Biopesticide Registration Improvement Course

Human Health and Safety Assessment of Microbial Pest Control Products: PMRA Approach

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Resources

- Regulatory Directive DIR2001-02, “Guidelines for the Registration of Microbial Pest Control Agents and Products”
  - http://www.hc-sc.gc.ca/cps-spc/pubs/pest/_pol-guide/dir2001-02/index-eng.php
- Regulatory Directive DIR2007-02, “First Aid Labelling Statements”
  - http://www.hc-sc.gc.ca/cps-spc/pubs/pest/_pol-guide/dir2007-01/index-eng.php
- Evaluation Templates
  - http://www.hc-sc.gc.ca/cps-spc/pest/registrant-titulaire/prod/templates-modeles-eng.php

List of Abbreviations

CR	conditionally required
DACO	data code
DAR	draft assessment report (EU)
DER	data evaluation record (EPA)
EP	end-use product
EPA	United States Environmental Protection Agency
EU	European Union
MSDS	material safety data sheet
MPCA	microbial pest control agent
MRL	maximum residue limit
PAI	pure active ingredient
R	required
TGAI	technical grade active ingredient

Human Health and Safety: Tier I Studies

Title/Animal Species	Dose	Test Material
Acute oral tox/infect/path: Rat (preferred)	single high dose (10^8 MPCA units/animal)	TGAI
Acute pulmonary tox/infect/path: Rat (preferred)	intratracheal instillation of single high dose (10^8 MPCA units/animal)	TGAI
Injection (IV/IP) infectivity: Newly weaned mouse or hamster	single high dose (10^7 MPCA units/animal) injected intravenously	MPCA/PAI
Acute dermal toxicity: Rabbit	single high dose (2g/kg bw) applied to ~ 10% of body surface area for a 24-h exposure	EP
Dermal irritation study: Rabbit	single dose (0.5 mL or 0.5 g/animal) applied to small area (6 cm^2) for a 4-h exposure	EP
Reporting hypersensitivity incidence	all MPCAs are considered potential sensitizing agents	MPCA/PAI or EP

Conditionally Required Tier I Studies

- Additional data are required for certain MPCAs
  - Tissue or cell culture testing for baculovirus preparations
  - Genotoxicity or cytoxicity testing (cell cultures) of extracts for fungi and actinomycetes, especially if MPCA is intended for direct application to food crops

Human Health and Safety: Exposure

- Occupational exposure data/studies are not required for microbials
  - Detailed description of proposed use patterns (e.g., rates and methods of applications) and label instructions will be used in conjunction with toxicity/infectivity data to identify appropriate mitigative measures (i.e., PPE, REI, etc.) aimed at protecting workers and bystanders, including sensitive subpopulations

- No crop residue data, or MRL exemption waiver/petition, are required to support use on food crops
- An MRL does not need to be established for an MPCA if:
  - Characterization data indicate the lack of potential for production of known mammalian toxin(s)
  - Acute oral infectivity/toxicity testing reveals no significant human health concerns

Addressing Requirements

- PMRA strongly recommends presubmission consultations for microbials to identify required and conditionally required data as well as non-required data elements
  - PMRA prepares a customized data requirement (DACO) table (valid for 2 years)
  - DACO table must be submitted with the registration application to facilitate the screening/completeness check
- Test data/information requirements identified during presubmission consultation denoted by "R" or "CR"

Addressing Requirements

- "R" means data/information are required:
  - Actual test data on the MPCA
  - Published scientific literature
  - Surrogate information or bridging data to another strain/species, if both belong to a well-known (familiar) taxon
  - A rationale to waive the requirement for the MPCA because it is unnecessary or impractical
- "CR" means data are conditionally required if specified conditions are met or could be triggered based on results of required tests

Area(s) for Improvement: Data Issues

- Test substance not clearly identified in study report
- Inappropriate test material (PAI, TGAI, EP) and test concentrations selected
- Not enough raw data to allow for independent analysis by PMRA evaluators

Area(s) for Improvement: Labelling Issues

- Standard statements not followed as per Registration Guidelines (DIR2001-02) or First Aid Labelling directive (DIR2007-01)

- Always require “POTENTIAL SENSITIZER” and “CAUTION - EYE IRRITANT” (if no eye irritation study submitted) on principal display panel for microbials

Scientific Rationales for Data Omission (Data Waivers)

- Not every data requirement (DACO) for registration may be applicable or appropriate for an MPCA
- On a case-by-case basis, PMRA will consider written requests from applicants to waive certain data requirements
  - Applicants must provide rationales based on sound scientific reasoning accompanied by supporting evidence (e.g., studies on related strains/species) to address the underlying concern behind the data requirement

Scientific Rationales: Tips

- Avoid submitting rationales for all human health studies
- Some studies may be easier to consider scientific rationales for than others
  - Example: combine dermal toxicity and irritation into one study
  - Infectivity requirement may be waived for a particular route of administration, but NOT for all routes
- In rationales, include a discussion on:
  - Toxicity of metabolites/toxins
  - Toxicity of manufacturing impurities
  - Toxicity of formulation ingredients for EP studies

☞Additional PPE may be required

Scientific Rationales: Supporting Information

- Surrogate data
  - Data on a related strain or species
  - Relationship of tested strain to the MPCA must be well described
- Discussion of MPCA's mode of action, known pest/host range, temperature growth range, natural occurrence, ecological niche(s) and natural routes of exposure to humans (including the diet)
- Information on the effects of formulation ingredients/impurities
  - Material Safety Data Sheets (MSDS)
  - Published literature

Scientific Rationales: Supporting Information

- Literature search results in relevant databases
  - BIOSIS, PubMed, Biological Abstracts, AGRICOLA, TOXLINE, etc.
  - Include key search words
- Published scientific literature
  - Legible copies must be submitted
  - Certified translations in either English or French, if applicable

Scientific Rationales: Published Literature

- Multiple papers addressing a single data requirement should be accompanied by a literature review summarizing all the papers and demonstrating how each one addresses the data requirement

- Make sure all the necessary information required for verification is available in each published study submitted

Parting Advice

- e-Index of submitted data/studies
  - Ensure submitted test data and scientific rationales, including all supporting documents (e.g., published papers) are properly segregated in the e-Index Builder (i.e., each paper must be separately entered so that it is assigned a PMRA ID Number)
- PMRA encourages use of the OECD microbial evaluation templates (DERs) to prepare study protocols and create study reports
  - Submission of populated DERs by applicants will facilitate the registration review process
- PMRA encourages submission of foreign reviews (e.g., EPA DERs, EU DARs) of studies/data to facilitate the review process

THANK YOU!