



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 – Product Characterization and Analysis

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Approach

Detailed information on characteristics and biological properties of an MPCAs significantly influences the nature and extent of data required to assess its safety to human health and the environment



Origin, Derivation and Identity

- ◆ identification to lowest possible taxonomic position, serotype, composition, and strain, or by any other appropriate specific means to distinguish the MPCA from related microorganisms and known pathogens
- ◆ common, alternative and superceded names
- ◆ origin of the MPCA (e.g., soil, clinical, food), geographical location, isolation procedure, and history of the strain during product development



Biological Properties

- ◆ Natural occurrence of MPCAs (e.g., geographical distribution, preferred or obligate hosts, habitats, ecological niche)
- ◆ Target organisms: infective/toxic dose, mode of action, transmissibility
- ◆ Host range (including other pest species)
- ◆ Description of MPCA life cycle
- ◆ Description of plasmids or other extrachromosomal elements involved in pesticidal activity, pathogenicity, toxicity



Biological Properties

- ◆ Physiological properties (e.g., growth temperature range, redox potential, pH, nutritional dependence, susceptibility to antimicrobial agents used in human or veterinary medicine, tolerance to adverse environmental conditions)
- ◆ History of use
- ◆ Relationship to known pathogens of plants, vertebrates, invertebrates or other organisms
- ◆ History and relationship to any known human dermatophyte



Biological Properties

- ◆ If MPCA is closely related to a known toxigenic human pathogen, demonstrate that no mammalian toxins are produced or present in the TGAI/EP
- ◆ For fungi and actinomycetes, address potential for genotoxin production (e.g., aflatoxin), based on relationship to genus/species known to produce genotoxins
- ◆ Information on reported adverse effects related to human exposure (based on extensive search of published literature)



Manufacturing Process and Quality Assurance (QA)

- ◆ Details required on manufacturing methods and QA program including:
 - ❖ Preservation and maintenance of the production strain to ensure consistency and integrity of the MPCA production strain
 - ◆ MPCA strain identity must be verified upon regeneration of long-term stock cultures (e.g., RAPD, isozyme analysis, biochemical characterization)
 - ◆ MPCA must be deposited in an internationally recognized culture collection



Manufacturing Process and Quality Assurance (QA)

- ◆ Manufacturing processes for TGAI and EP
 - ❖ critical process points (preparation of culture media, inocula, scale-up production, pilot and/or commercial scale) cultivation, harvest, concentration and processing of final culture, formulation methods, packaging and storage)
 - ❖ measures taken to ensure consistent quality and limit extraneous contamination (chemical and biological)



Manufacturing Process and Quality Assurance (QA)

◆ QA program to include:

- ❖ quality control (QC) tests and criteria i.e., product release standards, that determine whether a product will be released for commercial use
- ❖ details of sampling programs including procedures, sample size, frequency and statistical validity
- ❖ measures taken when release standards not met



Manufacturing Process and Quality Assurance (QA)

◆ QC tests include:

- ❖ integrity of MPCA (standard, specific and sensitive chemical, serological or biological tests)
- ❖ product guarantee or certification of limits (in units of potency or biological activity per unit weight or volume)
- ❖ contaminant screening (toxins, microorganisms and pathogens, etc.)
- ❖ representative QC data from 5 production batches (pilot-scale batches may be acceptable)



Disclosure of Ingredients

- ◆ Product specifications/confidential statement of formula
- ◆ Potency estimation and product guarantee
- ◆ Discussion of formation of unintentional ingredients



Product Specifications

- ◆ Product Specification Form / Confidential Statement of Formula for TGAI and EPs
 - ❖ list all intentionally added ingredients (inerts/formulants)
- ◆ PSF and CSF must include:
 - ❖ type of formulation
 - ❖ nature and percent (by weight) of each ingredient, including identity (e.g., CAS No.) and purpose (e.g., emulsifier, diluent, stabilizer, preservative) in formulation
 - ❖ name and address of basic manufacturer
 - ❖ variation in percent composition of the MPCA preparation and inerts/formulants



