Risk Assessment and Weight-of-the-Evidence (WoE)

EPA's Office of Pesticide Programs (OPP), Biopesticides and
Pollution Prevention Division (BPPD)
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What data/information is needed for risk assessment?

BPPD's Risk Assessment Elements "Cheat Sheet" for Applicants (attached) will be provided to all biopesticide applicants during or before their pre-submission meeting with EPA, and at any other time by request. The purpose of the sheet is to guide applicants in compiling a complete profile of their use pattern and their chemical for submission to EPA. In addition to using this guidance, BPPD encourages the following:

1. Applicants should provide as much use pattern detail (specific use sites, rates, timing, application equipment, etc.) as possible in their Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) product registration or product amendment applications. This information is especially important if there are toxic effects and if a quantitative risk assessment is needed, e.g., one may be able to use this information to back calculate to the Point of Departure. Providing generic information often results in a very conservative risk assessment.

2. In satisfying human health toxicity and non-target organism toxicity data requirements, statements unsupported by literature citations are not useful in risk assessment. Data and/or information must be submitted or cited to support low risk statements, low exposure arguments, history of safe exposure rationales, etc. Particularly if a lack of exposure argument is being made, a robust scientific rationale must be submitted with a quantitative discussion. For example, the following statement must be supported with a credible quantitative comparison: "Exposure to *active ingredient* from use as a pesticide is anticipated to be less than exposure to the substance naturally or from use of personal care products such as cosmetics." Many tools exist online to assist in conducting exposure assessments (see citations in the attached "BPPD's Risk Assessment Elements "Cheat Sheet" for Applicants").

3. ECOSAR and other types of Structure Activity Relationships (SARs) information can be useful as one piece for a robust WoE approach.

4. Toxicity findings are encouraged to be presented in a pre-submission meeting between BPPD and companies before FIFRA applications are submitted in order for applicants to obtain general feedback on how they may impact the risk assessment process. In some circumstances, multiple pre-submission meetings might be mutually beneficial. For example, when an applicant has had an initial pre-submission meeting and then developed additional data or information, another pre-submission meeting could help decide whether a quantitative or qualitative risk assessment is needed or could be useful to strengthen or reaffirm the rationale for the scope of data requirements for a particular application.

5. The toxic effects for a proposed new pesticide, if any, need to be appropriately characterized. For example, no-observed-adverse-effect-levels (NOAELs) and/or lowest-observed-adverse-effect-levels (LOEALs) for human health studies – especially studies submitted from the public literature – are important for risk assessment. Studies from the literature are often not conducted according to EPA guidelines; therefore, as much information as possible about the toxicity and toxicological

mode of action of the chemical should also be submitted in order to characterize study outcomes as best as possible. Full studies with raw data should always be submitted when available. While EPA cannot provide a determination of toxicity or if a study will be acceptable in a pre-submission meeting setting, potential deficiencies in the database can be identified.

6. When submitting a literature search, please ensure your search terms are provided, as well as all relevant search results. Studies should not be excluded from your package simply because they do not pertain to a Tier I biochemical pesticide data requirement, especially if they indicate a relevant toxic effect. Should the chemical go to the Toxicology Science Advisory Council (ToxSAC) or Hazard and Science Policy Committee (HASPOC), the entire chemical toxicity profile is presented. OPP strongly discourages submitting rationales for the safety of biochemicals based solely upon a Food and Drug Administration Generally Recognized as Safe determination or their historical use as medicinal drugs. This type of information is useful and can be submitted as one piece of evidence but is not sufficient – on its own – to support the required safety finding.

7. If a toxicity endpoint exists for a proposed (or existing) food-use chemical, then a quantitative aggregate exposure assessment may be required. For this assessment, EPA must know the uses of the chemical in all cosmetics and food and drug industries, and the exposure to consumers from these uses. In these cases, applicants are strongly encouraged to quantify all non-pesticidal exposures before submitting their application to EPA.

