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Submitted via regulations.gov

RE: ***Docket # EPA-HQ-OPP-2017-0433;*** **Interim Process for Evaluating Potential Synergistic Effects of Pesticides during the Registration Process; Notice of Availability and Request for Comments. 84 Fed. Reg. 47287 (September 9, 2019).**

Dear Ms. Dunn:

CropLife America (CLA)[1] and RISE® (Responsible Industry for a Sound Environment)[2] appreciate the opportunity to comment on the Interim Process for Evaluating Potential Synergistic Effects of Pesticides during the Registration Process. The purpose of the interim process is two-fold. First, having an interim process that provides the United States Environmental Protection Agency (EPA) with a mechanism to determine if assertions of greater than additive (GTA) effects, in granted patent claims by U.S. Patent and Trademark Office (USPTO), impact EPA ecological risk assessments (ERA) for pesticide active ingredients. Second, having an interim

[1] CLA, established in 1933, represents the developers, manufacturers, formulators and distributors of plant science solutions for agriculture and pest management in the United States. CLA's member companies produce, sell and distribute virtually all the crop protection and biotechnology products used by American farmers.
[2] RISE represents more than 220 producers and suppliers of specialty pesticide and fertilizer products to both the professional and consumer markets. RISE member companies manufacture more than 90 percent of domestically produced specialty pesticides used in the U.S., including a wide range of products used on lawns, gardens, sport fields, golf courses, and to protect public health.

process gives EPA the opportunity to use this sub-set of active ingredients to evaluate the utility of reviewing such information in the future.

EPA initially developed the current process to analyze the relevance of granted patent claims and associated data asserting GTA effects and, if necessary, conduct further analyses. To date, EPA has used the interim process to evaluate 24 new active ingredient registrations, involving the review of approximately one thousand patents with assertions of GTA effects. None of these reviews have ultimately led to the modification of an existing EPA ERA, which strongly suggests that there is a low probability that future assessments will impact ERA's for new active ingredient registrations. Therefore, it is appropriate to regard this as an interim process, and CLA and RISE support EPA's future plans to evaluate the results of the interim process to decide whether continuing the process has utility. If the outcome does not demonstrate value or utility in evaluating ecological risk, CLA and RISE recommend that the interim process be discontinued.

I. General Comments

Under the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) a pesticide must be registered by EPA before it can be sold or distributed in the United States.[3] To register a pesticide active ingredient, the registrant must submit to EPA data required under 40 CFR Part 158 in the areas of product chemistry, environmental and mammalian toxicity, environmental fate, environmental exposure, and human exposure (including residue chemistry). These data allow EPA to evaluate whether the product will "perform its intended function without unreasonable adverse effects on the environment" and whether "when used in accordance with widespread and commonly recognized practice it will not generally cause unreasonable adverse effects on the environment." [4] FIFRA defines "unreasonable adverse effects" as "any unreasonable risk to man or the environment, taking into account the economic, social, and environmental costs and benefits of the use of any pesticide." [5]

Regulations establish the data requirements that must be satisfied by applicants before a pesticide can be registered.[6] However, the specific tests that must be conducted are determined in part by the nature of the product, its exposure and effects profile, and the types of uses for which the product is intended. In general, the testing regime is structured to develop a broad and comprehensive body of human and environmental safety data on active ingredients, and to require more narrowly targeted testing for the formulated products that incorporate those active ingredients.[7] Even after a pesticide is registered, registrants have a continuing obligation to

[3] 7 U.S.C. §§ 136-136y
[4] 7 U.S.C. § 136a(c)(5)
[5] 7 U.S.C. § 136(bb)
[6] *See* 40 C.F.R. § 158 (referred to herein as EPA's "Part 158" regulations).
[7] *Id.* Active ingredients are the unique chemicals that have pesticidal effects. Formulated products, on the other hand, purposefully combine an active ingredient with at least one other substance, either another active ingredient or

report to EPA additional information on unreasonable adverse effects to human health or the environment.[8] EPA has relied on this testing and reporting paradigm for decades to assure that risk assessments for registered pesticides are protective of human health and will not cause unreasonable adverse effects on the environment. However, in recent years, responding to the prevalence of granted patents with assertions of GTA effects, EPA developed the current interim process to address questions regarding the potential impact of the GTA patent data on the existing process for evaluating ecological risks of pesticide mixtures.[9]

EPA's process for evaluating human and environmental risks from pesticide is protective

