Biopesticides Registration Improvement Course

Human Health and Safety Assessment of Microbial Pesticides 4.2

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Microbial Pesticides Branch

OVERVIEW

Risks to Human Health are Based on Toxicity & Exposure from Proposed Uses & Use Sites

Toxicity Studies are Required to Identify Hazards that Could Increase Risks to Humans

OVERVIEW

- Microbial Pesticides Data Requirements are Tiered
- Tier I Includes
  - Acute Toxicity
  - Pathogenicity
  - Hypersensitivity Incidents
  - Cell Culture
  - Eye and Skin Irritation

OVERVIEW

- Acute Toxicity Evaluates a Single High Dose
- Acute Tox Studies Endpoint = LD50
  - Basis of Precautionary Label Statements
  - Support Tolerances/Exemptions
- Routes of Exposure Evaluated are Based Upon Exposure from Proposed Uses & Use Sites
  - Inhalation
  - Dermal
  - Oral

OVERVIEW

- Pathogenicity Studies Evaluate the Potential for Microbial Pesticide to be Pathogenic in Humans
- Acute Tox/Pathogenicity Endpoint = Clearance, Infectivity
- Routes of Exposure Evaluated are Based on Exposure from Proposed Uses & Use Sites
  - Oral
  - Inhalation
  - Intraperitoneal
  - Intravenous

OVERVIEW

- Toxicology Data Requirements for Microbial Pesticides are Codified at 40 CFR § 158.2140
  - **TGAI, Manufacturing & End-Use Products**
  - **Requirements Based on Uses, Use Sites**
  - **Conditionally Required Studies - End-Notes Describe Conditions**
- Each data requirement must be satisfied with acceptable study, alternative data, or data waiver

OVERVIEW

Triggers for Higher Tier Testing:

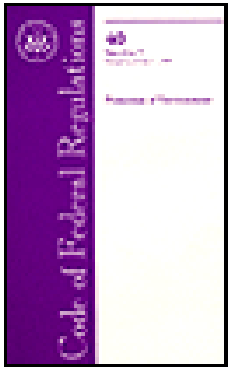
- **Infectivity, Unusual Persistence**
- **Pathogenicity**
- **Toxicity**

→ Indication of these signs can warrant additional subchronic testing to determine if repeated exposure is sufficient to cause toxic or pathogenic effects.

References- Human Health Data Requirements

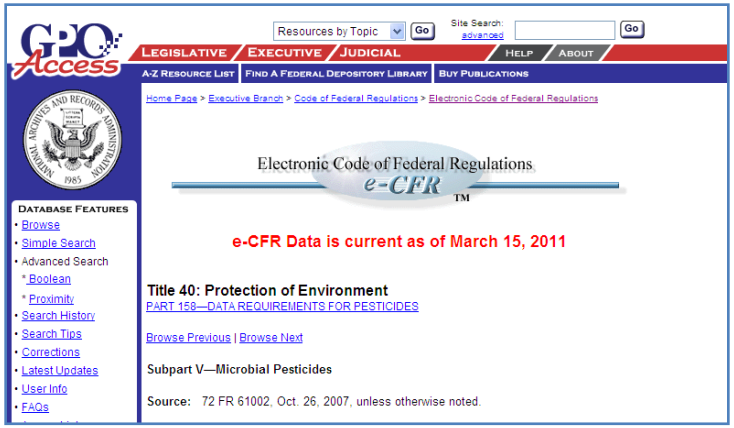
Described in 40 CFR § 158.2140

http://edocket.access.gpo.gov/cfr_2010/julqtr/pdf/40cfr158.2140.pdf



Electronic Version of CFR

http://ecfr.gpoaccess.gov/cgi/t/text/text-idx?c=ecfr&sid=328fd5c712107f745addfb8d4d30ae32&rgn=div6&view=text&node=40:23.0.1.1.9.16&idno=40



References: Microbial Pesticides Data Requirements (40 CFR § 158.2140)

