

## Draft Risk-Based Weight of Evidence Framework for Chronic/ Carcinogenicity Studies with Agrochemicals

### I. PURPOSE OF THIS ANALYSIS

[Chemical X] is being assessed for [registration review or new registration]. The toxicology database for [Chemical X] does not include a carcinogenicity study (870.4200) as is required in accordance with the current 40 CFR Part 158.500 (food use pattern) and conditionally required in accordance with current 40 CFR Part 158.510(nonfood use pattern) Toxicology Data Requirements. The registrant is requesting that the Hazard and Science Policy Council (HASPOC) determine if the required stud[y/ies] [is/are] necessary to support the [action (if appropriate)] for [Chemical X].

### II. STUDY WAIVER REQUESTS

**1. Use pattern & exposure scenarios:** Include a concise summary of the registered uses. Describe the potential dietary (food and drinking water) and/or non-dietary (occupational and residential) exposure scenarios that will result from those uses. Is there potential for chronic exposure? If so, which uses and for which populations? In some cases, a table may be necessary.

**2. Physical-chemical properties:**

- Provide a graphic of chemical structure.
- Identify chemical class.
- Summary of physical chemical properties (molecular weight, Log Kow, etc.).
- Provide mechanisms of pesticide activity.
- Summary of how these properties may or may not affect chronic toxicity (e.g. potential for bioaccumulation)

**3. ADME & Toxicokinetics:** The following information should be presented as it relates to the potential for chronic toxicity:

- Absorption
- Distribution
- Metabolism – Include any known information regarding toxicity profile comparison between metabolite and parent. Be sure to include which metabolites are formed in mammals and which are formed in the environment (not to exclude drinking water)
- Excretion - Include any known information regarding milk transfer as well as the standard urine, feces, and exhalation.
- Toxicokinetics
  - If only single-dose, <sup>14</sup>C-labeled kinetic data from a guideline metabolism study is available, this toxicokinetic data should be summarized.
  - Describe if repeated-dose toxicokinetic evaluations at various dose levels were conducted to assess the dose proportionality of AUC vs. dose (or lack of a linear relationship above a certain dose), and if whether it influenced the dose level selection in any of the studies.

**4. Toxicity:** summarize how available studies can be used to inform chronic outcomes.

**4.1 Acute Toxicity**

- Report any results of concern.

#### **4.2 Subchronic Toxicity**

- Identify target tissues
- Summarize dose response
- Summarize how each sub-chronic study can be used to inform chronic outcomes
- Compare species sensitivities and how that will drive the risk assessment

#### **4.3 Evidence of Hormone Perturbation**

- Report mode of action data that describes key events related to hormone mediated adverse effects.
- Report evidence (or lack of evidence) of hormonal perturbation in repeat dose studies, and developmental and reproductive studies. Such evidence can come from endocrine related:
- Weight change
- Gross and/or microscopic changes in endocrine organs (e.g., adrenals, ovaries, testes, or thyroid gland)
- Serum hormone levels (e.g., disruption in androgens, estrogens, glucocorticoids, and thyroid hormone levels)

#### **4.4 Evidence of Immune Suppression**

In the absence of genotoxicity, hormonal effects, or liver enzyme induction, indications of immunosuppression could raise concern for potential tumor formation.

- Report evidence of immune suppression. Some evidence might include:
- Hematological changes such as leukocytopenia/ leukocytosis, granulocytopenia / granulocytosis, or lymphopenia / lymphocytosis;
- Alterations in immune system organ weights and/or histology (e.g., changes in thymus, spleen, lymph nodes, and/or bone marrow);
- Changes in serum globulins that occur without a plausible explanation, such as effects on the liver or kidney, can be an indication that there are changes in serum immunoglobulins;
- Increased incidence of infections;

#### **4.5 Genetic toxicity:**

- Provide in vitro and in vivo results from all genotoxicity studies in a table format, including for active ingredients plant and/or livestock metabolites, and major degradants as appropriate
- If the chemical is positive in some genotoxicity studies and negative in others, provide details regarding the positive test result. (Note: none of the chemicals nominated for this review should be classified as genotoxic).
- If the chemical is mutagenic, then the evaluation is complete and no further documentation is needed (the pesticide would not undergo a cancer bioassay if the chemical is mutagenic, so no need to write a full carcinogenicity waiver).