EPA's process for evaluating ecological risks for pesticides has primarily relied on toxicity information from studies conducted with single active ingredients. This approach has historically enabled EPA to conduct assessments that are protective of the environment for several reasons, which include:

1. After decades of research, there is a common understanding within the scientific community that the potential for interactions among pesticide active ingredients that are relevant to ERAs is rare. Such interactions are generally a high dose phenomenon only observed in laboratory assays at concentrations that have effects for one or more of the components.[10,11] Observing GTA activity at these high exposure levels is generally not informative for an ERA because GTA interactions between pesticide active ingredients are not predicted to occur under realistic environmental exposure scenarios. In 2013, the National Research Council (NRC)[12] also concluded that toxicological interactions between pesticide active ingredients are rare and recommended that EPA assume that synergistic effects relevant to ERAs are not occurring unless relevant and reliable data indicate otherwise.
2. Analysis of environmental monitoring information and associated pesticide toxicological endpoints (e.g., U.S. Geological Survey's ambient water monitoring as discussed in

an inert ingredient (an ingredient that does not have pesticidal effects). One type of formulated product is an end-use product, which is labeled for use by an end-user. 40 C.F.R. § 158.300.

[8] 7 U.S.C. § 136d(a)(2)

[9] As EPA acknowledges, the "criteria for use of GTA data for patent applications are different than for EPA's quantitative analysis of risk." 84 Fed. Reg. 47288 (September 9, 2019). Thus, for example, the data supplied with a patent application for a pesticide do not necessarily reflect the registered uses of the pesticide, may not reflect application rates that are ultimately approved for the FIFRA-registered product, do not necessarily reflect the composition of the commercial formulation(s) that is registered, and may not have sufficient replication to satisfy EPA data quality requirements.

[10] Cedergreen, N. 2014. Quantifying synergy: a systematic review of mixture toxicity studies within environmental toxicology. PLOS One 9: e86580.

[11] Levine SL and Borgert CJ. 2018. Criteria to Evaluate Pesticide Interaction Data for Relevance and Reliability to an Ecological Risk Assessment. Chemosphere. 209:124-136.

[12] National Research Council (NRC) 2013. Assessing Risks to Endangered and Threatened Species from Pesticides. The National Academies Press, Washington DC.

Belden et al. 2007)[13] indicates that (a) the potential ecological risk from exposure to environmental mixtures of pesticides is often attributable to a predominant single active ingredient in the mixture, (b) these levels rarely exceed threshold effect levels[14]; and (c) the ecological assessment for the more toxic component is protective for the combination[15].

3. The tenets of independent action (*i.e.,* response addition) predict that mixtures of ingredients with different modes of action will not produce combined effects when components are present at levels that are not associated with adverse responses[16]. The concept that "0 + 0 = 0" or a "NOEC + NOEC = NOEC" is well accepted in the field of toxicology. The NOEC is the no observed effect concentration. Further, risks from components that could potentially interact are addressed through the concept of "interaction thresholds"[17]. The dose-dependent nature of GTA responses has been termed an "interaction threshold" and predicts that components will not interact below effect thresholds[18]. In other words, one or more of the components must exceed an effect threshold for a potential interaction to occur. Additionally, extrapolating GTA responses beyond the range of the data and from high effect doses to no effect doses is not a valid approach. Based on these principles, EPA recognizes that their assessments are protective of acute and chronic effects[19]. For chronic assessments, EPA uses no effect thresholds in ERAs (e.g., no observed adverse effect concentration values (NOAEC) or a surrogate measure) to be protective of chronic environmental exposures. For acute assessments, EPA uses safety factors to extrapolate to no effect thresholds to conclude that there is a low probability of acute effects from acute exposures. NRC (2013 at p. 134) provides consistent guidance on this point for ecological assessments, "… *such components do not need to be considered when present at concentrations below their toxic thresholds*". This guidance applies to FIFRA assessments as well as threatened and endangered species assessments.

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[13] Belden J.B., R. Gillion, J. Martin, M.J. Lydy. 2007. Relative toxicity and occurrence patterns of pesticide mixtures in streams draining agricultural watersheds dominated by corn and soybean production. Integrated Environmental Assessment and Management 3: 90-100.

[14] Könemann WH, Pieters MN. 1996. Confusion of concepts in mixture toxicology. Food Chem Toxicol. 34:1025-31.