Guideline Number	Data Requirement	All Use Patterns	Test Substance	Test Notes
Tier I				
885.3050	Acute oral toxicity/pathogenicity	R	TGAI	1
885.3150	Acute pulmonary toxicity/pathogenicity	R	TGAI	--
885.3200	Acute injection toxicity/pathogenicity/ (intravenous) Acute injection toxicity/pathogenicity/ (intraperitoneal)	R	TGAI	2
885.3400	Hypersensitivity incidents	R	All	3
885.3500	Cell culture	R	TGAI	4
870.1100	Acute oral toxicity	R	MP , EP	1, 5
870.1200	Acute dermal toxicity	R	MP , EP	5
870.1300	Acute inhalation toxicity	R	MP , EP	5, 6
870.2400	Acute eye irritation	R	MP , EP	5
870.2500	Primary dermal irritation	R	MP , EP	5

References: Microbial Pesticides Data Requirements (40 CFR § 158.2140)

Guideline Number	Data Requirement	All Use Patterns	Test Substance	Test Notes
Tier II				
885.3550	Acute toxicology	CR	TGAI	7
885.3600	Subchronic toxicity/pathogenicity	CR	TGAI	8
Tier III				
885.3650	Reproductive fertility effects	CR	TGAI	9, 13
870.4200	Carcinogenicity	CR	TGAI	10, 13
870.7800	Immunotoxicity	CR	TGAI	11, 13
885.3000	Infectivity/pathogenicity analysis	CR	TGAI	12, 13

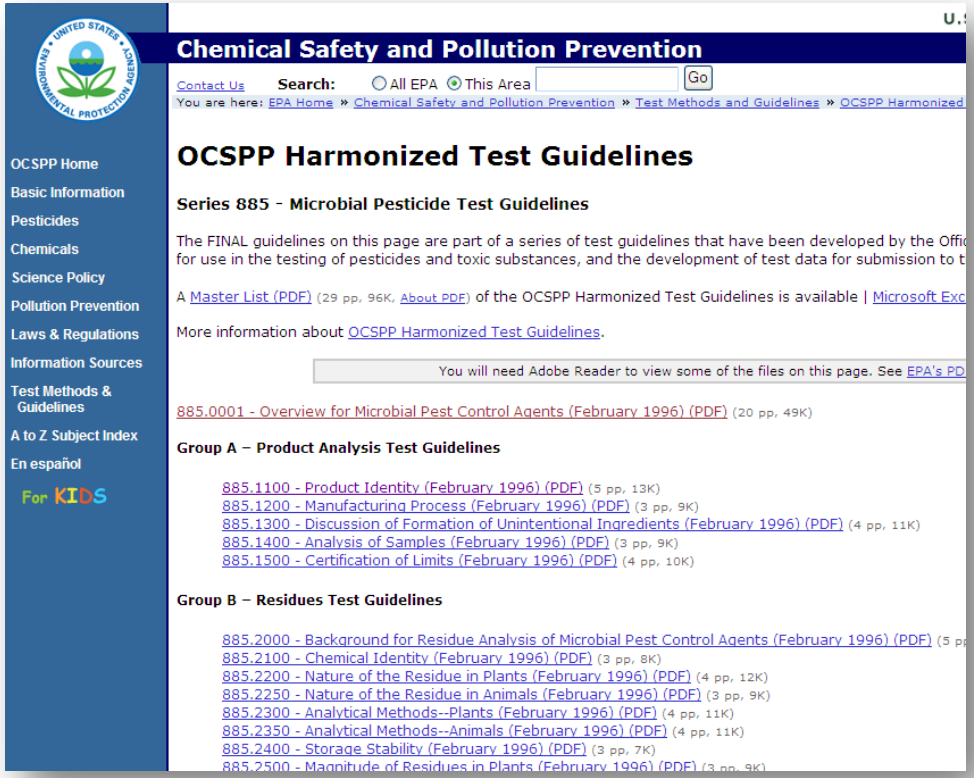
OVERVIEW

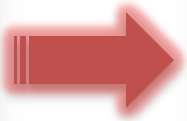
Test Guidelines

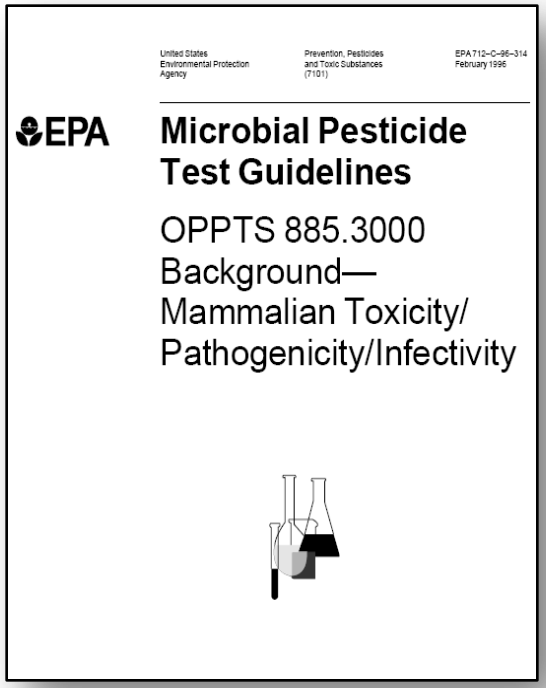
- Each requirement has associated harmonized test guideline (OCSPP Series 885 and 870)
- Criteria for standards of acceptability
- Study parameters and test end-points are established
- Guidance on evaluation and proper reporting of data;
- References are cited to provide useful information for designing test protocols

NOTE: Registrants can submit a proposed test protocol for EPA comments before study execution.

OCSPP Test Guidelines for Human Health Toxicity Studies (Series 885 and 870)







http://www.epa.gov/ocspp/pubs/frs/publications/Test_Guidelines/series885.htm
http://www.epa.gov/ocspp/pubs/frs/publications/Test_Guidelines/series870.htm

Common Problems - *Administrative*

- GLP Compliance (or Not)?
- Insufficient details of test materials/methods
- Alternative data referenced but not submitted
- Insufficient information on impurities

Solutions - *Administrative*

- GLP Compliance Must Be Addressed & True
- Methods should be valid and "reproducible"
  - Include Materials, Equipment
- Describe Test Material
  - Source, Concentration of AI
  - Viability
  - Purity
  - Stability
- Include cited references in submission

Common Problems - *Scientific*

- **Administration of Test Substance**
  - **Wrong test substance (TGAI vs. EP)**
  - **Concentration of Test Substance Dose Too Low**
  - **Inappropriate delivery vehicle**
  - **Clearance of microorganism not demonstrated**

- **Inadequate Explanation of Abnormal Results, Unexpected Findings, Effects on study**

Solutions - *Scientific*

- **Use Appropriate Test Substance**
  - **Refer to Data Requirements Tables**
  - **Dose High Enough to Determine Lowest Adverse Effect Level, or Test at Limit Dose**

- **Explain Abnormal, Unexpected Findings**

Common Problems - Waivers

- Criteria for Waiving a Data Requirement Not Demonstrated (40 CFR 158.45)
- Multiple data requirements addressed in a single waiver
- Waiver Justification Not Substantiated

Solutions - Waivers

- Criteria for Waiving a Data Requirement
  - Physical, Chemical, Biological Properties
  - Exposure considerations
  - Use Patterns
  - No Alternate Data (Scientific Literature) to Fulfill Requirement
  - Testing is not possible
    - Example: Particle Size of the Test Material is Not Respirable (Inhalation Studies)
  - Address Each Data Requirement Separately

Recommendations

- **Alternative Data: Compare with Test Guideline Parameters & Criteria**
  - **Scientific Literature: Provide same information as a guideline conducted study**
  - **Previously Reviewed (MRID) Study: Test material, concentration, dose appropriate for proposed product**
  - **Demonstrate equivalence of proposed active ingredient with material tested in alternate data source**

Recommendations

- Presubmission Meetings
  - Discuss Data Requirements, Waivers
- Joint Reviews – Products with Global Applications
  - Shared Reviews, Simultaneous Registration
- Resubmissions
  - Address Data Deficiencies in PR Notice 86-5 Format
  - Obtain New MRID to Supersede or Supplement Deficient Study

Recommendations

- **Use of Microbial Data Evaluation Report (DER) Templates**
  - **Exchange Reviews Among Countries**
  - **Harmonization of Data Codes, Guideline Numbers**
  - **Provides Frame of Reference for Execution of Study**
  - **Consistency in reporting & summarizing study results**
  - **Compliance with Internationally Accepted GLP**

SAMPLE Microbial DER template in OECD format

Acute Oral Infectivity and Toxicity - *[species, "Waiver Request", "Review of Published Study" or "Review of Published Literature"]* /1

Sub. No. / Company code

TECHNICAL (Active code) and/or MPCA / Active Code

Primary Reviewer: _____ **Date:**

[Name or No., title, and affiliation]

Secondary Reviewer: _____ **Date:**

[Name or No., title, and affiliation]

Approved by: _____ **Date:**

[Name or No., title, and affiliation]

REQUIREMENT: PMRA Data Code: M4.2.2–Acute Oral Infectivity and Toxicity
U.S. EPA OPPTS Guideline: 885.3050
OECD Data Code: IIM 5.3.2

TEST MATERIAL (PURITY): *[use name of material tested as referred to in the study and include its potency, biological activity or concentration per unit weight or volume] or [insert TGAI and EP names if a waiver request is made]*

SYNONYMS: *[other names, code names and acronyms]*

CITATION: Author(s). *[Year]*. Study Title. Laboratory name *[location if needed]*. Laboratory report number, full study date.Unpublished *[OR if published, list Journal name, vol.:pages]*. PMRA *[number]*. MRID *[no hyphen]*.

SPONSOR: *[Name and address of Study Sponsor - indicate if different from Applicant]*

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were *[not]* provided. The study was *[not]* conducted in compliance with GLP *[regulations or guidelines]*. *[Discuss deviations from regulatory requirements]* This DER does *[not]* contain CBI.

EXECUTIVE SUMMARY: In an acute oral toxicity study (MRID *[number]*), groups of *[fasted], [age] [strain] [species] [#/sex]* were given a single oral dose of *[formulation, note its potency, biological activity or concentration per unit weight or volume]* in *[name of vehicle]* at doses of *[in units of potency, biological activity or concentration per kg bw or animal]*. The animals were then observed for a period of up to *[#]* days with interim scheduled sacrifices on Days *[#]*. *[Identify other control groups, if applicable]*

Oral LD_{50} **Males** *[=, > or < concentration]* **(95% C.I. if available)**
Females *[=, > or < concentration]* **(95% C.I. if available)**
Combined *[=, > or < concentration]* **(95% C.I. if available)**
[or note if no mortality occurred, note if limit test]

Based on the results of this study, *[Formulation]* is of **[LOW, SLIGHT, MODERATE, HIGH] Toxicity** *[include EPA Toxicity Category I, II, III or IV if joint review]* and *[insert MPCA] [is or is not]* infective or pathogenic in the *[species]*. *[Include label comment(s) if applicable.]*

[Include only major treatment related clinical signs, body weight or necropsy signs including onset and/or duration if any or the following statement: There were no treatment related clinical signs, necropsy findings or changes in body weight. Indicate if a pattern of clearance was achieved and when it

NOTE: Each government will continue to apply their own criteria when making decisions!

Thank you!
Merci beaucoup!
¡Muchas gracias!

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Brian Belliveau, Section Head, Microbial & Biochemical Evaluation Section Head, PMRA