



NAFTA Technical Working Group on Pesticides
Grupo de Trabajo Técnico del TLCAN sobre plaguicidas
Groupe de travail technique de l'ALENA sur les pesticides

Microbial Pesticides – Health Assessment

Brian Belliveau, Ph.D., HED - PMRA

Michael T. Watson, Ph.D., BPPD - EPA

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Purpose of testing is to determine:

- ◆ Pathogenicity potential of the MPCA and microbial contaminants
- ◆ Infectivity/pattern of clearance/unusual persistence of MPCA and microbial contaminants
- ◆ Potential toxicological effects of the MPCA, of microbial contaminants, and of preparation by-products
- ◆ If further data (e.g., higher tier toxicity, short-term and/or chronic studies) are required to fully assess risks



Key Risk Considerations

◆ Tier I Tests

- ❖ Acute Oral Toxicity/Pathogenicity/Infectivity
- ❖ Acute Pulmonary Toxicity/Pathogenicity/Infectivity
- ❖ Acute Injection Toxicity/Pathogenicity/Infectivity
- ❖ Cell Culture (Viral Agents Only)
- ❖ Genotoxic Potential (Fungi/Actinomycetes)

- ❖ Acute Dermal Toxicity
- ❖ Dermal Irritation
- ❖ Primary Eye Irritation
- ❖ Reporting of Hypersensitivity Incidents

◆ Exposure Assessment

◆ Food and Feed Residue Studies



Waiver Requests

- ◆ EPA and PMRA will waive data requirements on a case-by-case basis, depending on use-pattern and nature of the MPCA
- ◆ Requests for data waivers must be submitted in writing and based on sound scientific reasoning



Waiver Requests

◆ **Waiver requests must:**

- ❖ explain why the data requirement should be waived
- ❖ describe any unsuccessful attempts to generate the required data
- ❖ furnish any other information that may support the request
- ❖ suggest alternative means of obtaining data to address the underlying concern of the requirement



Published Literature

- ◆ All requirements must be supported by relevant data and/or referenced scientific literature; legible copies of the papers must be submitted
- ◆ If assumptions on human health and safety rely heavily on published scientific literature, the relationship of referenced strains to the MPCA proposed for registration must be well described
- ◆ Bridging data to support claims of safety may be acceptable in some cases
- ◆ Information on the effects of inerts/formulants must also be addressed (e.g., MSDSs)



Substance to be Tested

- ◆ MPCA must be identical and equivalent in form and growth stage to that tested for all other parts of the registration requirements
- ◆ Test material should be from the same lot throughout the duration of the test; if not feasible, then all lots should be as nearly identical as practical



Substance to be Tested

- ◆ If contamination is probable, each lot sample should be tested for composition; identification and limits of microbial and other contaminants must be established
- ◆ Type of test substance (e.g., TGAI, EP) is specified in each test guideline



Special Design Considerations

- ◆ Pre-test viability or activity of test material
- ◆ Microbial contaminants identified and levels quantified
- ◆ Observation period: 21 days or longer/shorter depending on type of MPCA and pattern of clearance (absolute clearance/ elimination not required, but steady decline in numbers detected is)



Special Design Considerations

- ◆ Sufficient number of animals must be treated to allow for adequate controls and for interim sacrifice
- ◆ Appropriate measures must be taken to minimize potential for contamination or cross-contamination between treatments



General Study Requirements

- ◆ Detailed clinical examination of all animals at least once daily
- ◆ Body weight measurements taken just before dosing, weekly thereafter and at scheduled or unscheduled death
- ◆ Gross necropsy of all animals performed at scheduled or unscheduled death and all gross pathological changes must be recorded
- ◆ Microscopic examination of target organs, or organs showing evidence of gross pathology may yield useful information



General Study Requirements

- ◆ For all infectivity studies, infectivity or persistence must be assessed by a suitably sensitive method to detect the presence of the MPCA in tissues, organs and body fluids; report recovery (CFU/gm tissue) and sensitivity of the detection method



General Study Requirements

- ◆ Pattern of MPCA clearance must be established in all infectivity studies by examining:
 - ❖ liver, spleen, kidneys, heart, brain, blood, gastrointestinal tract, lungs, mesenteric and mediastinal lymph nodes, intraperitoneal fluid, and where appropriate, from lesions and the inoculation site
 - ❖ other tissues, organs and body fluids may have to be examined as indicated by the nature of toxic and pathogenic effects observed



General Study Requirements

- ◆ A sufficient number of animals for interim sacrifice must be included to establish a pattern of clearance adequately
- ◆ For acute oral infectivity and toxicity studies, feces from the test animals should also be collected after dosing and at regular intervals during the study period to establish the clearance pattern