[15] Belden JB, Brain RA. 2018. Incorporating the joint toxicity of co-applied pesticides into the ecological risk assessment process. Integr Environ Assess Manag. 14:79-91.

[16] COT. 2002. Risk assessment of mixtures of pesticides and similar substances. London: Committee of toxicity of chemical in food, consumer products and the environment. Available from: https://cot.food.gov.uk/sites/default/files/cot/reportindexed.pdf.

[17] Levine SL and Borgert CJ. 2018. Criteria to Evaluate Pesticide Interaction Data for Relevance and Reliability to an Ecological Risk Assessment. Chemosphere. 209:124-136.

[18] Gennings C, Hans Carter W, Carchman RA, DeVito MJ, Simmons JE, Crofton KM. 2007. The impact of exposure to a mixture of eighteen polyhalogenated aromatic hydrocarbons on thyroid function: Estimation of an Interaction Threshold. J Agric Biol Environ Stat. 12:96-111.

[19] EPA. 2019. Process for Receiving and Evaluation Data Supporting Assertion of Greater than Additive (GTA) Effects in Mixtures of Pesticide Active Ingredients and Associated Guidance for Registrants, August 2019. It is available at https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/ecological-risk-assessment-pesticides-technical.

Agronomic and economic importance of tank-mixing pesticide active ingredients

In the Federal Register's preamble announcing the interim process, EPA recognizes the economic and agronomic value of tank-mixing pesticides. Specifically, tank-mixing is important for the following reasons:

- Effective and timely management of co-occurring insect, pathogen and weed pests;
- Combining mechanisms of action to mitigate evolution of resistance;
- Broadening the spectrum of pests controlled and/or increasing the duration and consistency of control;
- Reducing application costs (e.g., fuel, labor, equipment wear);
- Reducing environmental impacts from increased use of application equipment;
- Reducing selection pressure for the evolution of pesticide resistance;
- Reducing negative agronomic impacts to crop and soil (e.g., application equipment damage, soil compaction and erosion); and
- Achieving desired agricultural production results (e.g., mixtures of cotton harvest aids).

In practice, mixtures are avoided when there are issues related to incompatibility, possible reductions in efficacy, potential for excessive crop injury, or when the cost is not justified compared to application of a single active ingredient. Growers and crop advisors are aware of the benefits and issues related to tank-mixing and avoid mixing ingredients that are not permitted on product labels.

Evaluating patents only from the USPTO is comprehensive

CLA and RISE agree that including non-U.S. patents in the reviews is not justified within the interim processes, for several reasons. First, there is an increased likelihood that the patent mixture data in other jurisdictions could involve pesticides not registered in the U.S. Second, the patent assertion processes and documentation in other countries will prevent efficient searching and analysis using a standardized method. Third, patents filed with and granted by the USPTO are commonly filed by pesticide developers and granted in other major jurisdictions. Thus, there is little if any utility to considering non-U.S. patents in the interim process.

EPA's interim process is amenable to self-certification

The process of data evaluation and ERA is frequently divided into smaller, stepwise components, so that evaluations can be easily managed. EPA's interim process is divided into the following steps: identifying potentially relevant GTA claims (Step 1); conducting a review of patent data for relevance to ERA (Step 2); and then assessing whether the reported GTA effect is statistically significant (Steps 3 and 4). In the relatively few cases where the GTA data is deemed to be relevant and statistically significant, the assessment advances to Step 5. Step 5 is a risk-based

analysis, which may or may not require additional guideline data to determine whether the observed GTA activity impacts an ERA. Because the interim process is stepwise, with built-in options for addressing the GTA assertions, there is flexibility in how the process can be applied. In particular, the interim process is suitable for self-evaluation and self-certification when assertions of GTA effects are shown neither to be relevant to an ERA nor statistically significant. EPA would have the ability to audit the documented evaluations that would be submitted for accuracy and compliance with the interim process.

To date, the interim process has been required as part of the registration process for new active ingredients and to approve a limited number of specific combinations with products registered for use on herbicide tolerant (HT) crops. For uses associated with HT crops, the interim process is required along with a wind-tunnel assessment that examines spray droplet size, in order to approve of a tank-mix partner product. To make the review process more efficient, and approve agronomically important tank mixtures in a timely manner, registrants should be given the ability to quickly enable additional combinations once the mixing partner has been shown to pass the wind-tunnel requirements and has been shown to not have a GTA claim, or the GTA data are shown to be not relevant in Step 2, or shown to be not statistically significant in Step 4. An in-depth discussion of enabling self-certification is included in the comments addressing EPA's question – "*Should EPA continue the interim evaluation process as described in this document?*" CLA and RISE recommend that EPA consider developing and implementing self-certification for the interim process as it relates to mixing partners for products for use on HT crops in cases where either Step 1 or Step 2 reach a conclusion of non-relevance or Step 3 and 4 reaches a conclusion of non-significance.