Product Specifications

- ◆ Submit a Material Safety Data Sheets (MSDS) or manufacturer's specification, as well as technical information, on all inerts/formulants
- ◆ If toxicological characteristics of an inert/formulant suggest a potential human health or environmental hazard (e.g., endocrine disrupter), submit rationale as to why its use in the formulation is necessary and why it should not pose a significant risk



Potency Estimation and Product Guarantee/Certification of Limits

- ◆ Guaranteed amount of MPCA must be expressed in units of potency or other expression of activity (e.g., biological, genetic, biochemical, serological) per unit weight or volume
- ◆ Analytical methods to verify activity must be described in detail, including standardization, sensitivity, reproducibility and statistical validity (with representative data)
- ◆ One or more methods to express guarantee or verify certified limits of the MPCA may be required (e.g., plate counts, infectivity assays)



Unintentional Ingredients

- ◆ Theoretical discussion on formation of:
 - ❖ allergens, microbial toxins, other toxic metabolites
 - ❖ mutant strains
 - ❖ microbial contaminants especially potentially infective or antagonistic forms
 - ❖ side products from chemical reactions employed in the manufacturing process, fermentation residues from the growth of bacteria or fungi
 - ❖ extraneous host residues from viruses produced in cell cultures, whole animals or other living forms
 - ❖ residues of contaminants remaining after purification or extraction
 - ❖ impurities in chemicals used in the manufacturing process



Analytical Data and Methodology

- ◆ Detailed methodologies and validated data required for detection, identification, enumeration or quantification of:
 - ❖ active ingredient
 - ❖ related metabolites
 - ❖ impurities
 - ❖ contaminants



Analysis for Active Ingredient or MPCA

- ◆ Methodologies for detection, isolation, enumeration, quantification of the entire microorganism, parts thereof, or specific chemical components or metabolites



Analysis for Active Ingredient or MPCA

- ◆ Apart from those used to estimate potency, more than one method may be necessary to:
 - ❖ distinguish MPCA from other closely related strains or unmodified forms for GEMs
 - ❖ monitor the active or relevant metabolite during production
 - ❖ quantify doses for infectivity and toxicity testing
 - ❖ enumerate viable forms of the MPCA in tissues



Analysis for Microbial Contaminants

- ◆ Presence of microbial contaminants must be checked during the manufacturing process and in the TGAI and EP (5 batches)
- ◆ Suitable indicator organisms include: total aerobes, total coliforms, fecal coliforms, fecal streptococci/enterococci, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Salmonella* spp., *Shigella* spp., *Vibrio* spp., and yeast and molds



Analysis for Microbial Contaminants

- ◆ Levels of contaminant microorganisms must not exceed those consistent with product safety and performance. It may be necessary to set limits for some microbial contaminants
 - ❖ must demonstrate an absence of primary human pathogens



Analysis for Microbial Contaminants

- ◆ Methods and criteria for contaminant testing should be consistent with international standards for food or related microbial products (e.g., supplements, probiotics)
- ◆ Recommend methods accepted by the International Commission on Microbiological Specifications for Foods (ICMSF), the Association of Official Analytical Chemists (AOAC) or other internationally recognized body



Analysis for Microbial Contaminants

- ◆ Details of the chosen methods (e.g., microbe-specific/selective growth media) used to assay for microbial contamination must be submitted and the validity, specificity, sensitivity and reliability of the detection method must be reported



Analysis for Other Unintentional Ingredients

◆ Toxic or sensitizing substances

- ❖ toxic or sensitizing substances that may be present at any stage of the manufacturing process must not exist in the final EP or exist in quantities too small to pose any hazard (to humans or other nontarget mammalian species)
- ❖ precise and detailed methodologies for identification and analysis



Storage Stability Testing

- ◆ Require studies to determine appropriate storage conditions and expiry date on label. Factors for consideration in study design:
 - ❖ Maintenance of physical properties of EP (e.g., suspendibility, wettability, viscosity, etc.)
 - ❖ Maintenance of certified limits of activity (potency)
 - ❖ Influence of environmental parameters (e.g., temperature, light, moisture content)



Physical and Chemical Properties

- ◆ Physical state
- ◆ Density, bulk density or specific gravity
- ◆ Viscosity
- ◆ Corrosion character, ie., oxidizing or reducing action
- ◆ Suspendibility, wettability and moisture content