8. Decisions on whether to do a quantitative verses qualitative risk assessment are usually made by OPP's HASPOC. All new active ingredient or new use applications that propose to satisfy one or more non-acute human health assessment data requirements with wavier rationales or citations to analog/surrogate chemicals must be presented by BPPD to HASPOC for acceptability. Applicants are advised to refer to the guidance for writing waivers for data requirements to ensure clean and thorough applications. When submitting waiver rationales for data requirements, OPP advises that applicants do so under a conditional ruling application code (B614) wherein HASPOC could opine and provide a determination before the FIFRA section 3 applications are submitted. HASPOC only opines on human health data requirements.

The following links maybe be useful when evaluating scientific literature to satisfy pesticide data requirements:

- Human Health Toxicity Literature Guidance: https://www.epa.gov/sites/production/files/2015-07/documents/lit-studies.pdf
- Ecological and Non-Target Organisms Literature Guidance: https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/evaluation-guidelines-ecological-toxicity-data-open

What is "BioDEEM" and when is its use triggered?

The term BioDEEM is nomenclature for IDEEM when used specifically for biopesticides. If an applicant is interested in using IDEEM to support a weight-of-the-evidence approach (for a chemical that has an identified dietary endpoint), OPP recommends requesting pre-submission meetings to discuss IDEEM results. Using the term BioDEEM in these scenarios will (1) simply communicate that the general model used for inerts is being used for a biopesticide active ingredient and (2) distinguish the model from IDEEM in instances where the registrant or OPP has modified the model assumptions to use inputs more relevant for biopesticides. Thus far, no such modifications to model assumptions have been proposed or used.

Is it possible to demonstrate that the conditions of use will be such that it can be reasonably assured there is an ample margin of safety between actual exposure and the level at which an endpoint/effect of concern occurs?

1. The Federal Food, Drug, and Cosmetic Act requires that a tolerance or a tolerance exemption be established for any pesticide residue on foods. Further, it is difficult to reason that a chemical applied directly to a commodity can be afforded a non-food determination (a situation where a tolerance or exemption from tolerance is not required), unless reliable, high-quality detection methods have been used to demonstrate that residues are truly unlikely. A pre-submission meeting should be requested to discuss residue study protocols before testing has begun to ensure that all parameters will be addressed (e.g., magnitude of the residue as well as the nature of the residue – such as metabolites or degradates).

2. A non-food determination is more typical for applications to plants when the food commodity is not present and is not made for all uses of an active ingredient; rather, it is specific to the chemical, the use site and the use rate. Some of these determinations have been published at 40 CFR § 180.2020, but this step is not required, and those not published can be found in EPA publicly available decision documents (found at www.regulations.gov).

3. If a naturally occurring chemical is applied to a commodity and the chemical residues a short time later are found to be within the range of the natural background levels, it is highly suggested to hold a pre-submission meeting to determine how to proceed as this scenario must be clearly defined. Sometimes, a radio-labeled study will be required in order to determine a path forward. BPPD acknowledges that there are often severe practical limitations of this type of study for a biopesticide, including: identification of the appropriate components(s) of a natural extract (biopesticide) to radio label, radio labeling component(s) of the extract, and the fact that the component levels of the proposed biopesticide naturally vary among batches, which often render this technique unreliable or technically infeasible. In these cases, IDEEM or a modified IDEEM approach may be a useful option.

4. If a chemical can be demonstrated to be "self-limiting" to a particular use pattern (i.e., plant regulator), this can be used as part of a WoE approach to support a qualitative risk assessment potentially resulting in support for an exemption from tolerance. Another "self-limiting" example is where a modest over application misuse would kill the target crop and could be used as one rationale in a WoE approach for why problem residue levels will not be reached.

Attachment: BPPD's Risk Assessment Elements "Cheat Sheet" for Applicants, Last updated: September 2019.

BPPD's Risk Assessment Elements "Cheat Sheet" for Applicants

Last updated: September 2019

When submitting a pesticide product registration application to EPA/OPP/BPPD, it is essential that you (applicant) address all applicable data requirements per the Code of Federal Regulations (CFR), part 158. However, it is also imperative that you (applicant) characterize your use sites, use patterns, rates and generally summarize your toxicity data so that a comprehensive risk assessment, taking into account all aspects of your product, can be performed by EPA. Often, when one or more of these pieces of information is missing from an application, the applicant is unsatisfied with the unavoidably conservative assessment that is performed. Further, presenting this information to EPA upfront can alleviate some unnecessary back-and-forth exchanges between EPA and the applicant and subsequent review time lost.

