Addressing biopesticide data requirements using scientifically-sound rationales

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Crafting scientific data rationales to support biopesticide registration

Outline

- Description and purpose of a scientific data rationale
- Data rationales useful for a submission to US EPA
  - Biopesticides, microbial pesticides
  - Mammalian toxicity, non-target species
- The basics of a data rationale
- What does BPPD look for in a data rationale?
  - BPPD has instructions
  - BPPD provides advice
- Where to find the scientific data and information to support the rationale
- Constructing the rationales
- Examples

Data rationales: description, purpose and the basics

Description source: new product, registered source of active ingredient

Requires tolerance petition or tolerance exemption petition and:

1. Submission of product specific data; or
2. Citation of previously reviewed and accepted data; or
3. Submission or citation of data generated at government expense; or
4. **Submission or citation of scientifically-sound rationale based on publicly available literature or other relevant information that addresses the data requirement**; or
5. Submission of a request for a data requirement to be waived supported by a scientifically-sound rationale explaining why the data requirement does not apply

Purpose of scientific data rationales to support biopesticide registration

- Purpose of a scientific data rationale
  - Provide the data / information expected from the guideline study for risk assessment of the biopesticide, or microbial pesticide

- Types of pesticide products data rationales may support
  - Biopesticide active ingredient (ai)
  - Microbial ai
  - Biopesticide or microbial pesticide end use product (EP)
  - Integrated Systems Product (ISP)

The basics: scientific data rationales to support biopesticide registration

- Description of a scientific data rationale

  - **Scientific data,** often from multiple literature sources, put together in a logical argument to answer the questions intended to be addressed by the guideline study

  - **Relevant information** may include product-specific details that inevitably limit exposure to the mammalian or non-target population of interest, or ubiquitous distribution of the proposed active ingredient in the environment, such that the use of the product will not increase the background environmental concentrations

The basics: to develop scientific data rationales to support biopesticide registration, or not

- Reasons for developing a data rationale instead of conducting a guideline study
  - Lots of information is in the public literature to support the rationale
  - Data rationales can be developed more quickly
  - Data rationales are generally less expensive than guideline studies
  - Data rationales reduce animal testing
- Reasons not to develop data rationales, but to conduct the guideline study
  - Insufficient information available in the literature to support a rationale
  - Lack of certainty that EPA will accept the rationale
  - Study data will be required by a regulatory agency other than EPA

BPPD Guidance for Data Waivers (2012); useful for biochemical pesticide, microbial pesticide data rationales

- EPA formatting preferences
  - Each data requirement is presented as a stand-alone rationale, with a guideline name and number, followed by a summary, a detailed justification section (with subheadings for each rationale), and a reference section
  - Complete copies of all references cited should be provided and relevant sections of references highlighted
  - If searches support “no evidence of adverse effects,” cite the searches and provide the search output with the references
- Example EPA recommended information – geared toward waiver requests
  - Proposed use of product is not expected to result in increased exposure to [non-target] based on rapid rate of environmental degradation to background levels (or innocuous metabolites)
  - Microbial active ingredient does not survive in water and so no effect on aquatic organisms is not expected

General BPPD staff advice for data rationales for biochemical pesticide, microbial pesticide data requirements

- EPA formatting preferences from previous slide apply
- For biopesticide active ingredients, EPA indicates it is always good to have a 90-day Oral Study Report and a Developmental Toxicity Report (unless robust data are available from the literature)
- For microbial pesticides EPA indicates that at least one tox/path study must be done with the relevant strain and demonstrate clearance
- Data from the acute tox studies are not accepted to fulfil the repeated dose data requirements, but can indicate whether portal of entry effects may occur in repeat-dose studies
- Studies from the literature should use exposure levels comparable to those for guideline studies
- If the rationale bridges data from an analog, be clear about why the analog is appropriate
- For ecotoxicity rationales, keep in mind that stabilizers in the product may increase the T1/2 in the environment compared to the ai alone

Starting information for biochemical pesticide, microbial pesticide data rationales

