, nontarget organisms may be much more sensitive to the control agent	7.6

### **Data requirements and exemptions**

The applicant should append specific studies relating to the environmental fate and effects (i.e. Sections 7.5 and 7.6) of the proposed agent on those organisms and sectors of the environment that have been identified as likely to be exposed to, and adversely affected by, the agent/organism.

Applicants will also need to demonstrate target species specificity where claimed, for example by presenting information on unique modes of action and the molecular basis for specificity, and/or some confirmatory tests.

Data exemptions may be accepted where it can be demonstrated that:

- the agent/organism will not survive in the Australian environment;
- a particular class of organism or sector of the environment will not be significantly exposed to the biological product; or
- it is known that the agent/organism is a member of a group of organisms known never to have been pathogenic to organisms other than the target group.

Details of registration status (both in Australia and overseas) and environmental safety assessments of overseas regulatory agencies should be appended where available. In the case of GMOs and their products, the review must include a record of approval by the OGTR.

### **Explanatory notes on environmental fate and behaviour**

The purpose of environmental fate testing for biological products is to evaluate:

- the population dynamics of the agent/organism; and
- the ability of the agent to survive or propagate in a niche or host, and to disseminate in the Australian environment, after introduction.

Therefore, depending on the circumstances, studies in the following areas may be relevant:

- amount of agent to be introduced, application rates, method(s) of application, geographic areas of proposed use;
- extent of, and potential for, exposure during manufacture and/or formulation;
- spread, mobility, multiplication and persistence of the agent in air, water and soil;
- ability to infect or cause disease in nontarget organisms;
- ability to be expressed in terrestrial, freshwater, marine or estuarine environments; and
- fate in food chains.

In the case of GMOs or GMO products, in addition to the above, a summary review of the information presented to OGTR will need to be provided. This could include,

for example, summary information on the potential for unintended transfer of the inserted genetic material (the ‘transgene’ or genetic construct) to organisms other than the ‘host’ agent/organism through processes such as hybridisation and recombination, on the environmental fate and persistence of the transgene itself, and on competition of the GMO with the nongenetically modified host agent/organism. The APVMA is able, under its legislation, to require further testing of data in regard to GMOs and GMO products, as it is for other agricultural or veterinary products.

### **Explanatory notes on environmental toxicology and pathogenicity/infectivity to nontarget organisms studies**

These studies are needed to determine possible infectivity, toxicity, pathogenicity to or hypersensitivity of, nontarget organisms resulting from the introduction of the proposed agents into the environment, and to evaluate the potential for direct or indirect adverse impacts on significant biota (e.g. endangered wildlife or flora) or on natural ecosystems. Tests may be on the agent/organism and/or the proposed product, as relevant, and may involve glasshouse or field tests under controlled conditions or simulations. If such studies were performed in Australia, the Department of the Environment and Heritage would require that it be satisfied that there was no unintended harm to the environment from conducting such studies (e.g. a condition of the study might be that the experimental plots be fumigated afterward). Data requirements may depend on whether the agent and its relative are endemic, native or otherwise already present in Australia, to better determine the novelty of the environmental exposure on release.

The following environmental toxicology studies may be relevant, depending on the likely routes and patterns of exposure (see Explanatory notes on environmental fate and behaviour, above).

- toxicity and/or pathogenicity or infectivity studies on a range of organisms, including mammals, birds or other wild vertebrates, fish, freshwater aquatic invertebrates (such as *Daphnia magna*), honey bees, earthworms and other soil invertebrates, soil microorganisms, and marine and estuarine organisms;
- plant toxicity (phytotoxicity) and infectivity/pathogenicity studies (nontarget native vegetation);
- algal growth studies; and
- toxicity and/or pathogenicity or infectivity studies on important parasitoids and predators of target species.