#### **4.6 Special studies and endpoints:**

- Data should be provided from the following special studies and endpoints, where it is available, to investigate a particular set of findings that were seen (or suspected) with the molecule in toxicity studies:
  - Mode of action studies
  - Biomarkers
  - New Approach Methods (e.g., *in vitro*, *in silico*, and computational models)

## 5. Evidence of Chronic Toxicity from Related Chemicals:

Read-across will be derived from other well-studied molecules that have structural analogs the same structural class(es) as the candidate molecule.

- If chemical read-across information is available, provide a list of chemical names, structures, common functional groups of interest, and percent similarity to chemical under question.
- Briefly describe the mode of action for chemical class and chemical target for pesticide action.
- Provide a justification for using, or not using, the chemicals in the read-across to support the carcinogenicity waiver.\*
- If adequate information is available for chemical read-across to strengthen the confidence in the waiver, then provide information outlined in ADME and Toxicity Studies (Sections 3 – 4), including chronic and/or carcinogenic study outcomes for the referenced read-across chemicals.

\*Note, not all chemicals in a read-across group will be appropriate to reference in the waiver (i.e., consider differences in metabolism). In addition, in a case where there are a large number of potential molecules in the same chemical class and/or pesticide MOA class, it will be most useful to summarize the class as a whole, but to only use one or a few key indicator molecules with more detailed information to illustrate the properties of the class (especially those with guideline chronic toxicity studies in their database). As outlined above, providing a rationale for why the indicator molecule(s) were chosen as the best comparators to the candidate molecule is an important element of this section.

## 6. Proposed Points of Departure and Prospective Risk Assessments\*

The proposed PODs and prospective risk assessments will be based on the available short-term through sub-chronic toxicity data and used to set the appropriate RfDs for chronic risk assessment in the absence of chronic/carcinogenicity studies.

- Describe level of exposure through drinking water, and the models used to derive those levels.
- Indicate what major metabolites or degradates would constitute the “definition of the residue” (for tolerance enforcement, and for risk assessment) based on all metabolism and environmental fate studies (this information often will be described in a US EPA review of the molecule, prior to a HHRA).
- Report the recommended tolerance levels.
- Report chronic exposure estimates and the models used to derive them.
- Calculate estimates for chronic risk (%cPAD) at the highest predicted exposure.
- Calculate estimates for cancer risk (the Margin of Exposure) – by linear or non-linear cancer risk assessment methods as appropriate for the molecule.
  - Calculate MOE from NOAELs of proliferative thresholds
- Summarize risk estimates (relative to the EPAs expected level of concern).

## 7. Conclusion

Based on a WOE approach, the registrant requests that the chronic/carcinogenicity toxicity studies **[be/not be (as appropriate)] required at this time for [Chemical X]**. This approach considered all of the available hazard and exposure information for **[Chemical X]**, including: [provide a summary of why studies should not be required]. (Note: This information is normally provided in a concise bullet point format of major supporting evidence.)

**Clearly summarize the following points:**

- Requested waiver for rat and/or mouse studies, and explanation for the waiver request based on:
  - The weight of evidence incorporating relevant information obtained from all available studies, including (but not limited to) subchronic toxicity studies, reproductive/developmental toxicity studies, neurotoxicity studies, immunotoxicity studies, genotoxicity studies, and special studies such as mode of action studies
  - Read-across to other chemicals for subchronic and chronic/carcinogenicity information (including reported tumors)
- Summary of potential human exposure
- Suggested POD for use in the chronic risk assessment

**8. References**

Registrant should provide a complete list of references used to support the arguments and data presented herein.

**Appendix**

- Provide tables to summarize toxicity and exposure results as appropriate (e.g., acute, subchronic, genetic toxicity, dietary exposure, occupational exposure, etc)
- Report chemical read-across results of all sub-chronic and chronic studies in a table format