- Understand the product – use information from the CSF and product label
  - Is the data rationale for an ai, an ISP, or an EP?
  - Know the identity and the percent of the ai (or potency, e.g., cfu/ml)
  - If there are inert ingredients, know the identity and CAS #
    - Double check that all inerts are approved for the proposed use
  - Know the proposed use pattern and if possible the application rate

- Set up the rationale document with the proper formatting for a data volume
  - Title Page
  - Statement of no data Confidentiality Claims
  - GLP Statement
  - Table of Contents
  - Placeholder page for deletion of confidential attachment (when the identity of inert ingredients are discussed in the data rationale)

Scientifically-sound rationale based on publicly available literature or other relevant information that addresses the data requirement

Sources of publicly available literature – free search sites

ECOTOX

Ecological Ecotoxicity Literature
ECOTOX, BioOne
http://www.bioone.org

National Toxicology Program

U.S. Government Studies
National Toxicology Program

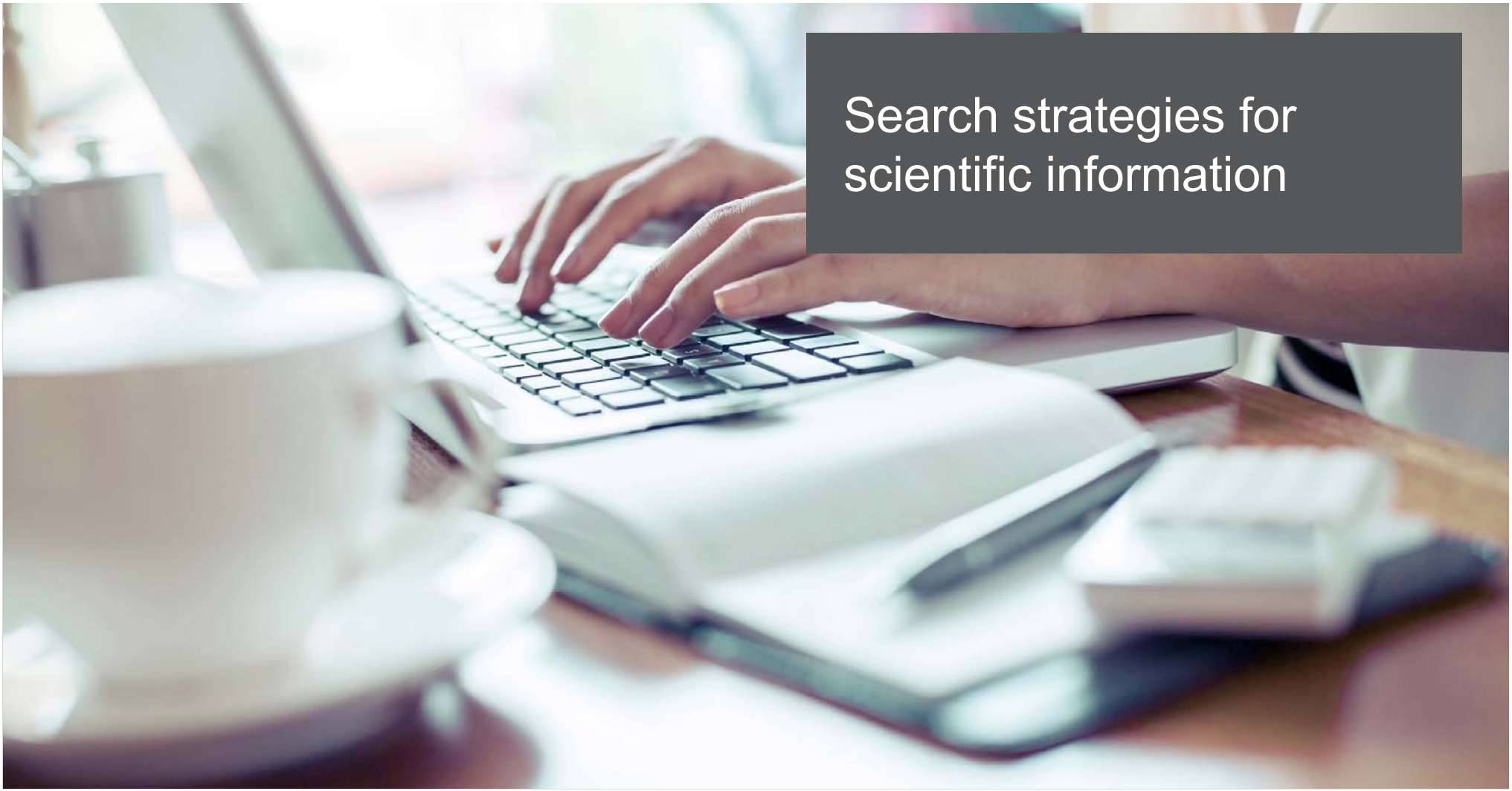
Google Scholar

Scientific Articles and Books