Hence, EPA/BPPD highly recommends that applicants answer the following questions in writing in either a cover letter, data volume, or both when submitting their new product application:

1. **What are the proposed uses for the product?**

   Please provide specific information on sites, application methods (i.e., equipment used), etc.

2. **What are the proposed use rates?**

   Please provide information on the maximum application rate for each use site/scenario as well as the maximum rates per season and the minimum reapplication time interval. For use in occupational and residential exposure assessments, depending on the use, it is helpful to provide application rates expressed in pounds active ingredient per acre, pounds active ingredient per gallon, pounds active ingredient per bottle or can, etc.

3. **What are the exposure scenarios?**

   Address exposure routes for human health toxicity: Will there be dietary exposure? Could there be incidental oral exposure? Will there be occupational (short-term, intermediate-term or long-term) dermal and/or inhalation exposure? Will there be dermal or inhalation post-application exposure? Will there be residential exposure?

   Address exposure routes for non-target organisms: Will the application methods, directions, use sites, etc. result in drift or run-off in the environment? Will the product, as applied, be available to non-target organisms (e.g., birds may be exposed to pesticides applied to soil pre-plant from foraging for insects)?

4. **What are the toxic effects?**

   What are the toxic effects in the human health and non-target organism studies? What are the NOAELs/LOAELs of these effects? Please characterize the effects. Are there any NOAELs below the study limit dose? When NOAELs are below limit doses, depending on the type, severity and incidence of effects, additional data may be required. Please suggest endpoints for each exposure scenario (e.g., dietary, occupational, etc.). Is an FQPA safety factor required (https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/determination-appropriate-fqpa-safety-factors)?

5. **What information on your compound can be found in the open scientific literature**?

Please conduct a thorough search of the literature. Are there any additional toxicity, environmental fate, metabolism, etc. data on your active ingredient? Please do not exclude data just because they aren't relevant to the biochemical pesticide data requirements (i.e., if a carcinogenicity study is available, please provide the data). Fully characterize your literature search by identifying for EPA the search engine used, search terms, and your results.

6. **What is the risk? Depending on the hazard and exposure profiles, should the assessment be quantitative or qualitative?**

Conducting a preliminary risk assessment could help you to identify and resolve any issues prior to submission of your package.

For dietary exposure: Are there residue data? If so, conduct a DEEM analysis to estimate dietary risk (https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/deem-fcidcalendex-software-installer). Make sure to consider the appropriate safety factors (including FQPA). If there are no residue data, is IDEEM an appropriate tool to characterize this active ingredient? Please provide any environmental fate data you have on your active ingredient. Also, what are the byproducts and/or degradates of your active ingredient?

For occupational and residential exposure: Please consult the Agency's SOPs for occupational (https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticide-handler-exposure-data. Note: an occupational exposure spreadsheet is not available online but can be provided upon request) and residential (https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/standard-operating-procedures-residential-pesticide AND https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/framework-assessing-non-occupational-non-dietary) exposure and risk assessment.

7. **Is an aggregate exposure and risk assessment required?**

Once a toxicity endpoint has been identified (regardless of the route of exposure), ALL exposures to a chemical must be aggregated (i.e., accounted for) if:

1. *the applicant is seeking to establish a tolerance or exemption from the requirement of a tolerance, OR*
2. *if a new pesticidal non-food use is being added to a chemical that already has an established tolerance or tolerance exemption.*

If an aggregate exposure and risk assessment is required, submission of as much exposure information as possible (e.g., exposure from other sources like cosmetics, foods, etc.) is useful and can speed up the Agency's review process. You may even want to conduct your own assessment to identify any issues prior to submission of your package. Refer to https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/general-principles-performing-aggregate-exposure-and for more information.