General Study Requirements

- ◆ Organ weights
- ◆ Data obtained from control animals may be required depending on the Tier I test, including: vehicle control, inactivated MPCA control, untreated (non-dosed) control, shelf control and, if available, historical control data



Acute Infectivity and Toxicity Studies

◆ Acute oral

- ❖ OPPTS Guideline 885.3050
- ❖ single high dose of TGAI (10^8 MPCA units/animal)* administered by gavage
- ❖ rat

◆ Acute pulmonary

- ❖ OPPTS Guideline 885.3150
- ❖ intratracheal instillation of single high dose of TGAI (10^8 MPCA units/animal)*
- ❖ rat

* equals approximately 3.5×10^{10} CFU/person



Acute Infectivity (IV or IP) Studies

- ◆ Intravenous injection (bacteria and viruses)
 - ❖ OPPTS Guideline 885.3200
 - ❖ single high dose (10^7 MPCA units/animal) of purest form of the MPCA
 - ❖ injected intravenously
 - ❖ rat or mouse



Acute Infectivity (IV or IP) Studies

- ◆ Intraperitoneal injection (fungi and protozoa)
 - ❖ OPPTS Guideline 885.3200
 - ❖ single high dose (10^7 MPCA units/animal) of purest form of the MPCA available
 - ❖ injected intraperitoneally, but will accept intravenous injection if possible with MPCA;
 - ❖ rat or mouse



Acute Dermal Toxicity

- ◆ OPPTS Guideline 885.3100
- ◆ Single high dose (2 g/kg bw) of the EP applied to approx. 10% of body surface area for a 24-h exposure
- ◆ Rabbit
- ◆ Infectivity testing not routinely required unless characterization data indicate MPCA is closely related to a known dermatophyte



Irritation Studies

◆ Acute dermal irritation

- ❖ OECD Guideline #404 or EPA OPPTS Guideline 870.2400 for chemical testing
- ❖ single dose (0.5 mL or 0.5 g per animal) of the EP applied to small area (6 cm²) for a 4-h exposure
- ❖ rabbit

◆ Acute eye irritation

- ❖ OECD Guideline #405 or EPA OPPTS Guideline 870.2400
- ❖ single dose (0.1 mL or 100 mg) of the EP applied to the conjunctival sac of one eye per animal
- ❖ rabbit



Reporting of Hypersensitivity Incidence

- ◆ Testing not normally required for MPCAs, as most contain substances that would elicit a positive response in test animals
- ◆ All MPCAs are considered potential sensitizing agents and PMRA requires "POTENTIAL SENSITIZER" to be displayed on the principal display panel of the label
- ◆ Require reports of any incidents of hypersensitivity observed during production, testing and manufacturing as well as after registration



Tissue Culture (Viral Agents Only)

- ◆ Viral MPCAs may be infectious to mammalian cells
- ◆ Purpose is to assess the capability of the viral agent for infection (overt, persistent, latent or abortive), transformation and toxicity;
OPPTS 885.3500



Tissue Culture (Viral Agents Only)

◆ Cell lines include:

- ❖ human cell line (WI38)
- ❖ primary cell type (foreskin)
- ❖ primate continuous line (monkey CV-1)
- ❖ Syrian hamster embryo (SHE/SA7) system
recommended for transformation assay if infectivity
demonstrated



Genotoxic Potential (Fungi/Actinomycetes)

- ◆ If characterization data indicate potential for MPCA to produce a known genotoxin (e.g., aflatoxin), an appropriate and sensitive analytical test (e.g., HPLC) must be conducted to confirm the absence of the toxin in the product



Exposure Assessment

- ◆ Use-pattern and worker/bystander exposure potential used to develop product label precautionary statements, guidance (e.g., PPE) and decontamination procedures
- ◆ Additional data only required if existing information inadequate to address potential safety concerns related to pathogenicity, hypersensitivity, dermal irritation



Exposure Assessment

- ◆ Recommend individuals involved in manufacture and application undergo medical examination prior to exposure and at regular intervals thereafter
- ◆ Report any significant clinical findings related to exposure to the Agencies



Food and Feed Residue Studies

- ◆ A Tolerance/Maximum Residue Limit will not be set for an MPCA if:
 - ❖ characterization data indicate the lack of potential for known mammalian toxin(s)
 - ❖ acute oral infectivity/toxicity testing reveals no significant human health concern
- ◆ If a mammalian toxin is present, the product will be subject to the same data requirements as a chemical pesticide to establish a tolerance/MRL