II. Specific Comments on individual Steps of the Interim Process

Step 1: Search for and identify granted and granted/unmaintained U.S. patents with applications that made assertions of pesticide interactions resulting in GTA effects involving the pesticide under EPA's regulatory consideration.

Comment:

Under Step 1, EPA is requesting the use of multiple chemical identifiers. One of these identifiers is the simplified molecular-input line-entry system (SMILES) code chemical structure. Structure searching (in SciFinder/STN) should not be required. Keyword searching (Patbase) including common name + IUPAC name + CAS numbers is generally sufficient to capture all "art". In addition, it is important to point out that patent claim applicants may not always follow the strict IUPAC naming convention, or even include the IUPAC name of the to-be registered chemistry, soon after discovery and when included in mixture patents.

CLA and RISE recommend that trade names of formulations should be optional (not required) search terms. Searching such trade names could unnecessarily identify too many irrelevant

patents, thereby making it very difficult to correctly identify granted patents with assertions of GTA effects.

CLA and RISE recommend additional tools for keyword searching as options or alternatives to Google Patents and USPTO search resources. The Derwent Innovation suite, Patbase and Orbit are the industry standards. They provide advanced searching criteria and sophisticated reviewing methods such as highlighting and marking; provide effective examination of searches; are less error-prone; and index USPTO patents exhaustively. In addition, since the interim process is only identifying USPTO granted patents, it may not be necessary to search the World Patent Index (WPI), though it is included in the Derwent Innovation suite.

Provided a registrant can justify that the databases employed for the search are comprehensive and accurate for granted USPTO patents with assertions of GTA effects, flexibility should be allowed in the searching process. Consequently, registrants should not need to query four different search tools with the same underlying data. Registrants should be able to pick one or two from an approved list e.g., USPTO, Google Patents, PatBase, Derwent, Orbit.

Step 2: Compare all applicable patent data supporting patents identified in Step 1 to Agency ecological risk assessment relevance criteria.

Comment: In Step 2, EPA has included five important relevancy criteria. Some of these criteria are used to evaluate the relevance of the claim and other are used to evaluate the relevance of the data used to support the assertion of GTA effects. It is implicit that additional relevance criteria are part of the data quality analysis in Step 2 based on EPA's general data quality standards for other scientifically relevant information. For example, if treatments are not replicated the data should not be considered relevant, since a statistical analysis (Step 4) cannot be conducted without replicated data. Accordingly, the requirement for multiple treatments should be added as an explicit relevancy criterion. Evaluating only a single treatment is not adequate for an analysis of GTA.[20] In addition, if only rates that exceed labeled rates have a statistically significant GTA response, the data should be considered not relevant -- particularly when labeled rates do not have statistically significant GTA responses. Concerns with extrapolating from higher rates to lower rates are discussed below under Step 5.

Step 3 and 4: Analyze the data to determine if observations of greater than additive effects in mixtures are statistically significant in the context of test variability.

Comment: In EPA's Excel-based calculator to assess statistically significant deviations from additivity, two established models are used; response addition (labeled as point estimate in the worksheet) and concentration addition (called the isobole method in the worksheet). These approaches, or a hybrid of these approaches, should address all the cases that require analysis. The validity and acceptance of these two methods for assessing the interactions is well

[20] Cassee FR, Arts JHE, Groten JP, Feron VJ. 1996. Sensory irritation to mixtures of formaldehyde, acrolein, and acetaldehyde in rats. Arch Toxicol. 70:329–337.

recognized, however, below are specific comments for consideration after reviewing the Excel sheets.