Tests would need to include an appropriate taxonomic range of test organisms, involve appropriate exposure routes (oral, dermal, subcutaneous, intravenous, pulmonary, eye irritation, etc) and dosages (including safety margins), apply other testing protocols as appropriate, and use adequately sensitive detection methods. Toxicity studies could generally be acute studies, but subacute and short-term studies may also be needed where environmentally significant effects are known from acute studies (e.g. known toxicity to birds or fish). Toxicity studies conducted overseas could be used for predictions of effects on suspected predators or parasites in Australia.

## Guidelines for the Registration of Biological Agricultural Products

Specific tests on Australian biota may be required where environmentally significant wildlife, flora or ecosystems are identified, or where commercially significant organisms or systems may be adversely affected, depending on the nature of the agent/organism and anticipated exposures.

### **Explanatory notes on environmental hazard**

As for conventional agricultural products, it is recommended that the applicant perform an assessment of environmental hazard posed by introduction of the agent/organism. Due to the inherent variability of organisms, the complexity of ecological interactions, and the consequent inappropriateness and lack of standard testing protocols, the assessment may be predominantly qualitative in nature where specifically designed tests are not practicable or would not be definitive.

Some overseas regulatory authorities, such as in the United States and Canada, adopt a tiered approach to testing for environmental effects. Tests relevant to the requirements listed above could be from the lowest tier only in cases where data showed no persistence or survival in the environment, and/or no adverse effects, and/or where environmental expression was not significant. However, where such tests had shown (or it was otherwise known) that the agent was likely to persist and be expressed in the Australian environment and/or significant hazards were expected, higher level testing would be required. Such higher tier testing might include, for example, chronic effects, reproduction and field testing, or other tests relevant to evaluating fate, expression in, and impacts on the environment.

### **Further advice**

It is recommended that the applicant should seek advice from the Chemicals Assessment Section of the Department of the Environment and Heritage for further guidance on the level of testing that may be required.

If known toxins are produced by the agent/organism, data outlined in Table 7-1 of the *Ag Requirements Series*, Part 7 (Environment) should be provided. Advice should be sought from the Chemicals Assessment Section of the Department of the Environment and Heritage.

In the case of GMOs or GMO products, a summary review of the pathogenicity and/or infectivity information and ecotoxicity information already presented to OGTR will need to be appended to the application for registration. This could include, for example, information on the impacts of the GMO on nontarget organisms and beneficials, information on the ecotoxicity effects of the novel expression of a toxin in a pathogen, or predictions on altered epizootiology.

### **Examples**

The following hypothetical examples may help applicants understand the Department of the Environment and Heritage's approach.

#### *Example for Group 3 — a virus*

The product Thegavirus is a GMO in which a scorpion toxin gene has been inserted into a virulent strain of TGV ('The Grail Virus') and claimed to be specific to a few genera of coleopteran (beetle) pests, most of which are native to Australia. The

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purpose of genetic modification is to shift the nature of control away from that of a viral biological control agent towards that of a knockdown biocide.

The company provided information on the biochemical characteristics, mode of action, toxicity and effects of the scorpion toxin per se from various literature sources. The company also provided information on the nature and stability of the genetic construct inserted into TGV, expression levels in target hosts, infectivity and pathogenicity of TGV in target species, and information on the host specificity of related strains of TGV.

The Department of the Environment and Heritage generally accepted these data, including that the fate of the expressed toxin per se, as expressed in target species, would probably be as predicted from the literature sources, taking into account that it is a well-studied protein toxin. Further data would be needed, however, relevant to a number of concerns not addressed in the submission. These are new concerns identified and consequent upon the novel presence of the scorpion toxin gene in the viral genome, and the novel expression of the scorpion toxin in hosts of TGV.

Potential adverse ecological impacts could result from novel epidemiology as the GMO TGV-infected target species that also are part of natural ecosystems, and/or from extended GMO TGV host range due to genetic recombination among closely related TGV strains (with differing host ranges). New information would be needed to enable assessment, including information on relatedness and host range of related TGV strains, background ecology of the TGVs and hosts in natural systems, GMO TGV epizootics, likelihood of genetic recombination and TGV persistence.

