

Environmental Protection Agency-EPA

EPA Registration Biochemical – Product Chemistry

<http://www.epa.gov/fedrgstr/EPA-PEST/2007/October/Day-26/p20828.htm>



Biological Pesticides (*40 CFR §180.65*)

- Unique modes of action
- Low use volume
- Target species specificity, or
- Natural occurrence



Biochemical Pesticides [*40 CFR §180.65 (a)*]

- Semiochemicals
- Plant and insect growth regulators,
and
- Enzymes



Biochemical Classification Committee

- *“When necessary the Agency will evaluate products on an individual basis to determine whether they are biochemical or conventional chemical pesticides”*
- 40 CFR §180.65(a)
- Necessary to distinguish between biochemicals and conventionals so that they can be reviewed in the appropriate Division



Biochemical Classification Data

- Generally are naturally-occurring substances
- Non-toxic mode of action against the target pest



Biochemical Classification Criteria

- A synthetic active ingredient can be classified as a biochemical if it is structurally similar, and functionally identical to, a naturally-occurring active ingredient



Biochemical Pesticides

- “Naturally-occurring” does not presume a non-toxic mode of action
- “Non-toxic mode of action against target pest” does not presume a lack of toxicity to humans and non-targets



Non-Toxic Modes of Action

- Growth/developmental changes (PGRs, IGRs)
- Lures/Attractants/Repellents (Irritants)
- Suffocation
- Dessication
- Coatings
- Systemic Acquired Response (SAR)- Induction



Other Criteria

- Potential Effects on Non-target Organisms
- No or low Persistence in Environment
- Low application rates/volumes
- Efficacy



Biochemical Classification Committee

Classification Process

- Receipt of Information
- Preliminary Review and Summary
- Full Committee Review
- Division Management Concurrence
- Letter to Applicant with Explanation of Decision



Information/Data Needed for a Successful Classification (I)

- Product Chemistry
 - Identify 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



Information/Data Needed for a Successful Classification (II)

- Target Pest
- Method, Rate, Time of Application
- Human Health Data/Information
 - Publically-available technical literature
 - MSDS
 - FDA GRAS Status
- Ecological Effects



Biochemical Classification Committee

Membership

Biochemical Pesticides Branch

- Biologist
- Chemist
- Environmental Scientist
- Microbiologist
- Toxicologist
- Registration Division
- Antimicrobials Division



Product Chemistry Data Requirements

- First, most important step in science review
- Required for ALL biochemical products
- Integrated System vs. Non-integrated System
- Biochemical Pesticide Product Analysis Data Requirements [Table in 40 CFR 158.690 (b)]



Product Chemistry Data Requirements

- Product Identity and Composition
- Manufacturing Process
- Discussion of the Formation of Impurities
- Five-batch Preliminary Analysis
- Certified Ingredient Limits
- Analytical Methods
- Physical and Chemical Properties

NOTE: *Read the Footnotes*****



Product Identity and Composition

- Data/Information regarding the active ingredient (a.i.) formulated product (TGAI, MP, EP)
 - Chemical Name (IUPAC and synonyms)
 - Structure, CAS No., Source, Manufacturer
 - MSDS, Other literature sources
- Other (inert) Ingredients*

*present in the formulated product



Manufacturing Process

- Information of ALL Starting Materials
 - MSDS, Source/Manufacturer
- Amounts of each ingredients (lbs, kg) used in a typical batch
- Complete description of the manufacturing process, including all chemical reactions (if any)
- Flow chart
- QA/QC procedures



Discussion of the Formation of Impurities

- Identify and discuss impurities present in formulated product (TGAI & EP) $>$ or $=$ 0.1% by weight
 - Carryover from starting materials
 - Side reactions amongst a.i. and other ingredients
 - Degradation products
 - Migration from packaging or formulating
 - Equipment
- Any impurities of potential/actual toxicological significance



Five-batch Preliminary Analysis

- Required for each TGAI in the formulated product
- Identify and quantify a.i.(s) and other/impurities
- Conducted at point in production/formulation process at which no further chemical reactions are intended.



Certified Ingredient Limits

- Legally-binding range of concentrations for each ingredient in formulated product
- Based upon five-batch analysis
- May also be proposed by registrant based on wgt %s of added ingredients
 - Must consider variability due to manufacturing process, stability of product on storage
 - Include an explanation/rationale for proposed limits



Certified Ingredient Limits

- Certified limits should be within the ranges established in the table found in 40 CFR 158.175 (b)(2)

<u>Nominal Concentration</u>	<u>A.I</u>	<u>Limits</u>
N \leq 0.1%		+/- 10%
N \geq 1% to $<$ 20%		+/- 5%
N \geq 20 to 100%		+/- 3%



Analytical Methods

- Not an “Enforcement Method”
- Method Used to Conduct Five-batch Preliminary Analysis
- Required Data:
 - Complete description of method
 - Precision and Accuracy Data
 - Representative chromatograms/GC-MS
 - Some validating data



Physical and Chemical Properties

- Color
- Physical State
- Odor
- Melting Point
- Boiling Point
- Density, Bulk Density, Specific Gravity
- Solubility
- Vapor Pressure
- Dissociation Constant



Physical and Chemical Properties

- Oct/Water Part. Coeff.
- pH
- Stability
- Oxidizing/Reducing Action
- Flammability
- Explodability
- Storage Stability
- Viscosity
- Miscibility
- Corrosion Characteristics
- Dielectric Breakdown Volt.



Environmental Protection Agency-EPA

EPA Registration Microbial Product Chemistry



Biological Properties

- Natural occurrence of organism (e.g., geographical distribution, preferred or obligate hosts, habitats, ecological niche)
- Target organisms: effective dose, mode of action, transmissibility
- Host range (including other pest species)



Biological Properties

- Description of 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



Biological Properties

- Relationship to known pathogens of plants, vertebrates, invertebrates or other organisms
- History and relationship to any known human dermatophyte



Biological Properties

- If organism 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



Biological Properties

- 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 production organism
 - Organism strain identity must be verified upon regeneration of long-term stock cultures (e.g., RAPD, isozyme analysis, biochemical characterization)
 - Should be deposited in an internationally recognized culture collection



Manufacturing Process and Quality Assurance (QA)

- Manufacturing processes for active ingredient and formulated product
 - 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 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 organism (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, CFU/g, virions/g, etc.)



Manufacturing Process and Quality Assurance (QA)

- Contaminant screening (toxins, microorganisms and pathogens, etc.)
- 5 Batch analysis-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

- Confidential Statement of Formula
 - List all intentionally added ingredients (inerts/formulants)
- 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



Product Specifications

- CSF must include:
 - Name and address of basic manufacturer
 - Variation in percent composition of the 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 (List 1 inerts-most concern List 4 inerts Least concern)



Potency Estimation and Product Guarantee/Certification of Limits

- Guaranteed amount of active ingredient 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)



Potency Estimation and Product Guarantee/Certification of Limits

- One or more methods to express guarantee or verify certified limits of the active ingredient 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



Unintentional Ingredients

- 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

- Apart from those used to estimate potency, more than one method may be necessary to:
 - Distinguish organism 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 organism in tissues



Analysis for Microbial Contaminants

- Presence of microbial contaminants must be checked during the manufacturing process and in the active ingredient and formulated product (5 batches)



Analysis for Microbial Contaminants

- 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 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 formulated product (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
- Suspendibility, wettability and moisture content