Under the concentration addition model, two examples are given, assessing additivity with IC_{25} values and IC_{10} values. An important assumption of the concentration addition model for isobole analysis is that the concentration response curves are parallel on a log-probit or log-logit scale.[21] However, with non-parallel response curves isoboles are not parallel and if there is a deviation from additivity the isobole is not a straight line and can confound an analysis.[22] The more complex Equivalents Model can handle non-parallel response curves and quantify any synergistic or antagonistic deviation from additivity. [23] An assessment of parallel concentration-response curves can be made visually or by comparing slopes statistically. Consequently, the analyst should perform an assessment before comparing predicted and observed values. CLA/RISE recommends that EPA call the method "concentration addition" over "Isobole" because the isobole method really refers to a graphical technique to see if the predicted value is above, below or on the line of additivity. Further, the Isobole method only works for mixtures with two components, while the concentration addition and response addition models can handle any number of components. Although the graphical isobole method does not include a formal statistical test, a confidence interval can be added to the isobole to reflect the variability around the line of additivity. An example of this is shown in Levine et al. 2019.[24] Interpretation of mixture toxicity calculations are commonly based on constructing a 95% confidence interval (CI) around the fitted response and then analyzing whether the predicted response is captured by this confidence interval. [25,26,27]

As additional guidance for the "isobole" or concentration addition assessment, it should be noted that the concentration used for assessing the combined mixture should reflect the combined concentrations of the mixture to get the correct prediction. In other words, if the lowest dose is 1 ppm of component A and the lowest dose of component B is 1 ppm the lowest dose is 2 ppm for

[21] Green JM, Jensen JE, Streibig. 1995. Models to assess joint action of pesticide mixtures. Aspects of Applied Biology. 41:61-68.
[22] Jensen JE, Streibig JC. 1994. Herbicide dose-response curves and sustainable agriculture. Proc, EU HARMA Concerted Action Workshop, Edinburgh, UK, 6/7 May 1994. pp. 15-33.
[23] Green JM, Streibig JC. 1993. Herbicide Mixtures, In Herbicide bioassays, pp. 117-135. Eds J C Streibig and P Kudsk. Boca Raton: CRC Press.
[24] Levine SL, Fridley JM, Uffman JP. 1029. Assessing the Potential for Interaction in Insecticidal Activity Between MON 87751 × MON 87701 Produced by Conventional Breeding. Environ Entomol. 30;48(5):1241-1248.
[25] Tabashnik, BE. 1992. Evaluation of synergism among Bacillus thuringiensis toxins. Appl Environ Microbiol. 58:3343-3346
[26] Jonker E, Gerhardt A, Backhaus T, van Gestel CAM. 2012. Test design, mixture characterization, and data evaluation. In: Mixture toxicity: Linking approaches from ecological and human toxicology. Edited by CAM van Gestel, MJ Jonker, JE, Kammenga, R Laskowski and C Svendsen. CRC press, boca Raton FL. Chapter 4 pg. 121-156.
[27] Kudsk P and Mathiassen SK. 2004. Joint action of amino acid biosynthesis-inhibiting herbicides. Weed Res. 44:313-322.

modeling purposes. This simple point is often overlooked when these calculations are made, particularly in the literature. A note in the Excel sheet should remind users of this.

Response addition can also be used for more than just simple point estimates if the data are sufficient for evaluating with the concentration addition model.[28, 29] This would allow response additions to be used in a similar way to the concentration addition model by comparing ECx estimates for predicted and observed values. This approach has been illustrated by Levine et al. (2019).

Step 5: The final step is an Agency review of the submitted information from Steps 1-4. To date, EPA has been using this information to determine the following:

- If any statistically significant observations will impact the conclusions of ERAs, risk mitigation efforts, or the registration decision;
- If statistically significant observations can be used to inform quantitative adjustments to the ERA or risk mitigation; and
- If additional mixture toxicity data using guideline protocols are needed.

Comment: The magnitude of a difference between observed and predicted mixture toxicity for pesticides has been discussed in the peer-reviewed literature for quite some time and in regulatory guidance documents (EFSA, 2013; SCENIHR, 2012)[30,31]. For example, Belden et al.[32] proposed, based on studies with aquatic organisms, that a biologically significant and reproducible GTA response can be defined as a more than two-fold deviation from predictions using the concentration addition model. Presently, there is no analogous metric to assess deviation from additivity for response addition. However, if one considers doubling of a response, an approach could be considered as shown by Levine and Borgert (2018). Boobis et al.[33] reported in a review of the mammalian literature, from 1990 to 2008, that GTA effects did not exceed a factor of 3.5 based on a ratio of observed and predicted EC_x values and that less than additive responses did not exceed a factor of 10. In addition, a FIFRA Scientific Advisory