Given the level of scientific uncertainty about some of the above hazards, new emphasis might need to be placed on empirical GMO TGV specificity testing of a wider range of nontarget species.

### *Example for Group 4 — a microscopic nematode*

The product Nemamusy contains *Nemamus nemesis*, a microscopic nematode isolated in Brazil, and is claimed to specifically control beetle larvae. The product is formulated as a dry granular formulation for incorporation into the soil, or application on top of the soil. The formulation contains  $5 \times 10^5$  eggs per gram and is proposed to be imported. As such, it is also the subject of Australian Quarantine and Inspection Service (AQIS) approval (see Section 1.3) and consideration may also be required by Wildlife Australia for approval under the *Wildlife Protection (Regulation of Imports and Exports) Act 1982*.

The applicant has made various claims and provided some data, but several concerns remain, as summarised in Table 5-2.

**Table 5-2: The Department of the Environment and Heritage’s concerns about *Nemanusdy***

Claim	Information provided by sponsor	The Department of the Environment and Heritage’s concerns
1 Specific to soil-dwelling beetle larvae	Literature references, including reviews, for the genus	Arguments provided are largely speculative, with data from other studies indicating other species of the genus to be at least parasitic in a wide range of soil invertebrates, including earthworms
2 No persistence of nematodes in soil	Efficacy studies performed overseas (i.e. the exporting country)  Laboratory studies	Only juvenile nematodes can be detected; there is a possibility that the nematodes persist as eggs, which cannot be identified  Data indicating the need for re-inoculation were collected only from laboratory studies
3 Genus is cosmopolitan and likely to have a very similar species in Australia	Various comparative data for two other species  Literature references	Not adequately demonstrated as the key taxonomic features are not well defined, with the genus under revision overseas

The table suggests that a major concern is the potential for adverse impacts on a wide taxonomic range of nontarget species. Furthermore, while *Nemamus* is distributed throughout the world, the genus includes a diverse range of species, differing in their geographic occurrence and parasitic host ranges. The genus is known to occur in Australia, but there is no clear knowledge on the range of species present, whether they are endemic and/or native or on their host ranges. The taxonomy of the genus is not well known, with taxonomic revisions on overseas species under way. This makes it difficult to assess how novel *N. nemesis* is in the context of Australian species diversity and, therefore, to assess potential impacts in the absence of new information.

The applicant was therefore asked to provide data relevant to addressing these major concerns such as further data supporting claims of specificity (e.g. empirical data on infectivity and pathogenicity in nontarget organisms and/or evidence relating to the biological basis [biochemical/molecular] for specificity) and congruent data to support claims of relatedness to, and genetic distance of *N. nemesis* from, other Australian species, or adequate information to demonstrate that *N. nemesis* already exists in Australia.

Adequate genetic information to demonstrate that *N. nemesis* is identical or extremely similar to other Australian species of this microscopic nematode would diminish environmental concerns relating to release in Australia.

## **PART 8 Efficacy and safety**

### **Summary and evaluation of efficacy data**

Efficacy data should be provided for all microbials and other living organisms used as pest control agents. Efficacy of end-use products can vary significantly due to biological variation and other factors such as manufacturer of the active constituent, site of manufacture of the active constituent, manufacturing process, formulation process of end-use product and ingredients in the formulation.

A microbial product will generally not be considered to be closely similar to a registered product unless it is a simple repack of an existing product. Thus, microbial product applications are more likely than chemical products to be treated as Category 24 applications rather than Category 26 applications. (Refer to the *Ag Manual –The Requirements Manual for Agricultural Chemicals* for further details on product application categories). Bridging data will be required for all significant changes, including source or process of manufacture, strain or formulation of product.

Because of this variability, active approval applications cannot be accepted without an accompanying end-use product application.

### **Justification for use**

Information should be provided as follows:

- the nature and economics of the pest/disease in Australia;
- performance of the microbial pest control agent, according to prescribed label conditions and claims;
- current management tools — status, benefits, problems; and
- the contribution of the microbial pest control agent to risk reduction and sustainable pest management in the specific crop/resource production system.

The purpose of justifying the use of the product is to promote balanced regulatory decisions that incorporate consideration of the potential unique or long-term benefits of the microbial product to sustainable crop/pest management or risk reduction with possible drawbacks or disadvantages. It is anticipated that microbial products will demonstrate special characteristics that adapt well to integrated management programs or may exhibit desirable safety features. Formal documentation of these characteristics is an important component of risk management decision making.

### **Product performance**

Product performance is defined as the ability of the product to fulfil the claims made on the proposed label. It includes the nature and extent of control/management of the pest or disease problem and also considers beneficial or adverse effects on the host crop and the crop production system.

Product performance data should provide information regarding the microbial agent's pest host range and time to mortality and the minimum dosage required to achieve the desired or claimed standard of performance, according to the specifics of the proposed use scenario. Such information is developed in order to support label performance

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claims and use recommendations, and is also important to nontarget organism safety assessment. Performance data will also serve to confirm, where applicable, the utility of the microbial product in the development of sustainable pest management practices, including integrated management strategies, resistance management and risk reduction.

### *Requirement for local data*

Where practicable, performance data packages should be based on original Australian data. Overseas data, which are collected under conditions comparable to intended Australian use situations and which meet Australian requirements, may be used to support Australian data.

For uses under confined or controlled-environment conditions (e.g. greenhouses, interior plantscapes), overseas data will normally be acceptable, provided the test conditions and crop management practices are demonstrably similar to those found in Australia. Home garden products should be tested under Australian conditions, which usually differ significantly from conditions in overseas countries.

### **Efficacy data requirements for agricultural products**

The following should be addressed:

#### *Advantages of the product*

#### *Laboratory assays (if relevant)*

#### *Preliminary range-finding tests*

#### *Field experiments under practical conditions in representative areas of Australia*

- For new products (including new species or strains), experiments should be carried out over at least two seasons and in representative areas in at least two States in which the product is to be used.
- For minor formulation changes to products already registered (e.g. a change in source or process of manufacture, or formulation), **EITHER** experiments should be carried out over at least two seasons and in representative areas in at least two States in which the product is to be used **OR** the same number of experiments should be carried out over one season, also in representative areas in at least two States in which the product is to be used.

#### *Information on resistance management if this is an issue*

#### *Consideration of any limitations posed by pest pressure*

#### *Compatibility with chemical products (where appropriate)*

- Chemical products that have been shown to be mutagens should not be mixed with biological agents.

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*Compatibility with integrated pest management and organic farming systems* (where relevant)

*Observations concerning undesirable or unintended side effects* (e.g. on beneficial and other nontarget organisms) on succeeding crops, other plants or parts of treated plants used for propagation purposes (e.g. seeds, cuttings, runners).

### **Phytotoxicity studies**

- Safety to target crop/animal
- Phytotoxicity to nontarget crops and other plants
- Animal safety

Further information on efficacy and phytotoxicity data requirements is given in the *Ag Requirements Series*, Part 8 Efficacy and Safety.

**ABBREVIATIONS**

AQIS	Australian Quarantine Inspection Service
CAS	Chemical Abstracts Service
GMO	Genetically modified organism
IUPAC	International Union of Pure and Applied Chemistry
MRL	Maximum residue limit
MSDS	Material safety data sheet
OGTR	Office of the Gene Technology Regulator
OHS	Occupational health and safety
RCD	Rabbit calicivirus
TGV	'The Grail Virus'

## REFERENCES

*Note: Details are provided for the current edition at the time of publication in each case. Applicants should always ensure that they obtain the most up-to-date version of any publication. These publications can be obtained from AusInfo shops (formerly Australian Government Publishing Service, AGPS) in capital cities. Phone 132444 or website [www.ausinfo.gov.au](http://www.ausinfo.gov.au).*

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