Google Scholar, AGRICOLA

Public Health Literature
Search PubMed, TOXNET, HSDB
https://www.nlm.nih.gov

General Scientific Search
Science Direct , PLoS One
http://www.sciencedirect.com
http://www.plosone.org

General Obscure Scientific Search
Microsoft Academic Research
http://academic.research.microsoft.com



Search strategies for scientific information

Search strategies

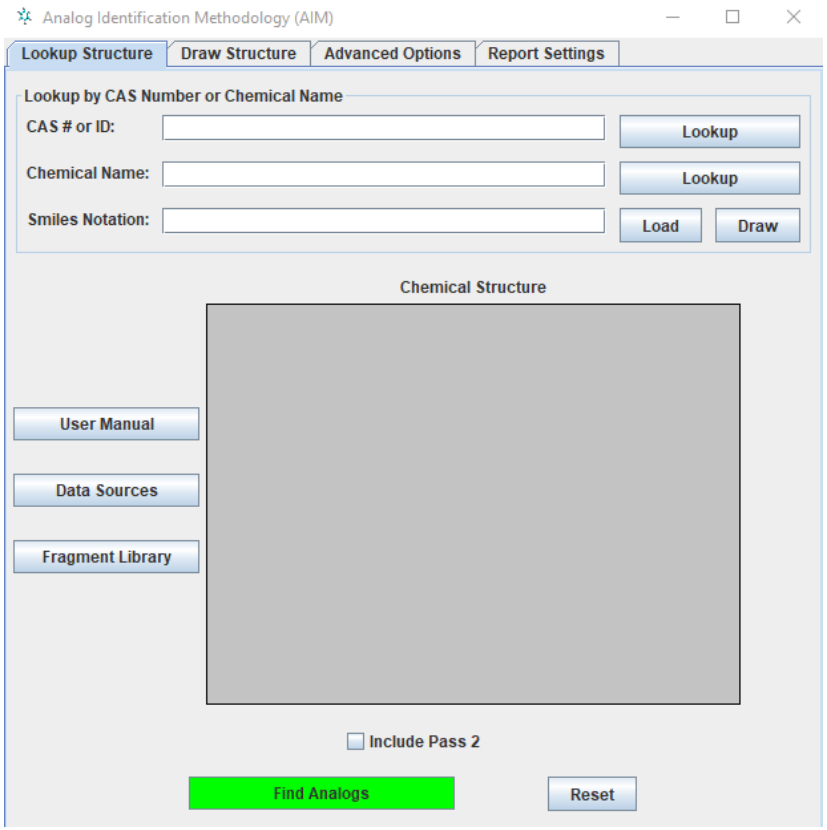
- Initially search for any red flags
  - For biochemical pesticide, search chemical name and toxicity, begin with HSDB, WHO, and other summaries looking for adverse effects at low exposures
  - For microbials, search species and strain, and pathogenicity, toxicity looking for potential human pathogens or toxic metabolites
- Search for primary literature
  - Initial summaries identified may cite primary studies from the literature
  - Search any relevant databases that may include peer-reviewed literature on health or ecological effects
- Recognizing important supporting information in scientific articles is key
  - Often the weight of the scientific evidence supports the rationale
  - Rarely is one published study sufficient to replace a guideline study

Biochemical Pesticides

- If references are sparse identify an analog and search for needed data and information
  - This may require software to identify potential analogs (e.g., EPA's AIM, OECD QSAR Toolbox)
- May require metabolism data on both substances to bridge the data
  - Some metabolism modelling capabilities in OECD QSAR Toolbox
    - Based on structural groups, chemical elements,
    - Simulated metabolism – can check for documented or simulated metabolites or hydrolysis products

Analog Identification Methodology (AIM) Tool

https://www.epa.gov/tsca-screening-tools/analog-identification-methodology-aim-tool



Microbes

- The rationale is supporting a specific strain but that strain generally is not in the literature
  - Rationales often require data from the literature on a variety of strains
  - The weight of evidence of all the strains should support the data requirement
    - If there are strains in the literature with results that have undesirable characteristics, present data that differentiate the literature strain from the proposed product strain (e.g. genetic information)

Making the argument based on the data and information

- Present a clear summary of the product, the identity of the active ingredient, how it will be applied and the general label claims
- In the summary, itemize in a single phrase for each bit of data and information the basis for the rationale
  - For example: “The existing data and information that fulfil the data requirement include: 1)…, 2)… and 3)…”
  - This distinctly identifies the rationale basis for the reviewer
- The body of the rationale is a logical presentation of data and information that elaborates on the points outlined in the summary and includes details and references
- A conclusion section summarizes the reasons the guideline study is not necessary
- The bibliography identifies all the references
- Copies of all non-EPA, non-US regulatory, non-MRID references are attached as pdfs
  - Sections of the references that are of specific importance to the rationale are highlighted

Example rationales

Bridge data for a microbial tox / path study

- Bridge available data for a microbial pesticide acute pulmonary toxicity / pathogenicity study based on available data and information
  - 1) an acute oral tox / path study demonstrated low TGAI toxicity and a pattern of clearance, 2) an acute inhalation study demonstrated low TGAI inhalation toxicity, 3) a literature search indicates that the microbe [*Genus species*] is not a human pathogen, and 4) the product is intended for drip application to the soil
- The body of the rationale:
  - Summarizes the oral tox / path study
  - Summarizes the acute inhalation study
  - Presents the results of the search for pathogenicity of the organism
- The conclusion section closes with the logical argument that the oral tox / path study demonstrated clearance, the inhalation study indicated no toxicity following inhalation exposure, a search of the literature indicates the microbe is not a human pathogen, and the product is a low risk for inhalation exposure during application and so no additional testing is necessary

90-day oral study for a biochemical pesticide

- Develop a rationale to support a 90-day oral study in rats on green tea extract for a food use biopesticide [45% EGCG + other catechins]
  - Search the literature for available data – find study by the NTP (TR 585, 2016)
    - Oral gavage study [48% EGCG + other catechins]
    - 3 month exposure in rats (0, 62.5, 125, 250, 500, 1000 mg/kg bw)
    - ⇩ body weight in 250 mg/kg bw group and higher compared to controls
    - NOEL = 125 mg/kg/day
  - NTP study includes 3-month mouse study, same doses as the rat
    - ⇩ body weight in female mice, 125 mg/kg bw group and higher compared to controls
    - NOEL = 62.5 mg/kg/day
- The data from the NTP study should fulfill the data requirement with a short rationale; unfortunately the NOELs may not be high enough to support a tolerance exemption. The target MOE is generally 100 or greater (NOEL / Exposure = MOE)

Avian dietary study for a biochemical pesticide

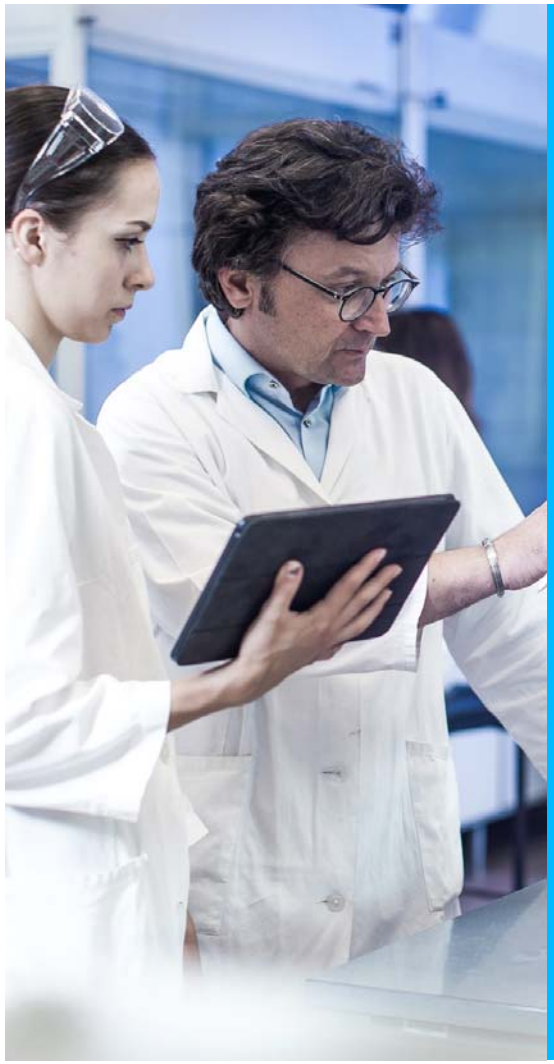
- Develop a rationale to support an avian dietary study for biochemical pesticide XX-OH, required for food uses
- Birds could be exposed to XX-OH in puddles but it readily degrades
  - Search the literature for available avian data – find EFSA review of feed additive studies in poultry (chickens) using XX-OH in place of antibiotics
- Locate primary study reports and develop rationale
  - Study 1: Two XX-OH dietary concentrations (5 & 10 g/kg), chick age (day 1), sex (M), breed, duration (42 days), number/ group provided (n=30)
  - Study 1: Not provided: daily body weights, feed consumed/day
    - Need additional data on chick breed weights, growth and feed consumption per day to estimate dose in mg/kg bw each day on study
    - Calculate average doses/day (515 and 1,029 mg/kg bw/day)
    - Effects measured slightly different than a toxicity study but reflect the health of the birds.
- Study 1 NOEL 1,029 mg/kg/day for 42 days

Avian dietary study for a biochemical pesticide, continued

- Continue the rationale to support an avian dietary study for biochemical pesticide XX-OH, required for food uses
  - Located an EFSA review of feed additive studies in poultry (chickens) using XX-OH in place of antibiotics
- Second primary study report to support rationale
  - Study 2: Dose-response study with XX-OH dietary concentrations 0, 5,10, & 20 g/kg, chick age (day 1), sex (M), breed, duration (42 days), number/ group provided (n=198)
  - Study 2: Same breed, age, growth as Study 1
    - Calculate average doses/day (515, 1,029, 1,544, and 2,059 mg/kg bw/day)
    - Effects measured include general health, growth performance, histopathology. ⇩ Feed intake at the 2 high doses
- Study 2 NOEL 1,029 mg/kg/day for 42 days

Avian dietary study for a biochemical pesticide, continued

- Continue the rationale to support an avian dietary study for biochemical pesticide XX-OH, required for food uses
  - The two studies are used to support the data requirement and in addition data on the chicken breed is used to estimate the dose in mg/kg/day based on the dietary concentration.
  - The proposed use pattern and the behavior of XX-OH in the environment are used to support the position that birds are not likely to be exposed.
    - This may include EpiSuite™ modeling to show XX-OH will not bioaccumulate
    - This may include data that demonstrate XX-OH readily degrades in the environment with a short half-life



Conclusions

Rationales for biopesticide data requirements

- Have a pre-submission meeting with EPA and listen carefully to their advice
- Review the Guideline that you are addressing
- Make an exhaustive search for data related to the requirement
- If you find results that are problematic, include and address them – EPA will also find these results
- Make your argument clear even if the data are not simple
- Persevere – it feels so good when you are done!

Thank you for listening!

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