[28] Lewis MA, Perry RL. 1981. Acute toxicities of equimolar and equitoxic surfactant mixtures in *Daphnia magna* and *Lepomis machrochirus*. Aquatic Toxicology and Hazard Assessment: Fourth conference, ASTM STP 737. DR Branson and KI Dickson, Eds., American Society of Testing Materials, pp. 402-418.
[29] Levine SL, Fridley JM, Uffman JP. Assessing the Potential for Interaction in Insecticidal Activity Between MON 87751 × MON 87701 Produced by Conventional Breeding. Environ Entomol. 30;48(5):1241-1248.
[30] European Food Safety Authority (EFSA). 2013. Scientific Opinion. Guidance on tiered risk assessment for plant protection products for aquatic organisms in edge-of-field surface waters. EFSA Panel on Plant Protection Products and their Residues (PPR)2,3 EFSA, Parma, Italy. EFSA Journal 11(7):3290.
[31] SCHER (Scientific Committee on Health and Environmental Risks), SCCS (Scientific Committee on Consumer Safety), SCENIHR (Scientific Committee on Emerging and Newly Identified Health Risks), 2012. Opinion on the Toxicity and Assessment of Chemical Mixtures, pp 55.
[32] Belden, J.B., R. Gillion, M.J. Lydy MJ. 2007a. How well can we predict the aquatic toxicity of pesticide mixtures? Integrated Environmental Assessment and Management 3: 364-372.
[33] Boobis A, Budinsky R, Collie S, et al. 2011. Critical analysis of literature on low-dose synergy for use in screening chemical mixtures for risk assessment. Crit Rev Toxicol. 41:369-83.

Panel recommended to EPA that for combinations of plant-incorporated-protectants previously registered as individual agents with proven safety records, GTAs less than 10-fold should not trigger additional testing on nontarget organisms.[34] The rationale for this recommendation largely reflects the risk assessment requirement to achieve a margin of exposure of ≥10-times the expected environmental concentration.[35] EPA's interim process will put the results into the context of an ERA, which is the most scientifically justifiable approach.

Under current guidance from the European Food Safety Authority (EFSA) on risk assessment for plant protection products, differences between observed and calculated (predicted) mixture toxicities of <5-fold would not impact the aquatic assessment[36]. Regulating on a >5-fold difference between predicted and observed toxicity is a pragmatic criterion because it acknowledges inter-assay variability and allows for a difference between predicted and observed toxicity that will not impact the outcome of the ecological risk assessment. In the EU, a Toxicity Exposure Ratio (TER) of 5 to 100 is typically used as the threshold for unacceptable effects in a baseline assessment. Therefore, uncertainty associated with <5-fold difference between predicted and observed values can be managed in the context of the assessment. Similarly, Belden and Brain recently recommended that to be considered GTA towards non-target plants, there should be greater than 5-fold difference between the observed values and those predicted by concentration-addition.[37] Moreover, most of the studies they evaluated had a single component that dominated toxicity to nontarget plants, leading them to conclude that the ecological assessment for the more toxic component is protective for the combination.

III. Comments Addressing the Four Questions on which EPA has Requested Feedback

1. What aspects of the process could be applied to the evaluation of open literature sources of GTA effects for pesticide interactions?

Step 2 of the interim process includes several criteria for determining whether any data reporting potential GTA activity are relevant to an EPA ERA. A thorough evaluation of any data that

[34] U.S. EPA. 2009b. Transmittal of Meeting Minutes of the FIFRA Scientific Advisory Panel Meeting Held February 25–26, 2009 on the Data Required to Register Plant-Incorporated Protectants; SAP Minutes No. 2009-04. http://www.epa.gov/scipoly/sap/meetings/2009/february/022526finalreport.pdf.
[35] U.S. EPA. 2010. Bacillus thuringiensis Cry1Ac Protein and the Genetic Material (Vector PV-GMIR9) Necessary for Its Production in MON 87701 (OECD Unique Identifier: MON 877Ø1-2) Soybean. https://www3.epa.gov/pesticides/chem_search/reg_actions/pip/bt-cry1ac-protien.pdf.
[36] European Food Safety Authority (EFSA). 2013. Scientific Opinion. Guidance on tiered risk assessment for plant protection products for aquatic organisms in edge-of-field surface waters. EFSA Panel on Plant Protection Products and their Residues (PPR)2,3 EFSA, Parma, Italy. EFSA Journal 11(7):3290.
[37] Belden JB, Brain RA. 2018. Incorporating the joint toxicity of co-applied pesticides into the ecological risk assessment process. Integr Environ Assess Manag. 14:79-91.

could be used to inform an ERA is a critical step in the process.[38,39] In addition to the data quality criteria EPA has included in Step 2, EPA has well-established data quality criteria to evaluate the relevance and reliability of ecotoxicity data from the open literature. EPA's current data quality criteria were summarized in an EPA memo in 2010 titled "*Evaluation Guidelines for Ecological Toxicity Data in the Open Literature*" and are available online.[40] Further to this guidance, specific relevance criteria to evaluate mixture data were published by Levine and Borgert (2018).

The criteria from Step 2 that are applicable to open literature data include:

- Are empirical data presented to support a mixture assessment?
- Are the taxa tested relevant to an EPA ERA?
- Are the observed effects relevant to direct effects on tested taxa?
- Are the active ingredients that are tested all considered relevant for regulation by the EPA?

Our comments on Step 2 above recommend additional criteria to be explicitly added to Step 2 that are also applicable to reviewing studies asserting GTA in the open literature.

Criteria from EPA's data quality guidelines for quantitatively using ecotoxicity data in EFED assessments include the following. EPA's flow chart for assessing studies in the ECOTOX database, that are potentially relevant to an EPA assessment, is provided in Figures 1 and 2 of Appendix 1. EPA uses this evaluation procedure to classify studies as quantitative (i.e., study can be used quantitatively in an ERA for risk quotients), qualitative (*i.e.,* not appropriate for quantitative use, but is of sufficient quality, relevant to issues of concern in the risk assessment, and can be used descriptively in the risk characterization); or invalid (inappropriate for use in derivation of risk quotients and in risk description because it is of insufficient quality and lacks scientific defensibility).

Specific criteria EPA uses to evaluate peer-reviewed scientific literature for its relevancy and potential use in an ERA are summarized at a high level below:

- Endpoints from literature studies should be comparable to those used as inputs to the Risk Quotient method for expressing risk. These endpoints would include acute EC_{50}, LC_{50}, or LD_{50} values and chronic NOAEC values for animal and aquatic plant studies and EC_{25}, EC_{05}, and/or NOAEC for terrestrial plant studies.

[38] Borgert CJ, Price B, Wells CS, Simon GS et al. 2001. Evaluating chemical interactions studies for mixture assessment. Hum Ecol Risk Assess. 7:259-306.
[39] Levine SL and Borgert CJ. 2018. Criteria to Evaluate Pesticide Interaction Data for Relevance and Reliability to an Ecological Risk Assessment. Chemosphere. 209:124-136.
[40] EPA. 2010. Evaluation Guidelines for Ecological Toxicity Data in the Open Literature. https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/evaluation-guidelines-ecological-toxicity-data-open

- The test substances must be clearly defined. The study must indicate the exact nature and source of the pesticide. The percent active ingredient and/or the purity of the test compound (i.e., identification of the test material as technical grade active ingredient) should be reported. If a solvent is used, it should not interfere with the absorption, distribution, metabolism or elimination of the test substance nor alter the behavior/response of the test organisms. Studies which rely on solvents should include solvent controls to document that the solvent did affect measurement endpoints.
- Species, age, sex, size, life stage, source, and health of the test species should be reported. The test organisms, to the extent possible, should be of uniform weight, size and age, and have no history of pre-exposure to pesticides or other contaminants. Observed diseases and treatment must be reported.
- A suitable number of controls must be run to test whether study conditions are adequate. Control performance should be used as an indicator of whether study conditions and animal performance are adequate. Controls must be run concurrent with the study and failure to do so would invalidate the study. Studies which rely on solvents should report concurrent solvent controls. Mortality of greater than 10% in controls for most test species would invalidate acute studies. Studies reporting test chemical residues in the controls >LOD are invalidated as the ability of the study to discriminate a treatment effect may be compromised.
- Replication must be sufficient to adequately test for treatment effects. Insufficient replication limits the ability to perform important statistical evaluations of the data.
- The number of organisms tested per concentration level and the number of concentration or dosage levels evaluated must all be adequate. This type of information should be reported and be sufficient to yield statistically sound results. An inadequate number of test organisms per test level can also produce unreliable results. The appropriate comparable guideline study Standard Evaluation Procedure and/or Office of Prevention, