Critical regulatory path for biocontrol agents

Prepared by Vijay Cuddeford, World Wildlife Fund Canada,
for Agriculture and Agri-Food Canada,
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This report is prepared as a background document to the AAFC workshop "*Microbial Biocontrol Agents: Registration, Commercialization & Adoption Issues*", held in Saskatoon on February 28th - March 1st, 2005. It describes the regulatory regime for several broad classes of biological pest control agents - microbial pesticides, pheromones, arthropod biocontrol agents, plant oils and extracts, food grade substances, entomopathogenic nematodes and rhizobial inoculants (not used in pest control) - in three different jurisdictions. The major focus is on microbial pesticides. The jurisdictions covered are Canada, the United States, and the European Union (EU). The report provides information on the 'critical path' to registering, importing and/or using/releasing a substance or organism, as well as legislative frameworks requiring and defining the method of its registration, assessment, import, use or release; the data which must be provided; the authorities to which it must be provided; and timelines for the various processes, whether regulatory or otherwise. It is hoped that providing a clear picture of this 'critical path' will facilitate the identification and resolution of any roadblocks in that path. Where possible, this document also provides recommendations, advice and tips for identifying, avoiding or resolving major barriers or pitfalls along the way.

Part I: Microbial Pest Control Products

A. Canada

The Pest Management Regulatory Agency (PMRA), under the authority of the Pest Control Products Act (PCPA), administers the regulatory and registration process for microbial pesticides in Canada. A microbial pest control agent (MPCA) is defined as "*a microorganism (bacterium, alga, fungus, protozoan, virus, mycoplasma or rickettsia and related organisms) and any associated metabolites, to which the effects of pest control are attributed"*, and the process for registering an MPCA and associated MPCPs (microbial pest control products*)* is laid out in PMRA Regulatory Directive 2001-2 "Guidelines for the Registration of Microbial Pest Control Agents and Products"[1], as well as in a number of other documents[2].

Regulatory Directive 2001-2 describes, inter alia, the required elements of a complete dossier for submission to PMRA, the process of registering a microbial pesticide, the nature and benefits of a pre-submission consultation, review timelines, fees, a detailed description of data requirements (including required and conditionally required data), the nature of tests which must be performed to satisfy the various data requirements, and the possibilities and conditions for data waivers. (See Table 1, which details Canadian data requirements for registration of microbial pesticides, and compares them with those in the US and the EU.)

Research permits

Researchers interested in conducting field trials to generate efficacy or other data for an MPCA or MPCP in Canada require a permit from PMRA. If the trial is:

- small-scale (up to 10 hectares for terrestrial field trials and 1 hectare for aquatic trials);
- with a registered active or registered products,
- involves an indigenous MPCA,

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[1] Available at http://www.pmra-arla.gc.ca/english/pdf/dir/dir2001-02-e.pdf

[2] Regulatory Proposal 96-01: Management of Submissions Policy. http://www.pmra-arla.gc.ca/english/pdf/pro/pro9601-e.pdf
Regulatory Proposal 2003-1: Organizing and Formatting a Complete Submission for Pest Control Products. http://www.pmra-arla.gc.ca/english/pdf/dir/dir2003-01-e.pdf
Regulatory Directive 98-05: Chemical Pesticides Research Permit Guidelines. http://www.pmra-arla.gc.ca/english/pdf/dir/dir9805-e.pdf
Regulatory Directive 99-05: User Requested Minor Use Registration (URMUR). http://www.pmra-arla.gc.ca/english/pdf/dir/dir9905-e.pdf
Regulatory Directive 2001-01: User Requested Minor Use Label Expansion (URMULE). http://www.pmra-arla.gc.ca/english/pdf/dir/dir2001-01-e.pdf
Registration Handbook http://www.pmra-arla.gc.ca/english/appregis/book-e.html
Proceedings of the NAFTA Biopesticide Registration Workshop, Nov. 13-15, 2001. Arlington, Virginia. http://ir4.rutgers.edu/RWP/

- is conducted on property owned by the researcher, and
- is applied only with ground equipment,

applicants are required only to submit a Notification of Pesticide Research form to the PMRA, accompanied by a minimal data set. Notification forms are processed within 30 days, and processing must be complete before a trial can begin. Applicants who wish to conduct field trials that do not meet these criteria must submit an Application for a Research Permit Form, along with a much fuller data set. The timeline for processing of a research permit is 90 days for a new use or new formulation of a registered active, and 180 days for a new active ingredient. Fees for research permits are $150 (federal agencies are exempted from charges), while notification permits are free of charge. All timelines are in calendar, not business days. For detailed guidelines and full data requirements, consult PMRA Directive 93-05: Research Permit Guidelines for Microbial Pest Control Agents, available at http://www.pmra-arla.gc.ca/english/pdf/pro/pro9305-e.pdf. Copies of both the Notification of Pesticide Research form and the Application for Research Permit form are included as appendices to this document.

Regulation under other Federal Acts

Importation, manufacturing and use of an unregistered microbial organism for research purposes is exempt from the New Substance Notification Requirements (under the Canadian Environmental Protection Act, CEPA), because the environmental assessment conducted under the PCPA is considered to be equivalent to that required under CEPA. However, importation of a microorganism intended for use as a pest control agent in Canada requires an import permit under either the Plant Protection Act (PPA), the Health of Animals Act and/or the Human Pathogens Importation Regulations, depending on whether the agent is known to be, or is potentially, a pathogen to either plants, animals or humans, respectively. Most MPCAs intended for pest control purposes would require an import permit under the PPA and not the other two Acts (i.e., most are insecticides, plant disease pathogens or plant pathogens, not animal or human pathogens). Upon receipt of an application to import, the Canadian Food Inspection Agency (CFIA), administrator of the PPA, determines whether the MPCA is a known plant pathogen. If not, then either an import permit is issued or a letter is provided by CFIA to the applicant stating that a permit is not required (to be presented to Customs). If the MPCA *is* a known plant pathogen, the applicant must apply for an import permit under Section 43 of the PPA, which regulates import of pathogenic cultures (among other commodities).[3] In this case, a permit is issued only if the material is intended for scientific research, educational, processing, industrial or exhibition purposes, and destined for an approved research facility with adequate containment and disposal measures. Note that the permit is for importation only; any pest control trials to be conducted in Canada will require approval by the PMRA under the PCPA as detailed above.

Pre-submission consultation

[3] Permits are downloadable from the CFIA website at http://www.inspection.gc.ca/english/for/pdf/c5256e.pdf

A pre-submission consultation is a meeting between the regulator, the applicant or developer and their industry partner, and any support persons (such as a regulatory consultant), involved in the application. The purpose of the pre-submission consultation is to determine the required data set; appropriate test substances and study protocols required to support the registration submission, and to determine the type of information required to support any data waivers. Data requirements established during a pre-submission consultation are valid for up to 24 months. This period is chosen because it is often the time required for development of safety and efficacy data to support registration for active ingredients for which little or no existing test data are available. Because PMRA and EPA have not changed their microbial data requirements for several years now, and no plans to amend these requirements are currently in the works, prospective applicants can expect the data requirements identified at the first pre-submission consultation to stand for longer than 24 months. The 24-month timeframe is also chosen to allow the Agencies an opportunity to amend the requirements based on any new information on the organism that suggests a change in approach, or to reflect global international harmonization efforts (e.g., at the OECD level).

One consultation is usually enough for experienced registrants, but, especially for inexperienced or less experienced registrants, two is the norm - one at the beginning stages of product development and another near the final stages and close to the targeted date of application to PMRA. Follow-up contact with PMRA by e-mail and phone is encouraged, both to ensure compliance with submission requirements and to determine whether the results of lower tier tests trigger additional data requirements.

The applicant should contact PMRA to request a pre-submission consultation date. Forty-five days before a pre-submission consultation, the applicant submits a data package to PMRA. Submitted information should include[4]:

- a formal request for a pre-submission consultation;
- a proposed label, including information on, inter alia, proposed use pattern, class designation, timing, application methods, rate, re-entry interval, environmental and human health precautionary statements, storage temperature, shelf life, product guarantee, and information on use in Integrated Pest Management or Integrated Risk Management programs;
- product profile and international regulatory status;
- a full characterization of the MPCA;
- a summary of available information on manufacturing process, product specifications, efficacy, and environmental and human health safety;
- scientific rationales for proposed data waivers; and
- proposed study protocols, if available.

Submitted materials may be taken from published or unpublished literature. If this kind of information is not available for the exact organism in question, published or unpublished material from a surrogate species may be acceptable, or data from original

[4] These requirements are more fully defined in Regulatory Directive 2001-2

tests with the MPCA. Although not a requirement, it should be noted that a pre-submission consultation is highly recommended before embarking on toxicity studies.

One week before the consultation, PMRA will send a DACO table, outlining the data requirements. This table provides the basis for further discussion at the meeting.

Required data for a complete submission (and differences between PMRA and EPA requirements)

Complete data requirements and study guidelines (i.e., directions for conducting tests to fulfill the data requirements) are listed in Regulatory Directive 2001-2. The data requirements for environmental toxicology and fate, human health, and for testing of non-target organisms are arranged in tiers. The functioning of the tiers is illustrated in Appendices IX and X of the Regulatory Directive 2001-2. Data requirements are customized to suit each MPCA and MPCP during the pre-submission consultation phase. It should be noted that Canada accepts all U.S. study guidelines.

Detailed characterization is critically important for microbials. The more comprehensive the data provided to the regulator at the pre-submission consultation stage, the more able the regulator will be to assess health and environmental safety. Detailed characterization also provides a strong foundation for requests to waive data requirements related to safety considerations.

The OECD has published a comparison chart of microbial data requirements in the EU, the US and Canada, as well as Japan and Australia, which is available at http://www.oecd.org/dataoecd/4/23/28888446.pdf. Based on this chart, the following table presents the differences in data requirements among the three jurisdictions.

Table 1 – Comparing data requirements for microbial pesticides - Canada, US, EU

Required by Canada and US, but not EU	• theoretical discussion of unintentional ingredients in technical grade active substances and in end-use products • quality control data for product
Required by Canada and the EU, but not the US	• efficacy data[5] • toxic or pathogenic effects on the crop or host which is to be protected • safety data sheets for each additive
Required by Canada, but not by the US and EU	• data on patent status
Required by the US and EU, but not Canada	• acute oral and inhalation data on end-use products, as well as different approaches to potential skin sensitization • eye irritation data[6] • toxicity studies on metabolites
Required by the EU, but not by Canada and the US	• short-term toxicity/pathogenicity data • operator/bystander exposure monitoring data • possible occurrence of the development of resistance or cross-resistance[7] • information on methods to render the product harmless in the case of an accident • post-registration monitoring methods to determine and quantify residues of viable or non-viable micro-organism and metabolites (especially toxins) on food, feed, animal tissue, in soil, water or air, where relevant. (conditionally required) • effects on algal growth and growth rate (2 species), on earthworms and non-target soil microorganisms

Conditions which trigger higher tier studies can vary between PMRA and EPA for environment testing beyond Tier I and for environmental fate requirements in Tier II. However, the vast majority of MPCAs that have been reviewed by both agencies have not triggered environmental testing beyond Tier II. Furthermore, the relatively minor differences between jurisdictions have not presented a barrier to registration in Canada for products first registered in the U.S. Since most MPCAs that are registered in Canada were registered first elsewhere (mainly in the U.S.), other than having to submit efficacy studies, there have been no or few differences in health or environmental data requirements from the two Agencies.

[5] While EPA does not review efficacy data, the registrant must have supporting data on file and produce it on request from EPA. It should be noted that in Joint Reviews, EPA does require submission of efficacy data.

[6] PMRA assumes that all microbial products have the potential to be mild reversible ocular irritants, and will label them as such. If an applicant does not want to have such a statement on the label, they are required to provide PMRA with an eye irritation study that shows that the product is not an irritant.

[7] This is required in Canada at the product, not the MPCA level, and a mitigation strategy is required as well. Neither is required for the US.

For registration of genetically modified microbials, a standard data package is submitted, along with additional studies in the following areas:

- Nature and expression of introduced or modified genetic material
- Taxonomy and characterization of recipient and donor microorganisms
- Construction of the recombinant microorganism
- Phenotypic characterization of the modified microorganism

While the Biopesticide and Pollution Prevention Division of the US EPA assesses Plant Incorporated Protectants (PIPs), such as Roundup Ready soybeans and Bt corn as biopesticides, in Canada, these transgenic crops are regulated under the Seeds Act by CFIA.

General guidance on data waivers

Given the heterogeneity of MPCAs, it is unlikely that all non-target, environmental fate or toxicity studies will be required for a given application. Data requirements and waivers are thus determined and granted on a case-by-case basis. Waiver requests should:

- provide a rationale for the proposed waiver,
- describe unsuccessful attempts to generate the data, and
- recommend alternative methods to obtain the data required to address the concern.

The effective customizing of the data requirements on a case-by-case basis (and the potential for data waivers) depends on a thorough and accurate description of the MPCA and a reliable taxonomy for the class of microorganism to which it belongs. Because of their significance in terms of health and economics, bacteria which are pathogenic to animals and plants may be better studied and classified than, for example, protozoa and fungi, whose characteristics may be difficult to predict from their taxonomy. Thus, justification for waiving test requirements may be more difficult for these kinds of organisms.

Additional testing may be required for MPCAs which are taxonomically similar to clinically or agriculturally significant microorganisms. On the other hand, if the taxonomy of the MPCA suggests a lack of pathogenicity, there is a case for reducing or waiving testing requirements. Tier II ecological exposure data (e.g., an LC50 or LD50) which demonstrate that the agent will not survive or persist in the environment is a good basis for a request to waive some or all of Tier I testing requirements.

Health testing

The purpose of human health testing is to determine:

- The potential pathogenicity of the MPCA (and its contaminants)
- The infectivity, pattern of clearance and any unusual persistence of the MPCA and its contaminants
- Any toxic effects of the MPCA, contaminants or preparation by-products

- Whether higher tier health testing is required.

There are three types of tests which help determine health hazard and risk: toxicology tests; exposure tests; and, if a mammalian toxin is present, food and feed residue studies (the same that are required for a chemical pesticide), to establish a maximum residue limit (MRL) in foods under the Food and Drug Act (FDA), which is administered by Health Canada. Tier I tests include: acute oral, pulmonary and injection toxicity tests; tests of dermal toxicity and irritation; cell culture for viral agents; and a test of genotoxic potential for fungal agents. Tier 2 toxicology requirements include tests of sub-chronic toxicity, reproductive/fertility effects, mutagenicity and further acute tests. Tier 3 toxicology studies include chronic toxicity, teratology and reproductive toxicity. Exposure studies assess the use pattern and resulting potential for worker/bystander exposure. Based on test results, precautionary statements are placed on labels, as well as information on post-application field entry and decontamination procedures.

Determinations of human safety rely strongly on full characterization of the MPCA. If this relies chiefly on scientific literature, the relationship of referenced strains to the MPCA must be well described. Bridging data to support claims of safety may be acceptable in some cases.

If toxicology and characterization data demonstrate no concerns, further testing is not required (the usual scenario). If characterization shows a lack of potential for mammalian toxicity, the MPCA is exempted from the need for an MRL under the FDA. If there is a proposed food use and indication of mammalian toxicity via oral exposure, the product will be treated as a conventional chemical and a data set such as is required for conventional chemicals must be submitted.

If the MPCA is closely related to a known dermatophyte, infectivity testing may be required. Intravenous infectivity tests are required for bacteria or viruses, intraperitoneal infectivity tests for protozoa and fungi, and tissue cultures for viral agents. If characterization of a fungal agent shows a potential for production of a genotoxic substance, genotoxicity testing is required.

Further details on testing requirements, test substances, dosage, and other details can be found in Regulatory Directive 2001-2, and also at
http://ir4.rutgers.edu/RWP/PowerPoint/Wed-M.Watson-B.Belliveau.pdf

Environmental toxicology and fate testing

Data requirements for environmental toxicology and fate vary depending on how a pesticide is used. For example, data requirements differ between aquatic, terrestrial and greenhouse food or non-food uses, with outdoor uses generally requiring more extensive environmental data than indoor use products, because of greater potential for exposure of non-target organisms. Data requirements also differ for end-use products and manufacturing-use products, which may be technical grade products or formulation intermediates.

Data requirements for non-target organism and environmental fate testing are tiered. Tier I tests for all MPCAs involve exposing species from up to seven broad taxonomic groups to a high dosage of the MPCA. If results show adverse effects at proposed field rates, testing at the next level may be required. Applicants should consult with PMRA on how to proceed with higher tier testing. Most MPCAs do not require testing beyond Tier I. Management or mitigation of risk is usually accomplished via restrictive language on the label, for example by restricting usage in habitats of wildlife at risk.

Because Tier I tests represent a maximum hazard approach to testing, negative results allow a high degree of confidence that no unreasonable adverse effects are likely to occur from use. When there is hazard at doses close to expected environmental concentrations, higher tier testing is required.

Guidance on specific studies, selection of test organisms and test substances, data waivers, dosage levels, and other details are available in PMRA Regulatory Directive 2001-2, and also in EPA documents.[8]

Environmental toxicology and fate requirements are slightly different for MPCAs that are considered indigenous and those which are genetically engineered or non-indigenous. Consult Regulatory Directive 2001-2 for details. 'Indigenous' is defined as those microbials which have been "isolated from or are known to occur"[9] in the zone of intended use.

Data waivers for non-target testing

If the scientific literature shows that exposure of non-target organisms - fish, plant, insect and avian species - does not result in toxicity and/or pathogenicity, a request to waive data requirements can be considered. Also, non-target pathogenicity testing may not be required if the natural distribution of the MPCA overlaps with that of the non-target species normally tested in Tier I pathogenicity studies, and the MPCA has not been associated with non-target organism infectivity and disease. A waiver request may also be justified if it can be argued that the non-target organism in that particular environment will not be exposed to the product, unless agricultural doses greatly exceed natural concentrations of the microbe and its metabolites, in which cases acute studies may be required.

Tests for value (including efficacy)

As defined by Regulatory Directive 2001-2, there are four elements in a value assessment. The first element involves field and lab tests, while the latter three require written descriptions.

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[8] Microbial Pesticide Test Guidelines. http://www.epa.gov/opptsfrs/OPPTS_Harmonized/885_Microbial_Pesticide_Test_Guidelines/Series/885-0001.pdf and http://www.epa.gov/pesticides/biopesticides/regtools/guidelines/microbial_gdlns.htm

[9] Regulatory Directive 2001-2, page 3.

1. *Product performance* is the ability of the product to fulfill the claims made on the proposed label. Lab and field studies assess product performance as well as documenting any beneficial or negative effects on the host crop and crop production system. It is recommended that a minimum of three field studies be conducted in those Canadian regions where use is proposed. At least two seasons should be represented in the trials submitted, though not all trials are required to be multi-season. Foreign data collected in comparable conditions may be acceptable; consult PMRA. Regional variability may necessitate additional trials to demonstrate performance under all conditions, sites and areas of intended use.
2. The nature and economics of the pest or disease problem in Canada;
3. Current management tools: status, benefits, problems; and
4. The contribution of the product to risk reduction and sustainable pest management in the specific crop or resource production system.

Guideline documents on product performance include Regulatory Directive DIR96-01, *Guidelines for Efficacy Assessment of Fungicides, Bactericides and Nematicides*, and Regulatory Directive DIR93-07*b*, *Guidelines for Efficacy Assessment of Herbicides and Plant Growth Regulators.* PMRA recommends that the principles of performance testing as outlined in these documents be thoroughly understood before performance trials are begun.

Because most registered MPCAs are effective only when used in an inundative fashion, similar to conventional chemical pest control products, the principles of efficacy testing are the same. For MPCAs intended for use as inoculative or augmentative measures, assessment of performance is different, benefits may be direct and/or indirect, and may involve criteria which are very different from those used for conventional chemicals. Therefore, it is vital that performance criteria and goal(s) of treatment be precisely defined. Further details on data requirements, testing protocols and testing principles are available in Regulatory Directive 2001-2.

Submission package

It is recommended that applicants consult the appropriate guidance documents to ensure that all the required elements of a complete package are included in their submission.[10] Besides the required testing data, this includes a covering letter, various forms, a draft label, several required letters, and an index to the submitted studies/data.

The Registration Process

There are three steps in the submission evaluation process, once PMRA receives a submission package. The *verification* process (7 days) involves checking to ensure that submissions contain all required elements. If complete, the PMRA next *screens* the

[10] More info available from Regulatory Proposal 2003-1: Organizing and Formatting a Complete Submission for Pest Control Products. http://www.pmra-arla.gc.ca/english/pdf/dir/dir2003-01-e.pdf and http://ir4.rutgers.edu/RWP/PowerPoint/Tue-L.Lange.pdf

application for acceptability (45 days), based on current data requirements. Next, PMRA's science divisions perform a full *review* and scientific *assessment* (365 days), and a proposed regulatory decision document is prepared for public comment. Based on the proposed decision and comments received, a decision document is prepared, the applicant receives a PCP# and certificate of registration (or temporary registration, pending submission of further data).

Common Screening Deficiencies

There are a number of potential missteps along the registration path. Many can be dealt with via a phone call or fax, but others may cause significant and potentially costly delays, as the submission will be returned to the applicant until the deficiency is resolved.

Clarification of minor points (not requiring new data) is dealt with by contacting applicants by fax. Applicants are given 10 days to respond to the request; the review and time clock continues during this time. If no response is received within the allotted period, the review is stopped and the submission withdrawn. If more critical deficiencies are identified, the applicant is sent a preliminary letter of deficiency, describing the data needed to continue with the review. The review and the time clock stop, and the applicant is given 90 days to fulfill the requirements. When the deficiency is resolved, a new 45-day screening period and new 365-day review period commence. If the data are not provided within 90 days, the submission is withdrawn. If all science reviews are complete, but additional data is required, a letter of evaluation deficiency is sent to the applicant, to which the applicant has 90 days to respond. Upon receipt of a response, there is an additional 45-day screening period, and a new 180-day review period.

Some of the more common deficiencies include[11]:

- formatting problems, such as not organizing chemistry data according to Canadian DACOs or omitting the phrase "Potential Sensitizer" and "Caution – Eye Irritant" on the principal label, and
- data problems, such as not adequately addressing the data requirements with the submitted data, omission of QA/QC data, not responding to letters of deficiency within the allotted period, or not submitting sufficient data for an independent analysis.

Submission Categories

Submissions will be classified as **Category A** if they involve:

- a new technical grade of active ingredient (TGAI) or integrated system product (ISP) not previously registered in Canada, and their related end-use product(s) (EPs);
- manufacturing-use products (MPs) or a major new use, defined as the addition of a new use-site category to the use pattern for a specific registered TGAI;

[11] For a fuller discussion, see presentations included in "Panel Discussion; Common Pitfalls in Submissions" at http://ir4.rutgers.edu/RWP/Agenda-Tue.htm

- establishing an import maximum residue limit(s) (MRLs) for a new active ingredient.

Category A submissions also include URMURs and Joint Reviews. Because one of the requirements for acceptance into the Joint Review process is that the active ingredient be new to both Canada and the U.S., Joint Reviews are, by definition, Category A submissions. These submissions normally involve a significant amount of data regarding safety and value.

URMUR review timelines are 5 months. Review timelines for other Category A submissions are 12 months.

Category B submissions are:

- submissions to register new products which contain an active currently registered in Canada, or
- amendments to existing products. These include changes in product chemistry or labeling, the conversion or extension of temporary registrations, and the addition of import MRLs for previously assessed technical grade active ingredients (TGAIs).

Category B submissions include a smaller database (not all DACOs), as the PMRA has some of the data on file from previous registrations.

The review timeline for a Category B submission is 6 months.

Category C submissions include reviews of minor label and/or formulation changes, and do not require supporting data.

Category D submissions include new or amended registrations in the Importation for Manufacturing and Export Program (IMEP), Pesticide Own Use Import (OUI), Master Copy, Private Label, and User-Requested Minor Use Label Expansion (URMULE). Consult Appendix A of the Registration Handbook for more details on these kinds of registration submission.[12]

Category E submissions include research permits for new actives, new uses of registered actives, and research notifications.

Applicants usually request a pre-submission consultation for submissions which fit Category A criteria, at which time an application would be appropriately categorized. For other types of submissions, most applicants will propose a category based on guidance in the Registration Handbook, and PMRA determines whether the proposed category is appropriate during the screening stage. If it is not, the applicant is informed of the category change and the submission is returned to the applicant for additional data as necessary.

[12] http://www.pmra-arla.gc.ca/english/appregis/book-e.html

Timeline, registration fees and other costs

As stated above, review timelines range from 5-12 months for new microbial pest control products. For Category A submissions which are not URMURs, the 12-month review timeline includes a 120-day preliminary assessment, then preparation of formal documentation for public consultation. From initial application to public consultation, then, the timeline is 417 days.

PMRA requires a fee of $524 for registration of an MPCA and one MPCP (this fee is for label review). The fee is submitted with the full data package. This compares to a $15,000 - $25,000 fee in the U.S, approximately $42,000 US in the UK and approximately $212,000 US in Sweden. Annual maintenance fees are set at a maximum of $2,690 per registered product (PCP number). For products with annual sales of less than $89,667, the fee is a maximum of 3% of sales, with a minimum fee of $75.

It is expected that the total costs incurred in registering a microbial pest control agent requiring only Tier 1 studies will be approximately $500,000. This is about 1/10th the amount required to register a chemical pesticide, which typically costs the registrant in the order of $5 million.

Importation into Canada

Importation of registered microbial pest control products (from any country) requires a Declaration by Importer of Control Products. Products are released only when this documentation is provided.

To import an MPCA intended for use as a pest control agent in Canada, an import permit either under the Plant Protection Act (PPA), Health of Animals Act and/or Human Pathogens Importation Regulations is required, depending on whether the agent is known to be, or is potentially, a pathogen to plants, animals or humans, respectively. Most MPCAs intended for pest control require an import permit under the PPA and not the other two Acts (i.e., most are insecticides, plant disease pathogens or plant pathogens, not animal or human pathogens). CFIA, administrator of the PPA, provides comment on whether the MPCA is a known plant pathogen. If not, then either an import permit is issued or a letter is provided by CFIA to the applicant stating that a permit is not required for importation (to be presented to Customs). If the MPCA *is* on the list of known plant pathogens, the applicant must apply for an import permit under Section 43 of the Plant Protection Act, which regulates import of pathogenic cultures (among other commodities).[13] A permit is issued only if the material is imported for scientific research, educational, processing, industrial or exhibition purposes, and destined for an approved research facility with adequate containment and disposal measures. Note that this permit is for importation only; any pest control trials to be conducted in Canada will require approval by the PMRA under the PCPA.

[13] Permits are downloadable from the CFIA website at http://www.inspection.gc.ca/english/for/pdf/c5256e.pdf

The CFIA website at http://www.inspection.gc.ca/english/plaveg/oper/orglste.shtml contains a list of organisms which do not require permits for importation purposes. Most of the listed species are microbial.

Export

If an MPCP is registered in both Canada and the U.S., a Canadian firm requires only a standard import notice to export the product to the U.S. If the product is registered in Canada but not in the U.S. (an unlikely scenario), then only small amounts of the MPCP (or MPCA) could be exported for research purposes, an undertaking that would be regulated under U.S. pesticide law (Federal Insecticide, Fungicide and Rodenticide Act – FIFRA).

Provincial/territorial jurisdiction

Alberta has a Code of Practice which regulates the use of pest control products by applicators, services and vendors, and prescribes requirements to ensure that all activities are in compliance with Alberta's environmental laws. However, application of registered pesticides, including microbial pesticides, to cultivated land for agricultural purposes is exempted from these requirements. Thus, there is no provincial oversight in Alberta related to the deployment of federally-registered microbial pest control products for agricultural purposes which is additional to the use restrictions stated on the pest control product label. This statement is also true for British Columbia. In B.C., the Integrated Pest Management Act and regulations also exempt agricultural applications from the need for a license and associated requirements. To the best knowledge of B.C. provincial regulators, there are no other provincial Acts or Regulations that would impact or affect a potential user of microbial pesticides. In Ontario as well, according to Ministry of Environment officials, there appear to be no Acts or regulations that would pose a barrier to potential users of a microbial pesticide for agricultural uses.

B. United States

In the U.S., microbial pesticides include bacteria, fungi, viruses, and protozoans. Within the Office of Pesticide Programs of the U.S. Environmental Protection Agency, a separate division called the Biopesticide & Pollution Prevention Division (BPPD) was established in 1994 to take the lead for all U.S. Federal regulatory activities on biopesticides. BPPD remains the lead agency for regulation of microbial and all other types of biopesticides even when other Federal agencies are involved [e.g., Department of Interior for Endangered Species or the Food and Drug Administration (FDA) for tolerances or MRLs].

The major Federal acts which regulate pesticides (including microbial pesticides) in the U.S. are the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA); the Federal Food Drug and Cosmetic Act (FFDCA); and the Food Quality Protection Act (FQPA).

The human health and environmental safety data requirements for microbial pesticides are very similar for Canada and the U.S. Both EPA and PMRA have adopted a tiered approach for setting data requirements for microbial biopesticides.

Experimental Use Permits (Research Permits)

For small-scale field tests
Experimental Use Permits are not required for field tests that occupy less than 10 acres. However, to qualify for this exemption, a USDA permit is required for the actual field release of the MCPA or MCPP, as well as an import permit if the microbial agent is non-indigenous (see section below on Entomopathogens). It may be necessary to destroy the experimental crop after the test is completed; check with EPA as these decisions are made on a case-by-case basis. If the test is on a food or feed crop, the MPCA will require either a food tolerance or an exemption from a tolerance.

Notification is always required prior to small-scale field-testing of genetically modified organisms. Guidance on how to apply for notification is provided in the Code of Federal Regulations (CFR), parts 40CFR172.46 and 40CFR172.48.[14]

Large scale field testing
Data requirements for large-scale tests may include any or all of the data required for registration, though efforts are made to limit the data required to the most likely areas of concern as predicted by the properties of the MPCA and similar microorganisms. Data waivers may be justified in certain exposure situations, for example, when there is limited capacity for the MPCA to survive at, or disseminate from, the field test site, and where there are containment or mitigation provisions in the test protocols.

Data in support of permit applications are generally the kind of information generated during the initial stages of product development, including product analysis information, Tier I toxicology, and non-target organism toxicity tests. These tests are normally conducted first in preparation for registration. Unless there is test evidence that the MPCA is toxic, pathogenic, or has other adverse properties, residue and environmental fate data is not ordinarily required.

Regulation under other Federal Acts

Food Quality Protection Act

The FQPA, promulgated in 1996, requires EPA to use a health-based standard of risk as well as several methods for more accurately determining health hazards when assessing the acceptability of pesticide use and setting tolerance limits for crops. However, because microbials and other biopesticides are normally exempted from tolerances, these considerations do not apply to them.

[14] See http://www.access.gpo.gov/nara/cfr/waisidx_04/40cfrv22_04.html for relevant parts of the CFR.

Endangered Species Act: Under the Endangered Species Act, and in consultation with the U.S. Fish and Wildlife Service and the National Oceanic and Atmospheric Administration, EPA must ensure that its regulatory actions are not likely to jeopardize threatened and endangered species or destroy or adversely modify their critical habitats.

Migratory Bird Act: When assessing the environmental safety of a pest control product, EPA assesses potential effects to birds when products are used in a way that may cause exposure to migratory populations.

Pre-registration meeting

It is recommended that applicants request a pre-registration meeting in advance of submitting a registration package. While there are no prescribed data requirements, applicants should provide sufficient background materials to address meeting objectives at least 2 weeks before the meeting. The objectives of the meeting or meetings are:

- to present the active ingredient and products to the regulator;
- to discuss the MPCA and MPCPs, use patterns, relevant policies, rules and petitions;
- to identify potential issues; and
- to agree on data requirements and requirements for waiver requests.

In preparation for the meeting, it is recommended that applicants update their literature search, and prepare a product dossier with all pertinent information on the product, including toxicology and environmental fate data, planned studies and waiver rationales. It is recommended that the applicant carefully prepare their presentation and that a follow-up letter be sent subsequent to the meeting, clearly defining all agreed-upon points.

Two or more pre-registration meetings may be required, especially for a new MPCA. The first should be held prior to beginning key toxicological and environmental studies, and the second after completing the key studies, but 3-4 months before submission.

Required data

As in Canada, there are several tiers of data requirements for microbial pesticides. Typically, only Tier I studies are required, while higher tier studies may be triggered by the results of Tier 1 studies.

Specific studies and the conditions under which each is required or waived are described in the following Data Tables:

- 40 CFR 158.740(a) Product Analysis
- 40 CFR 158.740b) Residue Data Requirements (typically not required for microbial pesticides)
- 40 CFR 158.740(c) Toxicology Data Requirements
- 40 CFR 158.740(d) Non-target Organisms and Environmental Expression Data Requirements

These guidelines are available on the BPPD Website at: http://www.epa.gov/pesticides/biopesticides/regtools/guidelines/index.htm. All studies are either Required [R] or Conditionally Required [CR]. 'Conditionally Required' means that EPA may request this study based on what is known about the manufacturing use product or the end-use product. It is recommended that applicants focus primarily on the Required studies. An overview of testing guidelines is available at http://www.epa.gov/opptsfrs/OPPTS_Harmonized/885_Microbial_Pesticide_Test_Guidelines/Series/885-0001.pdf

It should be noted that, although EPA does not review efficacy data for MPCPs designed to manage agricultural pests, if the microbial is making a claim to control a public health pest such as fire ants, rodents, mosquitoes or cockroaches, efficacy data will be reviewed.

General guidance on data waivers

In general, the requirements for waiving a specific study are dependent on:

- the use pattern: food or non-food use, terrestrial, aquatic, greenhouse, forestry, domestic indoor, domestic outdoor
- whether the application is for a Manufacturing Use Product (MP) or an End Use Product (EP)

As noted above, the bases for waiver requests are detailed in the Data Tables. Because toxicology and environmental fate requirements are reduced substantially compared to synthetic chemicals, complete product characterization is critical; thus it is difficult to obtain waivers of product analysis requirements. Discussions to determine which studies are most appropriate for the organism take place at the Pre-Registration Meeting.

Health testing

As in Canada, the purpose of human health testing is to determine:

- The potential of the MPCA and microbial contaminants to be pathogenic;
- The infectivity, pattern of clearance and any unusual persistence of the MPCA and microbial contaminants;
- The potential toxicological effects of the MPCA, of microbial contaminants, and of preparation by-products;
- Whether further data (e.g., higher tier toxicity, short-term and/or chronic studies) are required to fully assess risks

For health studies, EPA's data requirements and approach are virtually identical to those of the PMRA. Three tiers of toxicology data requirements are listed on EPA's website at http://www.epa.gov/pesticides/biopesticides/regtools/guidelines/40cfr158_740c.htm

For toxicology studies, the following are the respective tiers:

- Tier 1: acute, including infectivity/pathogenicity studies
- Tier 2: sub-chronic, mutagenicity, etc.

- Tier 3: chronic, teratology, reproduction, etc.

Tier I consists of a battery of short-term tests designed to evaluate the potential for toxicity, infectivity, and pathogenicity. Tier II evaluates situations where, in the absence of evidence of pathogenicity, either toxicity or infectivity is observed in Tier I. Tier III tests are designed to resolve issues of known or suspected human pathogenicity and tests for particular adverse effects of intracellular parasites of mammalian cells.

Triggers for various tests include the following:
- Acute inhalation data are required if > 20% of particulates are < 10 microns.
- Dermal infectivity testing may be required if the microorganism is closely related to a known dermatophyte.
- Intravenous infectivity tests are required for bacteria or viruses, and intraperitoneal infectivity tests for protozoa and fungi.
- Tissue cultures are required for viral agents.
- If fungal characterization suggests the potential for production of a genotoxin, then appropriate testing will be required.
- Hypersensitivity studies are required if there is repeated human contact by inhalation or by a dermal route, and hypersensitivity incidents must be reported if they occur.

Environmental fate and toxicology testing

Data requirements for environmental fate and toxicology are very similar in Canada and the U.S. While there can be some differences at higher tier testing levels, in reality these tiers are hardly ever triggered for microbials.

As in Canada, Tier I tests are maximum dose single species hazard tests on nontarget organisms. If adverse effects are observed in Tier I, potential exposure to the MPCA is estimated by means of Tier II testing for population dynamics, environmental fate and expression. If Tier II tests show a potential for significant exposure, Tier III studies determine a dose response effect or examine chronic effects. These tests are designed to determine if the lowest infective dose is less than the expected exposure, or if there are other considerations that would decrease the observed effects in the environment. Tier IV tests, conducted under simulated or actual environmental conditions, are designed on a case-by-case basis to evaluate specific problems that cannot be resolved by lower tier testing.

Submission package

A complete submission package includes:

- A transmittal letter: this identifies the submitter, date of transmittal, type of regulatory action to be considered (e.g., amendment, Experimental Use Permit, new active ingredient registration, etc.), and the list of studies.
- All required studies, waivers, a proposed label, Confidential Statement of Formula, data matrix, and forms

- A Tolerance Petition, if required.

Links to all registration application forms, along with important pesticide registration notices are available at http://www.epa.gov/pesticides/registrationkit/

The Registration Process

BPPD conducts a five-stage review of biopesticides.

- Phase 1 includes a review of the submission package for compliance with the Pesticide Registration Improvement Act (PRIA), a screen for completeness of the package, and assignment of the submission to administrative and science reviewers.
- In Phase 2, the Registration Action Leader, a BPPD staff who manages the submission through the whole registration process, reviews the package.
- In Phase 3, there is a preliminary review of the data provided; this is often outsourced.
- Phase 4 is a secondary, more thorough review.
- Finally, Phase 5 is the risk management decision, which, as in Canada, involves a period of posting for public comment.

BPPD'S Administrative Screening Checklist for Completeness of Applications is included as Appendix V of this report. More details on BPPD's registration process are available at http://ir4.rutgers.edu/RWP/PowerPoint/Tue-S.%20Mattan.pdf

Common Submission Pitfalls

As in Canada, the path to registration is strewn with potential pitfalls. It is recommended that applicants adopt several strategies to avoid these pitfalls:

- plan thoroughly and well ahead of time,
- ensure that the submission is reader-friendly (on CD if possible),
- avoid unstated or unrealistic expectations and assumptions,
- follow study protocols carefully to avoid extra work,
- maintain close contact with the Registration Action Leader,
- keep confidential business information (CBI) in separate, clearly marked sections – no CBI in cover letters, and
- become knowledgeable of the registration history of similar strains.

Some of the more common pitfalls include:

- *Labeling* problems such as the ingredient statement not matching the Confidential Statement of Formula (CSF);
- *CSF* Issues, for example, the CSF not including a viability measure or a nationally recognized culture collection number;
- *Forms and Administrative* Issues, for example missing forms, a missing data matrix, or no narrative description of how the submitted data meets the data requirements;
- *Data* issues, including omission of the scientific rationale for a data waiver, or citations without copies of literature.

Timeline, registration fees and other costs

Regulatory decision timelines for microbial pesticides under the Pesticide Registration Improvement Act (PRIA) are 18 months for a new active ingredient (AI) with a food use and requirement for a tolerance, 16 months for a new AI with a food use and tolerance exemption, and 12 months for a non-food use. Registration costs are $40,000, $25,000 and $15,000, respectively. (This compares to $330,000 for a synthetic chemical pesticide). However, under PRIA, collection of tolerance fees will not commence until October 2008.

Decision timelines for Experimental Use Permits are 9 months for a food use with a temporary tolerance exemption and 6 months for a non-food use permit. Costs are $10,000 and $5,000, respectively.

Decision time review periods begin 21 days after receipt date or when EPA receives the fee payment, whichever is later. In some cases, fee waivers are available, in particular if the application has gone through the IR-4 program, has a Federal or State Agency exemption, comes from a small business, or is a minor use application. Check http://www.epa.gov/pesticides/fees/ for details.

Registered pesticides are subject to annual maintenance fees, which can be, in certain circumstances, reduced or waived. There is a complex cost recovery formula for calculating the amount of the maintenance fee, which is detailed in FIFRA s. 4(i)(5).[15]

Importation

Importation of pesticides, including microbial products, is governed by FIFRA Section 17(c), which allows entry only to products registered in the U.S. The importer should submit a Notice of Arrival (NOA) of Pesticides and Devices to the appropriate EPA Regional Office.[16] Upon Regional Office approval, the NOA form is returned to the importer, and upon arrival of a shipment, the importer presents the approved NOA form to the district director of Customs at the port of entry.

The US Department of Agriculture (USDA) regulates importation of entomopathogens (fungi, bacterial, viral agents and nematodes) for small-scale experimental use (less than 10 acres). As mentioned above, large-scale testing and commercial use is regulated by the US EPA under FIFRA. If the entomopathogen is non-indigenous, USDA may require additional information on the purpose of the action, the biocontrol agent, the target pest and the environmental and economic impacts of release.

State jurisdiction

[15] See http://www.epa.gov/opp00001/regulating/fifra.pdf
[16] NOA forms can be downloaded from http://www.epa.gov/oppfead1/international/noalist.htm#D1

All products must be registered at the State level before being used in that State. In most cases, registration is a simple form-filling exercise, but in New York and California, there is a full risk assessment, and California requires and reviews efficacy data. Data is submitted to Californian authorities concurrently with submission to the EPA. In all other states, data submission and registration begins only after EPA registration is complete.

C. European Union

EU Directive 91/414/EEC is the major piece of legislation governing marketing and use of plant protection products, including microbial products[17], in the European Union. Data requirements for microorganisms are listed in Annex VIB of the Directive, and detailed in EC Directive 2001/36/EC.[18] Risk assessment principles and guidelines are also set out in Annex VIB to the Directive, which is currently available in draft form.[19]

Regulatory control of these pesticides in Europe is based on standards established for chemical pesticides. However, in recent years, a number of countries have introduced their own individual registration requirements to address the distinct characteristics of microorganisms. This has led to higher regulatory demands in individual countries, and hence to a lack of a harmonized approach, both for registration requirements and for interpretation of the data obtained. Annex VIB to Directive 91/414 is designed to harmonize requirements across the EU.

The EU regulatory process for pesticides is two-tiered. Active ingredients are assessed at the Community level for inclusion in Annex 1 of EU Directive 91/414/EEC. Products containing chemicals listed on Annex 1 must then be assessed and registered by Member States. Member State assessments need only consider areas relevant to the products that were not covered in the EU-level assessment.

Research Permits

There are no EU-wide guidelines, policies or data requirements with regard to research permits for microbial pesticides. Rather, procedures and requirements are country-specific.[20] In some countries, if the crop is destroyed and environmental release

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[17] The term "micro-organism" is used in the EU and is defined as follows: "A microbiological entity, cellular or non-cellular, capable of replication or of transferring genetic material". The definition applies to, but is not limited to, bacteria, fungi, protozoa, viruses and viroids

[18] Available on-line at http://europa.eu.int/smartapi/cgi/sga_doc?smartapi!celexplus!prod!DocNumber&lg=en&type_doc=Directive&an_doc=2001&nu_doc=36

[19] (Draft) Proposal for a Council Directive amending Annex VI to Directive 91/414/EEC as regards plant protection products containing micro-organisms. April 28, 2004.

[20] Consult individual Member States regarding this and other issues. Websites for the appropriate authorities are available at the following OECD website: http://www.oecd.org/document/15/0,2340,en_2649_34383_1933455_1_1_1_1,00.html

prevented, a permit is not required. Other countries may grant permits for small-scale release, based on submission of a small information dossier.

Regulation under other Directives

A microbial cannot be authorized in the EU if, as a result of expected use, it will

- contravene or exceed parameters for contamination of groundwater,
- exceed maximum permissible concentrations laid down by Directives 98/83/EC and Directive 2000/60/EC, or
- exceed parameters defined in Annex I of Directive 91/414 (normally 1/10 of the accepted dietary intake), whichever is the lower.

It also cannot be authorized if concentrations contravene drinking water quality parameters mandated in Directive 75/440/EEC.[21]

Pre-submission consultation

A pre-submission consultation is encouraged, though not required. While there is no prescribed data package that must be submitted to the regulator at this time, it is recommended that the meeting be scheduled early enough in the process of developing data to allow the technical advice received at the meeting and the other meeting outcomes to influence the development of the package to be submitted.

Required data

In Europe, microbial products generally have smaller dossiers than conventional chemical substances because they often rely on published literature to meet data requirements. As in Canada and the U.S., the most critical information is the characterization and identification of the MPCA. This information forms the basis of the human health and environmental effects assessment.

As in Canada and the U.S., data is required on[22]:

- Identity and biological, physical, chemical, and technical properties of the microorganism
- Physical, chemical and technical properties of the product
- Quality control of the product
- Efficacy

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[21] The Directives are available on-line at, respectively, http://europa.eu.int/eur-lex/pri/en/oj/dat/1998/l_330/l_33019981205en00320054.pdf; http://europa.eu.int/eur-lex/pri/en/oj/dat/2000/l_327/l_32720001222en00010072.pdf; http://europa.eu.int/comm/food/fs/ph_ps/pro/legal/dir91-414-eec_en.pdf; and http://europa.eu.int/smartapi/cgi/sga_doc?smartapi!celexplus!prod!CELEXnumdoc&lg=en&numdoc=31975L0440

[22] Data requirements are detailed in http://europa.eu.int/smartapi/cgi/sga_doc?smartapi!celexapi!prod!CELEXnumdoc&lg=EN&numdoc=52003PC0814&model=guichett

- Analytical methods
- Effects on human and animal health
- Fate and behaviour in the environment
- Effects on and exposure of non-target organisms

There is no comprehensive list of test guidelines to be used for generating data on microorganisms in the EU, so applicants are required to use U.S. and Canadian test guidelines appropriately modified to meet the EU data requirements. Applications for data waivers are encouraged; applicants should consult with the appropriate Member State authority. These would include statements that explain a certain type of data is not required because, for example, there will be no exposure in a certain environmental compartment.

If the microorganism is genetically modified, there are substantial additional regulatory requirements under separate GMO legislation. In this case, registration is granted only if it is has been judged acceptable under Directive 2001/18/EC that the organism be released into the environment. This Directive lists information requirements and procedures for assessment, and is available at http://europa.eu.int/comm/food/food/biotechnology/index_en.htm

Health testing

The purpose of health testing is to provide sufficient information to determine whether the MPCA will cause human health effects, including infectivity, pathogenicity and toxicity. Data requirements in this area are determined on a case-by-case basis. Tier I studies include basic information in these areas, while Tier II studies focus on specific areas of toxicity, pathogenicity and infectiveness studies, where further data is required.

Environmental Toxicology and Fate Testing

Data requirements in this area are designed to generate sufficient information to permit an assessment of the impact on non-target species. As in Canada and the U.S., a range of non-target species are tested, though, as can be seen in Table 1 , the range of species is wider in the EU. There is no formal tiered structure of data and testing requirements for environmental toxicology and fate studies; rather, further testing may be required on a case-by-case basis.

Efficacy testing

Product performance, including the level, consistency and duration of control, protection or other intended effects, must be comparable to suitable reference products, which should be used in trials for comparative purposes. If no suitable reference product is available, or if performance fails to meet the comparable standard, registration is still possible, if a case can be made for a defined benefit under the agricultural, plant health and environmental conditions in the area of proposed use.

As in Canada, regulators in the EU must ensure that the registered rates and number of applications represent the minimum amounts necessary to achieve the desired effect, even where higher amounts would not result in unacceptable risks to human or animal health or to the environment.

Submission package

Applicants should consult the Guideline on the Preparation and Presentation of Complete Dossiers for the Inclusion of Active Substances in Annex I of Directive 91/414/EEC, available at http://europa.eu.int/comm/food/plant/protection/resources/publications_en.htm. Each individual Member State has its own requirements for application packages, typically including a fairly extensive application form and a draft label, as well as the data listed in Directive 2001/36/EC. For details, applicants should consult the appropriate authority in each Member State. Dossiers must be formatted in accordance with OECD standards.[23] It is important that a dossier be complete in order to avoid delays.

The Registration Process

Registration of an MPCA or MPCP requires submission and evaluation of a dossier of data and information on the active substances (Annex IIB data) plus a representative formulation (Annex IIIB data). If the new MPCA is accepted, it will be listed in Annex I of Directive 91/414/EEC. The evaluation criteria with which plant protection products must comply are provided in Annex VI to the Directive.

New MPCAs are processed by a designated 'Rapporteur' Member State that is allocated to review the submission package. After Rapporteur review, there is a five-stage Peer Review Process; procedures for Peer Review are still under development at this time.[24] Some Member States have published their individual authorization procedures, with timetables set in law.

Submission categories

Individual Member States have designed a variety of schemes to classify submissions, set fees and establish review timelines for the various categories of submission. Consult individual Member States for details.

Timelines, registration fees and other costs

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[23] *Guidance for Industry Data Submissions for Microbial Pest Control Products and their Microbial Pest Control Agents (Dossier Guidance for Microbials), OECD Series on Pesticides No. 23.* Available at http://www.oecd.org/document/7/0,2340,en_2649_34383_32286855_1_1_1_1,00.html

[24] European Food Safety Authority, 2003. Proposal for the Peer Review of active substances used in plant protection products evaluated in the 2nd stage of the review programme.

The Rapporteur must publish a draft assessment report within one year of receiving a technically complete dossier. The subsequent peer review stages are more time-consuming and do not have legally enforceable timelines. However, under transitional arrangements, an applicant may be able to enter the market before listing on Annex I.

Registration fees vary between countries. Under a new UK pilot scheme, fees for microbial pesticides have been reduced from £40,000 to £22,500 (~$42,000 US), which compares to >£100,000 (~$187,000 US) for a conventional pest control product. In Sweden, the fee for a microorganism to be included in Annex I is 1,500,000 kroner (~$212,000 US), which compares to double that amount for a chemical active. Some countries also charge annual fees for maintaining the registration of a product. This varies between countries, but is typically a percentage of annual sales. In Sweden for example, the charge is 1.8% of the annual sales value for biological pesticides, and 2.6% for chemical pesticides.

It has been estimated[25] that the costs associated with bringing a new fungal biocontrol product to market are about $3 million US, with $1 million of this dedicated to registration-associated costs.

Importation

Importation regulations vary between countries. For example, in the UK, it is prohibited to use an imported product which is not approved in the UK. However, when such a product is identical to one available in the UK, a 'Parallel Import' approval may be obtained from the regulatory authorities.[26]

[25] Correspondence with Alison Hamer, Regulatory Project Manager, JSC International Ltd, UK.
[26] See http://www.pesticides.gov.uk/applicant_guide.asp?id=1254

Part II: Pheromones and other Semiochemicals

A. Canada

Legislation

Active ingredients and products which are pheromones or other semiochemicals or contain these substances as active ingredients, and which are used to affect the behaviour of arthropods are regulated by the Pest Management Regulatory Agency (PMRA) under the authority of the Pest Control Products Act (PCPA). Where a maximum residue limit is necessary for these active ingredients, it is established by the PMRA under the Food and Drug Act (FDA).

A *semiochemical* is defined as *a message-bearing substance produced by a plant or animal, or a synthetic analogue of that substance, which evokes behavioural response in individuals of the same or other species*.[27] Semiochemicals include allomones, kairomones, pheromones, and synomones. It should be noted that semiochemicals used in traps to attract and monitor arthropods, but not for direct pest control, are exempt from registration under the PCPA. More precise guidance on the kinds of semiochemicals which do and do not require registration under PCPA can be found in PMRA's document, PRO 2002-02: *Updated Procedures for Joint Review of Microbials and Semiochemicals*, available at http://www.hc-sc.gc.ca/pmra-arla/english/pdf/nafta/naftajr/nafta_jr_micro-e.pdf

Research Trials

There are two options for researchers wishing to conduct research trials: researchers can apply for research permits or for exemptions from a permit. Exemptions are available only for the control of arthropod pests on land. To qualify for an exemption, applications must meet all of the criteria in one or more of the three categories listed below:

1) pheromones contained in "affixed solid matrix dispensers or in retrievable sized polymeric matrix dispensers when applied in either food–feed or non-food–non-feed use areas, providing the treated area does not exceed 100 ha and the maximum use rate does not exceed 375 g a.i./ha/year"[28] (of Technical Grade Active Ingredient (TGAI) per research establishment).
2) pheromones applied in "non-food–non-feed use areas, providing that the treated area does not exceed 100 ha and the maximum use rate does not exceed 375 g a.i./ha/ year" (of TGAI per research establishment).
3) semiochemicals applied through any method with any application rate, with the following limitations:

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[27] NAFTA Technical Working Group on Pesticides, 2002. Updated Procedures for Joint Review of Microbials and Semiochemicals. Available at http://www.pmra-arla.gc.ca/english/pdf/nafta/naftajr/nafta_jr_micro-e.pdf

[28] The quotations in this section are from Regulatory Proposal PRO 2002:2, Guidelines for the Research and Registration of Pest Control Products Containing Pheromones, page 13-14, available at http://www.pmra-arla.gc.ca/english/pdf/pro/pro2002-02-e.pdf

a. For "*Unregistered* semiochemicals: research must involve only the researcher, and the treated area must not exceed 5 ha on land owned or operated solely by the research establishment, i.e., no cooperator participation."
b. For "*Registered* active ingredients (research on new sources, new formulations, or new uses): the treated area must not exceed 10 ha without restrictions on cooperator participation or land ownership."

A researcher requires a *research permit* if one or more of the following conditions are met:

- the product contains formulants not on the U.S. EPA Inert list 4A;
- application will be in aquatic areas;
- application will be aerial;
- the product will be directly applied to food or feed crops "when the raw agricultural commodity can be used for human consumption or animal feed" with the exception of products described in section 1) above; and
- "all of the criteria within one or more of the three exemption categories listed above have not been met."

Some provinces may require provincial permits to conduct trials. Researchers are responsible for applying to the provincial regulatory officials for such a permit.

Data Requirements for Research Trials

Research permits are Category E submissions, thus the following timelines are in place for a research permit for a new semiochemical active with a food use: 7 days for verification, 45 for screening and 365 for review.[29] For a new active with a non-food use and where the treated crop is destroyed, the review period is shortened to 165 days.

Applicants for a research permit are required to submit, inter alia, the following information before the intended trial:

- seven copies each of: the research permit application form; the statement of product specification form; a description of the dispenser; manufacturer's name and address; and proposed experimental label, including application rate and method of application;
- two copies each of MSDSs for non-active ingredients and the TGAI, if available; and the location and a map of the area to be treated;
- for each active ingredient:
    - common name, IUPAC name and CAS #;
    - structural and molecular formulae and molecular weight; and
    - manufacturing methods or methods of synthesis.

If the product will be used on food and feed for sale, additional information on physical and chemical properties may also be required.

[29] http://www.pmra-arla.gc.ca/english/pdf/pro/pro9601-e.pdf

If the product is intended for broadcast or spray application, acute toxicity data for freshwater invertebrates (e.g., *Daphnia* sp.), and freshwater fish (e.g., salmon or rainbow trout) is required. Without this information, an untreated buffer zone may be required adjacent to aquatic systems.

Data Requirements

Data requirements for registration of pheromones and other semiochemicals are currently harmonized at the OECD level. Because semiochemicals act not by killing pest species but by modifying behaviour, because they are target-specific, and because they are used at concentrations close to background levels and dissipate rapidly, most products pose a reduced risk to health the environment. Data requirements for these products and actives are therefore reduced compared to conventional chemicals. Further reductions in data requirements are available for straight-chained lepidopteran pheromones (SCLPs).

While data requirements for environmental and human health safety may be significantly reduced, requirements associated with chemical characterization are the same as conventional pesticides. For details, see PMRA Directive 98-03, *Chemistry Requirements for the Registration of a Manufacturing Concentrate or an End-Use Product Formulated from Registered Technical Grade of Active Ingredients or Integrated System Products*, available at http://www.pmra-arla.gc.ca/english/pdf/dir/dir9803-e.pdf.

Full data requirements for semiochemical TGAIs and EPs are outlined in Appendices I and II of PMRA PRO2002-2, *Guidelines for the Research and Registration of Pest Control Products Containing Pheromones and Other Semiochemicals*[30], respectively. Data screening tables are included as Appendix III (Tier I) and Appendix IV (Tiers II and III).

Request for *data waivers* are considered on a case-by-case basis, with consideration given to the nature of the product and the proposed use pattern, upon receipt of a scientific rationale accompanying the request.

Health Testing

Generally speaking, health testing involves two kinds of tests: those which determine toxicology characteristics, and those which determine expected levels of dietary, occupational and bystander exposure.

Toxicology testing is tiered. Tier I includes:

- acute studies,
- short-term studies,
- developmental studies,
- genotoxicity potential studies, and
- medical data.

[30] Available at http://www.pmra-arla.gc.ca/english/pdf/pro/pro2002-02-e.pdf

Additional testing may be required if Tier I results suggest toxicological concerns or the potential for human exposure of exposure of food. The need for higher tier studies is determined on a case-by-case basis. Studies may include:

- further short-term studies,
- long-term studies,
- developmental-reproductive studies,
- further studies on the potential for genotoxicity,
- metabolism studies,
- neurotoxicity studies, and
- special studies.

Exposure testing includes studies of occupational and bystander exposure (for the product only), and metabolism and residue studies (when the product is applied directly to food, feed or tobacco crops). The requirement for residue data may be waived in cases where a determination has been made that detectable residues are unlikely, or that residue levels are unlikely to exceed natural background levels during pest outbreaks, and that the residues are not toxic.

Environmental toxicology and fate testing

Environmental data is requested in order to assess the potential hazard towards terrestrial wildlife, aquatic animals, plants, and beneficial insects. Data is required only if product use results in environmental contamination greater than natural background levels. For example, for SCLPs, it is believed that application rates of up to 375 g SCLP/ha/year result in exposure levels comparable to background levels safe for nontarget species. For other semiochemicals, applicants are invited to request waivers of environmental testing, based on information which indicates that application rates are comparable to natural emissions.

Avian dietary toxicity is required only for formulations that might be ingested, e.g., granules. No terrestrial non-target testing is required, as human toxicology data is considered sufficient to assess potential effects on wild mammals. Nontarget terrestrial plant studies are required when there is reason to suspect possible effects. Aquatic invertebrate and fish toxicity data are required for direct application to aquatic sites for all semiochemicals, but not for fixed-point dispensers applied over land.

For nontarget insects, a discussion of available information, particularly on specificity to target insects, may be sufficient. The registrant should also report any adverse effects on nontarget insects noted during efficacy testing, particularly effects on insect predators or parasites of the target organism, species closely related to the target pest, and pollinators. For more details, consult PRO 2002-02: *Updated Procedures for Joint Review of Microbials and Semiochemicals*, available at http://www.hc-sc.gc.ca/pmra-arla/english/pdf/nafta/naftajr/nafta_jr_micro-e.pdf

Environmental data and testing requirements are structured in three tiers. Tier I involves acute studies on representative non-target aquatic species and, for semiochemicals other

than SCLPs, an acute avian study and an avian dietary study. Further tiers of testing are required when the results of Tier I testing indicate hazard to organisms. Tier II consists of environmental fate testing. If Tier II results indicate the potential for hazard to the environment or biota, Tier III tests on non-target species are required.

Efficacy testing

Applicants should include a description of the mode of action of the product, in terms of how it modifies pest behaviour. Information is also required to support the claim that the active is a naturally occurring arthropod semiochemical. Product trials, conducted according to the proposed label rate, application method, timing, and site of application, are required to support control claims listed on the product label. When possible, applicants should include treatment with a commercial standard product for purposes of comparison. At least one study should evaluate a range of rates in order to demonstrate the lowest effective rate of application.

Registration Process

It is strongly recommended that applicants meet with PMRA in a pre-submission consultation to ascertain the adequacy of available information, the need for additional trials, and the performance standard for registration.

For further details of the registration process, see the section on microbials above.

Joint Review

PMRA and the US EPA have established a process for joint review of products whose new active ingredient is an arthropod semiochemical, and the proposed use pattern is the same in both countries.[31] In addition, there must be a complete database available on the active ingredient to qualify for joint review. Requests for joint pre-submission consultations for a new microbial or semiochemical pesticide should be submitted in writing to Lisa Lange at the PMRA and Brian Steinwand of the US EPA.[32] Data packages to support submission, prepared according to the pre-submission consultation agreement, should be submitted to the same contacts. For more information and guidance concerning pre-submission consultations and other details of joint reviews, see the discussion on pre-submission consultations in the microbial pesticides section above and Appendix III - Joint Reviews.

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[31] See Updated Procedures for Joint Review of Microbials and Semiochemicals at http://www.hc-sc.gc.ca/pmra-arla/english/pdf/nafta/naftajr/nafta_jr_micro-e.pdf

[32] Contact information can be found in NAFTA Technical Working Group on Pesticides, 2002. Updated Procedures for Joint Review of Microbials and Semiochemicals, page 2, available at http://www.pmra-arla.gc.ca/english/pdf/nafta/naftajr/nafta_jr_micro-e.pdf

B. United States

Legislation

In the U.S., insect pheromones and other semiochemicals are classified as *biochemicals*, (along with microbial pesticides and plant-incorporated protectants, one of the three classes of biopesticides), and regulated under FIFRA, FFDCA and FQPA by the US EPA, specifically by the Biopesticide and Pollution Prevention Division (BPPD).

Because it is sometimes difficult to determine whether a substance meets the criteria for classification as a biochemical pesticide, EPA has established a special committee to make such decisions. See the US section on plant extracts or oils below for more details on the work of the Classification Committee. As in Canada, registration is not required for semiochemicals that are used to attract and monitor pests in fixed-location lures and with minimal impact on environment or human health. For further details on those semiochemical products (including pheromone-based products) which do and do not require registration see the presentation at http://ir4.rutgers.edu/RWP/PowerPoint/Wed-C.Adcock-R.Sjoblad%20History.pdf

Experimental Use Permits (EUPs)

Permits for field-testing of biochemicals are generally treated similarly to permits for field-testing of conventional chemicals.[33] Any use on a food or feed crop which will not be destroyed requires a EUP and a tolerance decision.[34] Non-food/feed uses do not require a permit if the test area is restricted to no more than one surface acre of water per pest or 10 acres of land per pest. Further qualifications to this exemption are described in 40CFR172.3. As well, there are two kinds of special circumstance that allow testing of semiochemicals on up to 250 acres without a EUP:

1. non-food uses of arthropod pheromones at a maximum use rate of 150 grams a.i./acre/year, and food uses in a solid matrix dispenser,
2. all food and non-food uses of certain straight chain Lepidopteran pheromones.

Data requirements for EUPs involving pheromone-based products are similar to those for microbial products. See Data requirements in the microbials section.

Data Requirements

U.S. data requirements for registration of pheromone-based products are largely identical to Canadian requirements. As for microbials, there are several tiers of data requirements for toxicology and non-target and environmental expression testing, and higher tier studies are triggered by adverse results in Tier I studies.

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[33] See 40CFR172.3 for details.
[34] See 40CFR180 for details.

Studies are required in the following categories:

- Product identity and composition
- Analysis and certified limits
- Physical and chemical characteristics
- Toxicology
- Residue data
- Nontarget Organism and Environmental Expression

While data requirements for pheromone products are often substantially reduced, a new pheromone product which is not an SCLP, is not in a trap, or may cause higher exposure to humans or food, has the same data requirements as other biochemicals.

Test guidelines for biochemicals are available at http://www.epa.gov/pesticides/biopesticides/regtools/guidelines/biochem_gdlns.htm

Health Testing

As in Canada, Tier I (required) tests for the technical active ingredient include the usual battery of acute studies plus studies on genotoxicity potential. Waivers may be available for these if supported by a sound scientific rationale. In most cases, Tier I toxicity testing is waived for pheromone products, based on a long history of a lack of adverse effects associated with their use.

Higher tier studies are triggered by toxicological concerns or the potential for exposure of humans and/or food, and include short-term studies, long-term studies, further genotoxicity studies, reproduction/development studies, neurotoxicity studies, metabolism studies and other studies as required. Tier I toxicology tests may be required of the end-use product if it contains a formulant of toxicological concern. MSDSs must be submitted for all formulant ingredients.

Full biochemical data requirements are listed, along with a description of the conditions under which they are required or when they can be waived, in the Code of Federal Regulations (40CFR 158.690), available at http://a257.g.akamaitech.net/7/257/2422/12feb20041500/edocket.access.gpo.gov/cfr_2004/julqtr/40cfr158.690.htm

Environmental toxicology and fate testing

Non-target organism testing requirements are normally waived for pheromone-based products.[35] Tier I environmental toxicology tests include:

- acute avian oral,
- avian dietary,
- freshwater fish LC_{50}

[35] See presentation at http://ir4.rutgers.edu/RWP/PowerPoint/Wed-S.Reilly.pdf

- freshwater invertebrate LC_{50} and, depending on the use pattern,
- nontarget plant studies, and
- nontarget insect studies.

Tier II environmental fate and expression tests are required if the product will be applied on land and Tier I tests indicate potential adverse effects on nontarget organisms. Further (Tier III) non-target tests will be required if Tier II tests show that the expected concentration in the environment is of concern to avian or aquatic species, or if the product (or its metabolites or degradation products) are persistent in the environment, or if Tier I tests indicate potential adverse effects on nontarget insects and Tier II results indicate exposure of nontarget organisms.

Registration Process

For details on the process of registration, see the microbials section above.

C. European Union

Pheromones and other semiochemicals[36] used in agricultural pest control are covered under the main EU Plant Protection Product legislation, Directive 91/414/EEC. The EU has adopted the harmonized OECD approach to data requirements for these products, in which there is a much reduced core chemical data set. Further reductions in data requirements are possible for Straight-Chained Lepidopteran Pheromones (SCLPs).

Data Requirements and Waivers

Data requirements for semiochemicals are listed in Appendix I of the OECD document, Guidance for Registration Requirements for Pheromones and other Semiochemicals used for Arthropod Pest Control, 2004, available at http://www.oecd.org/dataoecd/44/31/33650707.PDF

Data requirements are in some cases triggered by specific conditions, as are data waivers. The following headings are cases in point.

Product Analysis

- If the formulation process introduces or enhances impurities of toxicological concern, they should be identified along with upper limits and an enforcement analytical method for such impurities.

[36] defined as: "… chemicals emitted by plants, animals, and other organisms - and synthetic analogues of such substances - that evoke a behavioural or physiological response in individuals of the same or other species"

Toxicology

- If long-term exposure above background levels can be excluded or if a substance is a member of a well-characterized chemical group (e.g. SCLPs); studies of subchronic exposure may be waived.
- Forms of semiochemicals containing aromatic structures may be more toxic than the SCLPs; thus might potentially require long-term tests.

Dietary, Occupational, and Bystander Exposure

- If detectable residues on the consumable commodity are unlikely, or if residue levels are unlikely to exceed natural levels during pest outbreaks, and the residues are not toxic, applicants may present a scientific rationale for waiving residue data.

Environmental Risks

- If use results in environmental contamination exceeding natural background levels[37]; test data will be required. However, if information indicates that application rates are comparable to natural emissions, applicants may request waivers of environmental testing. Compared to conventional pesticides, fewer tests are required for semiochemicals and the number of organisms per test is reduced.
- If formulations have the potential to be ingested, *e.g.* granules, avian dietary toxicity data are requested.
- If products are applied directly to aquatic sites, one species of fish, an aquatic invertebrate and an algal species must be tested.
- For fixed point dispensers applied over land; aquatic testing is not required

Environmental Fate

- If ecotoxicology data or public literature indicate a hazard to non-target organisms, persistence data and data on off-site transport of the semiochemical may be required
- If the data indicate significant persistence and transport, such that significant exposure to non-target organisms could be expected, additional environmental testing is required.

Registration Process

The regulatory process for pheromones and other semiochemicals used for arthropod pest control in the EU is the same as that described above for microbial pest control products. See The Registration Process above.

[37] application rates up to 375 g SCLP/ha/yr are generally understood to result in exposure levels which are comparable to natural emissions and safe for non-target species

Part III: Arthropod Biological Control Agents

A. Canada

A researcher or pest manager who wants to import an arthropod biocontrol agent for agricultural pest management is required to petition the CFIA for an import permit.[38] The importation and release of non-indigenous, arthropod biocontrol agents used to suppress weeds is regulated under the Plant Protection Act (PPA) as a potential plant pest. Any organism that is directly or indirectly injurious to plants is considered to be a pest under the Act. Also, predators and parasites of phytophagous organisms may be considered indirect plant pests according to the Act, and thus, the import and release of entomophagous arthropods for biocontrol is also regulated by CFIA.[39]

Petition process

The petition and release proceeds as follows:

1. The applicant fills out the petition and provides supporting documents for phytophagous or entomophagous organisms, in compliance with North American Plant Protection Organization (NAPPO) guidelines.[40]
2. The applicant submits the petition to the CPQP (Centre for Plant Quarantine Pests) at the Canadian Food Inspection Agency (CFIA).
3. The petition is received by the Chairperson of the AAFC Biological Control Review Committee (BCRC), and proceeds to committee review. In the case of weed biocontrol agents, the petition is also sent to the USDA-APHIS (United States Department of Agriculture Animal and Plant Health Inspection Service) Technical Advisory Group (TAG).
4. The BCRC (and APHIS for weed biocontrol agents) submits comments to the BCRC Chairperson, who then makes recommendations to the CPQP Regulatory Entomologists. At this point the petitioner may be asked for more information if there are remaining questions about safety.
5. The CPQP Regulatory Entomologists summarize comments received and make a recommendation to the Director of the Plant Health and Production Division (PHPD), CFIA, forwarding the petition and all reviewers' comments.
6. The PHPD Director either sends a letter to the applicant outlining the reasons for rejection of the application, or gives permission with conditions for import. The Director may also ask the petitioner for further testing or experimentation.
7. With approval, organisms can be imported under permit through a containment facility, their health and identity confirmed, then released into the environment.

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[38] Permits are available on the CFIA website at http://www.inspection.gc.ca/english/for/pdf/c5256e.pdf

[39] Details of the permitting process can be found in the unpublished draft document, "Guide for the Importation, Release and Use of Arthropod Biological Control Agents in Canada"

[40] NAPPO, 2001. Guidelines for Petition for Release of Exotic Phytophagous Agents for the Biological Control of Weeds. http://www.nappo.org/Standards/OLDSTDS/RSPM7-e.pdf; NAPPO, 2001. Guidelines for Petition for Release of Exotic Entomophagous Agents for the Biological Control of Pests. http://www.nappo.org/Standards/OLDSTDS/RSPM12-e.pdf

Data requirements

Information required by CFIA in the petition includes:

- a statement of the proposed action;
- characteristics of the biology, regulatory status, distribution and economic impact of the target pest;
- the biology, source, known host organism(s), related species in the proposed area of introduction, and quarantine procedures for the biological control agent;
- environmental and economic impacts of the proposed release; and
- a plan for post-release monitoring.

The more information that is provided on the prospective biocontrol agent, including host specificity test results, host records, impact on target pest and known ecological interactions in place of origin, the easier it will be to produce a fair and accurate assessment of potential environmental and economic impacts of the agent once released. If the organism is highly host-specific, there will very likely be fewer direct non-target impacts. While predicting complex, indirect ecological interactions that may occur post-release are more difficult, and may only be revealed by post-release monitoring, the petitioner is required to make an attempt to predict some indirect non-target effects. The reviewer weighs the benefit, risk and cost of a release against the benefits, risks and costs of other pest control choices.

For weed biocontrol agents:
It is recommended that, prior to beginning testing, researchers who wish to implement a biocontrol program on an invasive weed species for the first time prepare and submit a proposed test plant list for review by the AAFC-Biological Control Review Committee (BCRC). In addition to helping set the direction of what may amount to many years of testing, an approved test list can prevent unnecessary testing of species.

For insect biocontrol agents:
Though North American Plant Protection Organization (NAPPO) guidelines do not require host-specificity testing prior to a petition for release of entomophagous arthropods, there are growing calls for it. Non-target concerns for release of insect biocontrol agents centre not only on the impact of introduced agents on indigenous arthropods, but also on previously introduced weed biocontrol arthropods. Thus, CFIA requests that candidate entomophagous agents be tested against existing weed biocontrol arthropods, especially if existing weed biocontrol arthropods are taxonomically similar to the target host and occur in areas where releases are being proposed.

Containment facilities

Containment facilities for the importation, rearing and handling of entomophagous and phytophagous exotic biocontrol organisms are certified in Canada according to NAPPO

protocols.[41] Certification of facilities is performed by Regulatory Entomologists at the CPQP. Any plan to construct a containment facility or modify an existing facility should be communicated as soon as possible to the CPQP.

Facility operators must provide specimens to AAFC's Central Experimental Farm in Ottawa for verification of identity prior to the release of the agent from the facility. In addition to the central facility in Ottawa, certified arthropod containment facilities can be found at Simon Fraser University in Burnaby, BC; the Canadian Forestry Service Centres in Victoria, BC and Sault Ste. Marie, Ontario; and at AAFC containment facilities at Lethbridge and Saskatoon. Since each importation is unique, and has unique requirements, it is important that arrangements for shipment be made ahead of time between the Regulatory Entomologists, the exporters, containment laboratory personnel, the systematists (taxonomists) and the importers.

Timeline and fees

The review and response to the petition for release of a phytophagous or an entomophagous agent takes an average of 6-12 months. However, the whole process, including testing, can take 3-10 years or longer for some classical biocontrol programs. There are two types of permit available: single permits, which allow a single importation, and multiple permits, which allow repeated importations of the permitted materials for up to one year. Fees for single permits are $35, for multiple permits, $60. The costs of getting a new agent approved, including foreign exploration, research and other processes are typically between $250,000 and $1 million.

Research exemption

Permits may be granted by CFIA to biocontrol scientists wishing to import candidate arthropods to a certified containment facility for study. In these cases, a permit application which provides a rationale for the proposed import is required, rather than a full petition. However, release is permitted only when a petition is reviewed and CFIA approval is granted. At the end of the process, successful petitions are granted an Issue Letter and permit with conditions for release.

Regulation under other Federal Acts

Regulation of arthropod biocontrol agents under the New Substances Notification Regulations (NSNRs) - Canadian Environmental Protection Act (CEPA)

The importation, use and manufacture of arthropod biocontrol agents is also regulated under the NSNRs, administered by Environment Canada.[42] Under the NSNR, any person in Canada who manufactures or imports a new arthropod BCA must provide a

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[41] NAPPO, 2004. Guidelines for Construction and Operation of a Containment Facility for Insects and Mites used as Biological Control Agents. http://www.nappo.org/Standards/NEW/RSPM%20No22-e.pdf

[42] The main reference source for this section is *Guidelines for the Notification and Testing of New Substances: Organisms, Pursuant to The New Substances Notification Regulations of the Canadian Environmental Protection Act, 1999.*

notification package to Environment Canada. In the context of the Canadian Environmental Protection Act, a 'new' substance means one that is not included on the Domestic Substances List (DSL) or added to the DSL because of notification through the New Substance Notification Regulations. The purpose of the notification and assessment scheme, which is jointly administered by Environment Canada and Health Canada, is to ascertain whether the organism is CEPA-toxic, and to ensure the protection of human health, the environment and biological diversity. To this point in time, no notifications have been received by Environment Canada for arthropod biocontrol agents (nor for microbial biocontrol agents).

Research exemption

An arthropod biocontrol agent that is an R&D substance and that is imported to or manufactured in a facility meeting the specified conditions for containment is exempt from notification.[43]

Definitions

Arthropods fit into the category of *organisms other than microorganisms,* which are defined as including all living organisms not captured in the definition of microorganism. *Microorganism* is defined in subsection 2(1) of the NSNR as *a microscopic living organism that is:*
a) classified in the Bacteria, the Archaea, the Protista, which includes protozoa and algae, or the Fungi, which includes yeasts;
b) a virus, virus-like particle, or sub-viral particle;
c) a cultured cell of an organism not referred to in paragraphs (a) and (b), other than a cell used to propagate such organism; or
d) any culture other than a pure culture.

Significant New Activity (SNAc)

A SNAc is defined in section 104 of CEPA 1999 as

in respect of a living organism, any activity that results or may result in
(a) the entry or release of the living organism into the environment in a quantity or concentration that, in the Ministers' opinion, is significantly greater than the quantity or concentration of the living organism that previously entered or was released into the environment; or
(b) the entry or release of the living organism into the environment or the exposure or potential exposure of the environment to the living organism in a manner or circumstances that, in the Ministers' opinion, are significantly different from the manner and circumstances in which the living organism previously entered or was released into

[43] The appropriateness of the containment facility is determined in accordance with guidance in the *Laboratory Biosafety Guidelines* or Appendix K of the U.S. National Institute of Health (NIH) document entitled *Guidelines for Research Involving Recombinant DNA Molecules.*

the environment or of any previous exposure or potential exposure of the environment to the living organism.

Use, manufacture or importation of a living organism for a SNAc is prohibited by Subsection 106(3) of CEPA 1999, where the organism is listed on the DSL with an indication that the SNAc provisions apply, while subsection 106(4) carries a similar prohibition for living organisms *not* listed on the DSL, but for which a notice has been published in the Canada Gazette indicating that the SNAc provisions apply.

CEPA includes SNAc provisions which allow new or existing living organisms to be listed on the DSL with an attached set of conditions for use. Under these provisions, an arthropod biocontrol agent can be imported, manufactured or used without notification, provided that there is compliance with the conditions stated in the SNAc notice. If the proposed importation, manufacture or use goes beyond the specified conditions, there is a requirement to provide specified information within the time frame stated in the DSL amendment. Gazetted SNAc notices for organisms which are ineligible for DSL listing allow the notifier to continue to import, manufacture or use without re-notification, provided that these actions are in accordance with terms specified in the SNAc notice. Persons other than the notifier who propose to import, manufacture or use the living organism are required to notify under the NSNRs.

Data requirements

For organisms other than microorganisms (which includes arthropod biocontrol agents), notifiers are required to provide the information prescribed in Schedule XIX of the NSNRs. This includes:

- identity, strain history and details of any modifications to the organism;
- biological and ecological characteristics of the organism;
- status of patent or other rights on the organism;
- manufacturers or importers information;
- estimate of quantity to be imported or manufactured;
- quality control and quality assurance methods;
- history of use, intended use, and potential locations of introduction;
- mode of action;
- procedures for introduction;
- recommended methods for terminating the introduction and disposing of remaining biomass and residues;
- environmental fate of the organism;
- ecological effects of the organism;
- potential for and mostly likely exposure route involved in adverse human health effects; and
- description of test procedures followed in developing testing data.

It is expected that most data required will be available in the scientific literature or in unpublished test lab or field studies. If available, the applicant should provide

information on the specific organism. If unavailable, a surrogate can be used (check with the NSN hotline at (800) 567-1999 on choice of surrogate).

Data Waivers

Waivers can be obtained via three different kinds of rationale:

- if the information is unnecessary to determine whether the arthropod BCA is toxic or capable of becoming toxic;
- if the arthropod BCA will be used for a prescribed purpose or manufactured at a location where it will be contained so as to satisfactorily protect the environment and human health; or
- in cases where generating the information is not practicable or feasible.

Waiver requests should be submitted along with applications, and granted waiver requests are published in the Canada Gazette.

Pre-Notification Consultation

Applicants should request a pre-notification consult with Environment Canada before submitting the final package. At this meeting, issues that may cause concern are discussed. A preliminary package should be prepared and submitted prior to the meeting. The package should provide sufficient information to give an informed response to the questions at hand.

Process and timeline

Environment and Health Canada have 120 days to assess the received information. The time clock begins when the Ministries receive a complete and correctly filled-out package. After a preliminary screen, which certifies that all required information has been received, an acknowledgement is sent out, specifying the start date of the assessment period and the NSN Reference Number. The assessment period may be extended once "for a length of time not exceeding the initial assessment period" when the applicant has been notified.

In cases where the arthropod BCA is suspected of being toxic or capable of becoming toxic, the Minister may, before the expiry of the assessment period,
(*a*) permit manufacture or importation, subject to specified conditions;
(*b*) prohibit manufacture or importation; or
(*c*) request the applicant to provide additional information or test results considered necessary to assess whether the organism is toxic or capable of becoming toxic.

Currently, no fees are charged for the notification and assessment process.

Endpoint

When a New Substances Notification has been processed by Environment Canada and accepted, the substance is added to the DSL, and a note to this effect is published in the Canada Gazette Part II.

B. United States

Regulation under Federal Acts

FIFRA: Under the Federal Insecticide, Fungicide, and Rodenticide Act, the US EPA has the authority to regulate arthropod biological control agents as pesticides, as well as the authority to exempt them from regulation if they are adequately regulated by other agencies. Currently, two other agencies have oversight over arthropod biocontrol agents: U.S. Fish and Wildlife, and the United States Department of Agriculture Animal and Plant Health Inspection Service (USDA-APHIS), although until the new Plant Protection Act came into effect, APHIS did not have statutory authority.

Endangered Species Act of 1973: Under this act, the Department of the Interior has jurisdiction over 'natural enemies' that threaten endangered species.

NEPA: The National Environmental Policy Act of 1969 requires that Federal agencies examine their actions for impact on the environment. Thus, APHIS must conduct an Environmental Assessment and either record a Finding of No Significant Impact, or undertake an Environmental Impact Statement before it issues permits for importation of new non-indigenous arthropod biocontrol agents (and other 'natural enemies').

Plant Protection Act: This act gives the USDA the authority to *"prohibit or restrict the importation, entry, exportation, or movement in interstate commerce of any plant, plant product, biological control organism, noxious weed, article, or means of conveyance, if the Secretary determines that the prohibition or restriction is necessary to prevent the introduction into the United States or the dissemination of a plant pest or noxious weed within the United States."*

Upon receipt of permit applications, APHIS makes a decision on whether an arthropod biological control agent poses a threat to US plants (other than weeds) as well as beneficial insects (for example pollinators, or other beneficial insects).

Currently, most but not all previously imported *commercial* arthropod biological controls are being granted permits to enter the United States. APHIS evaluation related to importation of new species *from the wild* for biological control in the United States is much more careful. Preliminary screenings are done offshore, especially for weed biological controls. Offshore screening of weeds entails testing the candidate biological control against crop plants and other desirable plants to determine if the biological control presents any risks to non-target plants. APHIS grants importation permits for experimental biological control agents with the provision that they are kept in an APHIS certified quarantine facility. A second permit must be obtained before these experimental organisms are released into the environment outside of quarantine. In the case of

biological controls for arthropods, APHIS requires data similar to that in the NAPPO Guidelines for Petition for Release of Exotic Entomophagous Agents for the Biological Control of Pests, and strong emphasis is placed on collecting disease-free, unparasitized specimens. For weed biocontrol agents, data requirements are consistent with NAPPO Guidelines for Petition for Release of Exotic Phytophagous Agents for the Biological Control of Weeds (see footnote #25).

The Permitting Process

For biocontrol agents of arthropod pests

If there is no movement of the biocontrol agent (BCA) across international boundaries and the BCA is not considered a plant pest, there is no regulation under the Plant Protection Act. If one or both of these contingencies applies, then the applicant must submit a petition entitled *Application and Permit to Move Live Plant Pests and Noxious Weeds* (Form 526) to the APHIS Plant Protection and Quarantine Division.[44]

Once APHIS receives the petition, it is determined whether the arthropod has been previously released and has posed any known harm. If there has been a previous release with no known harm, APHIS sends the permit application to State Plant Health Officials in the states where it is proposed that the agent be released. If State officials have objections, the permit is denied until the objection is dealt with, at which time the applicant can resubmit the application. If there are no objections, APHIS signs and dates the permit and issues an expiration date. Over the last decade, permit durations have ranged from 2 years to 10 years. The permit is then returned to the applicant, accompanied by stickers to place on the exterior of the box being shipped across the border.

If the arthropod has not been previously released, has been released and has posed known harm, or if APHIS believes that there is a potential for harm, additional information is requested, preferably in compliance with the NAPPO Guidelines for Petition for Release of Exotic Entomophagous Agents for the Biological Control of Pests.[45] Upon receipt of the petition, APHIS reviews it and solicits information from knowledgeable experts in order to determine if there is any risk to desirable non-target species or endangered species. If the decision is that there is no risk, APHIS writes an Environmental Assessment incorporating the applicant's data and data from its own experts. Permitting officials then decide if they can issue a Finding of No Significant Impact (FONSI). If the answer is yes, APHIS sends the permit application to State Plant Health Officials and asks if there are any objections to the granting of the permit. Any State objections must be dealt with before the permit can proceed. If there are no objections, or once they are satisfactorily addressed, APHIS grants the permit (as detailed above).

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[44] Permits and other relevant information are available at http://www.aphis.usda.gov/ppq/permits/biological/predators.html.

[45] http://www.nappo.org/Standards/OLDSTDS/RSPM12-e.pdf

If, on the other hand, permitting officials make the decision that a FONSI cannot be issued, then APHIS requests an Environmental Impact Statement (EIS). The EIS is written by APHIS with substantial input from the applicant and, on two separate occasions, pubic comments. If APHIS makes a decision that the impact is unacceptable, then the permit is denied. If it is decided that impacts are acceptable, then APHIS sends the permit application to the State Plant Health Official and asks if there are any objections to the granting of the permit. Any State objections must be dealt with before the permit can proceed. If there are no objections or once they are satisfactorily addressed, then APHIS grants the permit (as detailed above).

In addition, under the National Environmental Protection Act (NEPA), applicants who are federal employees, applicants who have received any federal funding as part of a proposed action, applicants who employ federal workers, or applicants who plan to release a non-indigenous agent onto federal land may need to prepare an Environmental Assessment. An Environmental Assessment (EA) is a public document that provides sufficient evidence to determine whether an EIS or a FONSI will be prepared, depending on the level of impact on the environment as a result of the proposed action. This document presents the potential positive and negative environmental impacts that may occur as a result of the release of a non-indigenous organism into the environment.

For biocontrol agents of weeds

Applicants for importation of a weed biocontrol agent are required to prepare a petition for release (PPQ Form 526) and send it to APHIS Plant Protection and Quarantine (PPQ). (It is highly recommended that, prior to application for an importation permit, the applicant send a proposed test plant list and consult with APHIS on the content of this list.) The petition is then sent to the Technical Advisory Group (TAG) Executive Secretary, who establishes timelines and sends the petition to the TAG members for review. (Applications for permits and other relevant information are available at http://www.aphis.usda.gov/ppq/permits/biological/weedbio.html). TAG Members review and evaluate, synthesize comments from subject matter specialists, and submit their comments and recommendations to the TAG Chair. The TAG Chair consolidates the recommendations, submits them to TAG APHIS PPQ and the petitioner, and then files the petition and recommendation with the USDA Agricultural Research Service (ARS) and the Biological Control Documentation Center.

If the TAG recommends release, the petitioner submits a permit application (PPQ form 526) [46] to APHIS Plant Protection and Quarantine (PPQ). APHIS PPQ sends the permit application to state officials in those States where release is proposed, who return it with comments. APHIS PPQ prepares an Environmental Assessment (EA), welcoming EA drafts submitted by the applicant, and notifies TAG of the results. If APHIS PPQ reaches

[46] The same form – PPQ 526 - is used both for requesting that a product be imported from its original site to a containment facility and for requesting release from quarantine to a specified field location. It is filled out differently for the two uses. If there were a subsequent desire to move the BCA from one state to another, the same form would be submitted again, specifying the state of origin and the destination state, as interstate transport of plant pests (which includes weed biocontrol agents by definition) requires a permit.

a Finding of No Significant Impact (FONSI), then the permit is issued. It takes 4 to 6 weeks from submission of the application to receive a permit. Approved biocontrol agents can be imported only into an adequate high-security containment facility in the United States.

If the APHIS PPQ does not make a FONSI, it advises the petitioner that an Environmental Impact Statement (EIS) is needed. Based on the EIS, the petitioner may either receive the permit or discontinue the effort. For more information on submitting a TAG petition, see the TAG Web page at http://www.aphis.usda.gov/ppq/permits/tag/.

If TAG does not recommend release, the petitioner may conduct more research, continue consultation on the test plant list, discontinue the effort, or elect to submit the permit application to APHIS.

In addition to submitting a TAG petition, it is recommended that applicants contact the Department of the Interior to be sure that threatened and endangered species are considered while forming a test plant list. The appropriate agency is usually the U.S. Fish and Wildlife Service (FWS), but sometimes the National Marine Fisheries Service (NMFS) must be consulted, depending on the nature of the proposed action. Both these agencies have the responsibility of enforcing the Endangered Species Act (ESA). Although an FWS representative participates on the TAG, this does not substitute for the ESA consultation process. Separate and direct contact with these agencies will facilitate the consultation process.

For Entomopathogens

Entomopathogens include bacteria, fungi, viruses and nematodes used for control of insects and mites. USDA regulates importation of entomopathogenic nematodes, while interstate movement is not regulated by any agency. The USDA also regulates imports intended for small-scale (less than 10 acres) laboratory or greenhouse experimental use. The Environmental Protection Agency regulates large-scale experimental use or commercial use of entomopathogens under FIFRA.

Importation of juvenile, indigenous, entomopathogenic nematodes

Though there appears to be some regulatory overlap between USDA and EPA with regard to nematodes, EPA has never regulated nematodes. Until recently, 'courtesy' permits were issued for a list of less than a dozen nematodes common in commercial use. Thus, based solely on identity and purity, USDA APHIS granted permits for importation.

Recently, however, APHIS PPQ has been receiving applications for new species or new strains, and have, since 2000, a new Act, the Plant Protection Act, which gives them the express authority to grant permits.

Both indigenous and non-indigenous entomopathogenic nematodes require a permit for importation into the U.S. In addition, a U.S. Fish and Wildlife Service Form 3-177[47] should accompany shipments at the port of entry. For non-indigenous species, information to be submitted with the application includes data on:

- the proposed action,
- the biological control agent,
- the target pest, and
- the environmental and economic impacts of proposed release.

For details, see
http://www.aphis.usda.gov/ppq/permits/biological/entomopathogens.html#indigenous

For indigenous species that are not ubiquitous in the US (e.g., if distribution is limited to Florida), there could be a need to submit the same data as for non-indigenous species. The environmental assessment (EA) process for non-indigenous species (and sometimes for non-ubiquitous native species) takes about 6 months, followed by a 30-day posting for public comment on the Federal Register.

A certificate of purity and identity from the country of origin must accompany all shipments. Permit applications must be submitted for all U.S. States to which the applicant plans to ship the nematodes. It is recommended that the permit applicant consult with other State and Federal agencies (e.g., U.S. Fish and Wildlife Service), to ensure that there is compliance with regulations administered by these agencies.

Data requirements

Form 526 requires information, inter alia, on:

- identity of the BCA,
- host materials,
- destination and date of arrival,
- intended use, and
- methods to prevent escape.

The *Environmental Assessment* requires information on:

- the purpose and need for the proposed action;
- a description of the alternatives available for controlling the pest;
- current control practices;
- a description of the affected environment;
- the environmental consequences of each alternative action; and
- a list of agencies and persons consulted.

[47] Available at http://www.le.fws.gov/pdffiles/3-177-1.pdf

A *biological assessment* requires information on the status and pertinent biological or ecological information for all endangered, threatened, and candidate species in the action area (not just plant species).

Timeline/fees

An applicant for importation of a BCA should apply for a permit at least 60 days before the expected shipment date. No fee is charged for processing the permit at this time, though user fees may be charged in the future.

State regulation of arthropod biocontrol agents

While states have the right to regulate these agents, oversight is quite limited. For example, the Florida Department of Agriculture requires voucher specimens for all incoming products and issues 4-year permits to primary producers. The operational objective of the Department has been summarized by one of its taxonomic entomologists as "to assure only clean, properly identified organisms be introduced into Florida."

Some states maintain regulatory authority over the movement of all insects but exempt beneficial insects from permit requirements, as in the California regulatory code. However, most states do not specifically regulate intrastate or even interstate movement of macrobial biological controls, but defer to USDA APHIS in the determination of which beneficial organisms should be allowed to move into the state from other nations.

In California, the Department of Food and Agriculture (CDFA) regulates all live insects and plant pests under the Food and Agricultural Code. Under the Code, a permit is required to import any live insect or plant pest into the state or to move any live insect or plant pest within the state, including those used for biological control purposes. Honeybees, weeds for identification, and beneficial or useful insects of common occurrence in the state are exempted. The Code contains a section which specifies which beneficial and useful insects are of common occurrence and exempt from the permit requirements, and also specifies that, in addition to the species named in the regulation, insects which have been introduced and previously released in California for biological control are also exempted from permit requirements. In addition, the Department often issues courtesy permits, upon request, to facilitate movement of permit-exempt species within the state.

C. European Union

There is currently no EU regulation required for the use of native arthropod biocontrol agents. For release of non-indigenous species, the FAO code of conduct must be followed.[48] Applications are considered at the Member State level. Assessments focus

[48] FAO, 1996. *International standards for Phytosanitary Measures: Code of conduct for the import and release of exotic biological control agents*, available at www.fao.org/docrep/x5585E/x5585e0i.htm. See also OECD 21 '*Guidance for Information Requirements for Regulation of Invertebrates as Biological Control Agents'* (2004).

on the likelihood of establishment and the potential impact of the release on ecosystems. OECD guidance is used to prepare this risk assessment.

Part IV: Plant extracts/oils and Food Grade Substances

A. Canada

Currently, PMRA has no separate regulatory framework nor established practices for the assessment and registration of pest control products whose active ingredient is a plant extract or oil (e.g., sesame, sesame oil, rosemary, rosemary oil, lemon grass oil, mustard oil), or a food grade substance (e.g., corn gluten meal, soybean oil). Rather, assessment and registration is carried out on a case-by-case basis, with waivers and published literature featuring prominently in the submitted data. For example, for the registration of corn gluten, PMRA waived the requirement to conduct new toxicity and environmental studies.[49] PMRA has established a small internal section that focuses on 'low risk' products, in order to address scientific issues and to develop a regulatory framework for these products. In addition, there is a new PMAC (Pest Management Advisory Committee) working group whose mandate is to address these issues.

Like microbials, plant oils and plant extracts are exempt from registration fees except for the $262 charge for label review. Annual maintenance fees are, like other registered pest control products, set at a maximum of $2,690.00 per registered product. For products with sales of less than $89,667.00, the maintenance fee is set at a maximum of 3% of sales with a minimum fee of $75.00 required.

B. United States

The Biopesticide and Pollution Prevention Division of EPA's Office of Pesticide Programs classifies pest control products whose active ingredient is a plant extract or oil and pest control products whose active is a food grade substance as biochemicals. The characteristics of biochemicals as defined by the EPA are:

- naturally occurring or identical to naturally occurring chemicals,
- typically used in low quantities (< 20 gm / acre), and
- having a nontoxic mode of action.

A synthetic active ingredient can be classified as a biochemical if it is structurally similar and functionally identical to a naturally occurring active ingredient. It should be noted that because a substance is "naturally occurring" does not mean it has a non-toxic mode of action, nor does having a non-toxic mode of action equate to a lack of toxicity to humans and non-targets. Some examples of non-toxic modes of action are:

- growth/developmental changes (plant growth regulators, insect growth regulators)
- lures/attractants/repellents (irritants)
- suffocation
- desiccation
- coatings
- systemic acquired response (SAR)-induction

[49] http://www.pmra-arla.gc.ca/english/pdf/reg/reg2003-09-e.pdf

The EPA has established a Biochemical Classification Committee which determines if an active submitted for registration will be regulated as a "biochemical". After receiving information from the applicant, the Committee conducts a preliminary review, then a full committee review, consults BPPD management, and sends a letter to the applicant with an explanation of the decision.

Information required for the classification includes:

- product chemistry
- identification of the active ingredient(s) structure
- CAS No. (if available)
- any other physical/chemical data
- evidence for natural occurrence
- evidence for non-toxic mode of action
- target pest
- method, rate, time of application
- human health data/information
- publicly available technical literature
- MSDS
- FDA GRAS status
- ecological effects

For more information on regulation of biochemicals, see the presentations at http://ir4.rutgers.edu/RWP/Agenda-Thur.htm

C. European Union

Plant protection products in which the active ingredient is a plant oil or extract or a food grade substance are regulated under the primary EU Directive for plant protection products, Directive 91/414/EEC. New active ingredients in these categories are assessed and registered similarly to other kinds of products or actives, with a Rapporteur taking responsibility for assessment, then proposing a registration decision (inclusion or non-inclusion in Annex I of 91/414EEC) at the EU-level. It is considered that the principles for semiochemicals are useful with respect to consideration of plant extracts and oils and food grade substances used in plant protection.[50]

While the required data set for plant oils and extracts is the same as that for chemical plant protection products, data waivers are available. A draft document outlining requirements for the following two categories of plant-based plant protection products, is available at http://europa.eu.int/comm/food/plant/protection/evaluation/plant_extracts.pdf

[50] The EU has adopted the OECD harmonized approach to regulation of semiochemicals, in which much of the core chemical data set can be reduced for semiochemicals that affect the behaviour of arthropods. See Guidance for Registration Requirements for Pheromones and other Semiochemicals Used for Arthropod Pest Control Available at http://www.olis.oecd.org/olis/2001doc.nsf/43bb6130e5e86e5fc12569fa005d004c/bf8feefe7a272650c1256b0600364359/$FILE/JT00121481.PDF

- Plant protection products made from one or several plants included in the reference list and mixed with water and plant protection products possibly with formulants added
- Plant protection products prepared with one or several ethanol/water based extracts made of plants included in the reference list and plant protection products possibly with formulants added.

Part V: Nematodes

A. Canada

Importation of nematodes for use as biological pest control agents (or for other uses) is regulated under the Plant Protection Act (PPA) by CFIA. Under the PPA, nematodes are regulated as direct or indirect plant pests. There is currently no regulatory oversight related to the use of native nematode species or products as biocontrol agents.

A researcher or other person wishing to import nematodes into Canada sends an application for an import permit to the Plant Health and Protection Permit Office of the CFIA.[51] After initial assessment, the application is forwarded to specialists at the Centre for Plant Quarantine Pests (CPQP). The permit form requires the applicant to provide information on:

- nematode species and origin,
- conditions of organisms intended for import,
- destination, and
- known distribution within Canada.

If the nematodes to be imported:

1) consists of species known to occur in North America, i.e.,
    a. *Steinernema* (= *Neoaplectana*) *carpocapsae*,
    b. *Steinernema* (= *Neoaplectana*) *feltiae* (= *bibionis*),
    c. *Steinernema* (= *Neoaplectana*) *glaseri*,
    d. *Steinernema riobravis*,
    e. *Heterorhabditis bacteriophora* (= *heliothidis*), or
    f. *Heterorhabditis megidis,* and
2) are produced by suppliers of established reputation (so far, only European),

then importers receive a permit without condition, essentially a courtesy permit. Also, US suppliers of nematodes and nematode products do not require a permit. Currently, only insect control products, and not mollusc control products, are being granted permits.

If the nematodes to be imported do not meet these criteria, the application is evaluated, like other applications for importation of arthropod biocontrol agents, i.e., on the basis of the potential for both direct and indirect impacts on plant health, and includes a consideration of the hazards associated with plant pests, parasites and pathogens; host materials or other means of transport; and indirect impacts such as nematode agents which negatively influence pollinator populations.

Once the permit application is received, it is evaluated by CPQP; recommendations are then forwarded from CPQP to the Plant Health and Protection Permit Office, who are responsible for issuing permits with conditions of importation indicated, maintaining records of permits issued, providing access to permits issued to ports-of-entry and Import Service Centres, and accepting fees.

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[51] Permits are available at http://www.inspection.gc.ca/english/for/pdf/c5256e.pdf

There are three possible outcomes of the permitting process: permits may be granted, they may be granted with conditions of entry intended to mitigate risks identified during assessment, or they may be denied.

Importers may also receive permits for importation of other nematode species under conditions of containment and control. The process for importation into containment is the same as for other import permits. However, CFIA's policy in this case is to err on the side of caution, i.e., if the presence of a species in Canada is unconfirmed, introduction will be discouraged by requiring containment conditions which would prevent environmental release, and commercial intentions will not be issued a permit. It is also recommended that the applicant contact the PMRA for information on current policy with regard to commercial use and registration of nematode-based products.

Invertebrates and microorganisms (including nematodes) that have been determined through pest risk analysis not to pose a quarantine risk, listed in Appendix 1 of Policy Directive 96-14[52], are exempted from the requirement for an import permit, as are organisms registered as fertilizers and biological control agents.

There are no defined review or processing timelines for import permits. Rather, assessors try to provide recommendations to the permit office as quickly as possible. An application for imports destined for scientific research costs $15 while applications for other purposes cost $35.

B. United States

For regulation of nematode biocontrol products in the U.S., see above under Entomopathogens**.**

C. European Union

There is no registration process for nematode pest control products in the EU. Importation and release of nematodes used for agricultural pest control is currently regulated in the same way as for other arthropod biological control agents.[53]

[52] The Directive is available at http://www.inspection.gc.ca/english/plaveg/protect/dir/d-96-14e.pdf and Appendix I is available at http://www.inspection.gc.ca/english/plaveg/oper/orglste.shtml

[53] There is a proposal currently being drafted by the Directorate General for Health and Consumer Protection which aims to bring nematode pest management products under the definition of 'plant protection products' as regulated by Directive 91/414/EEC, and have them subject to similar data requirements. The plan is for the proposal to be presented to the European Commission in the fall of 2005. (Correspondence with Wolfgang Reinert, DG Health and Consumer Protection, March 16, 2005.)

Appendix I – Comparison of regulatory systems for microbial pesticides

	CANADA	US	EU
Definition	Microbial pest control agent: *A microorganism (bacterium, alga, fungus, protozoan, virus, mycoplasma or rickettsia and related organisms) and any associated metabolites, to which the effects of pest control are attributed.*	Microbial pesticides include microbial entities such as bacteria, fungi, viruses, and protozoans.	Micro-organism: *A microbiological entity, cellular or non-cellular, capable of replication or of transferring genetic material.* *The definition applies to, but is not limited to bacteria, fungi, protozoa, viruses and viroids.*
Requires submission of efficacy data	YES - Product performance compared to stated performance claims and, where possible, to a 'registered commercial standard treatment.'	NO (but efficacy data must be kept on-file by registrant and produced on request from EPA). Also, efficacy data is required for conditional registrations.	YES - Product performance compared to a suitable reference product or products where available and/or untreated control
Review timeline	12 months	18 months	Draft assessment reports are published within a year of receiving complete dossier, while the following peer review stages are slower and do not have legally enforceable timetables. Company can enter market before the product is listed in Annex I of Directive 91/414/EEC (a list of all plant protection products registered in the EU) under transitional arrangements.
Requirements for GE microbials	Standard data package plus data on: * Nature and Expression of Introduced or Modified Genetic Material * Taxonomy and Characterization of Recipient and Donor Microorganisms * Construction of the Recombinant Microorganism	Standard data package plus data describing: * Complete characterization of the technology used to construct the GMO and an analysis of the organism's ability to inadvertently transfer the inserted DNA to other microorganisms and other organisms, and * Use of antibiotic	Many differences. Consult Directive 2001/36/EEC for details

	* Phenotypic Characterization of the Modified Microorganism	markers (Registrants are actively looking for alternatives)	
Provincial / state / Member state registration	Provinces regulate use through classification and permitting processes. No registration and/ or assessment process.	All States require registration. CA and NY have full risk assessment, with CA requiring efficacy data (this may be dropped in future – check with CA Department of Pesticide Regulation). Other states mostly require product analysis, label and contact info. CA assessment is concurrent with EPA – all others wait until EPA registration is achieved.	After inclusion in Annex I of Directive 91/411/EEC, Member States conduct their own assessment process, concentrating on areas not thoroughly covered in the EU-level assessment.
Registration fees (new AI)	$262 CAN	$15,000 or $25,000 US (respectively, new AI *without* food use and new AI *with* food uses but with exemption from tolerance)	Varies between member states: under new UK pilot scheme, fee is £22,500 (~ $42,000 US) as opposed to >£100,000 (~ $187,000 US) for a conventional chemical pesticide. Fee in Sweden is approximately $212,000 US.
Legislation covering/impacting	Pest Control Products Act (PCPA), Plant Protection Act (PPA) (for importation of microbial cultures), and Food and Drug Act (FDA) (for MRLs)	Federal Insecticide, Fungicide and Rodenticide Act (FIFRA), Federal Food, Drug and Cosmetic Act (FFDCA) (for MRLs) and Food Quality Protection Act (FQPA). Possibly the Endangered Species Act and Migratory Birds Act (EPA registration is one-window process encompassing these concerns)	Directive 91/414/EEC with various amendments, or Biocides Directive.
Waivers available or reduced data requirements	Toxicology and environmental fate requirements are reduced substantially compared to synthetic chemicals. Also, microbials are exempt from the requirement	Toxicology and environmental fate requirements are reduced substantially compared to synthetic chemicals. Also, most biopesticides are exempt from the	Scientific rationales for data waivers are encouraged. Information and direction in Directive 91/414 Annex VIB (final text available, not yet published).

	for an MRL.	requirement for a tolerance or MRL.	
Data requirements codified in what documents	Regulatory Directive 2001-2: Guidelines for the Registration of Microbial Pest Control Agents and Products [54]	40 CFR (Code of Federal Regulations) 158.740[55]	Commission Directive 2001/36/EC (amending 91/414/EEC)[56] If the microorganism is genetically modified, additional data requirements are listed in Directive 2001/18/EC.[57] *USEPA Guidelines* for *Microbial Testing are acceptable*
Test guidelines	Detailed in Directive 2001-2	Available on-line[58]	There are no comprehensive lists of test guidelines for microorganisms, so applicants are required to use US and Canadian test guidelines appropriately modified to meet the EU data requirements. Awaiting OECD harmonized guidelines.

[54] http://www.pmra-arla.gc.ca/english/pdf/dir/dir2001-02-e.pdf

[55] http://a257.g.akamaitech.net/7/257/2422/12feb20041500/edocket.access.gpo.gov/cfr_2004/julqtr/pdf/40cfr158.740.pdf

[56] http://europa.eu.int/smartapi/cgi/sga_doc?smartapi!celexplus!prod!DocNumber&lg=en&type_doc=Directive&an_doc=2001&nu_doc=36

[57] http://europa.eu.int/eur-lex/pri/en/oj/dat/2001/l_106/l_10620010417en00010038.pdf

[58] http://www.epa.gov/pesticides/biopesticides/regtools/guidelines/index.htm

Appendix II - Joint Reviews

Most microbials are registered in Canada through the Joint Review Process.

To be eligible for a joint review, the active ingredient must be a new active in both Canada and the U.S., must share common use patterns and formulations in both countries, and must have a complete database of information available.

An information package, to be submitted 90 days before a joint pre-submission consultation, must include the following elements:

- a cover letter requesting a joint pre-submission consultation (letter should identify company contacts in both countries);
- formal letters from EPA and PMRA, consenting to consultation during joint review and agreeing to public announcement of the submissions;
- a draft label;
- an ingredient list for the proposed product, including active ingredient and formulants;
- short summaries of available data on efficacy, safety to the environment and human health, and scientific rationales for proposed data waivers;
- identity of organism; survivability; manufacturing methods; potential health or environmental issues; protocols of studies if they differ from standardized protocols described in guidelines.

At the joint pre-submission consultation, decisions are made on which agency will take the lead and what the timeframes will be, as well as decisions on data requirements and data waivers. The meeting will also identify which part of the review process each Agency is responsible for.

Joint reviews have a 12-month review period.

For more information, see http://ir4.rutgers.edu/RWP/PowerPoint/Tue-L.Hollis.pdf and http://www.pmra-arla.gc.ca/english/pdf/nafta/naftajr/nafta-jr-pest-e.pdf

Appendix III - Keys to a Successful Registration Effort

- Achieve consensus with agencies on specific data requirements. Pre-registration meeting is critical
- Submit a complete dossier:
    - microorganism's characterization
    - conduct all agreed-upon studies
    - well-written justification for waivers
    - high quality data and reports
    - lack of negative effects in the database
- No major changes in formulation or manufacturing process
- Maintain close follow-up and continued coordination with Agency.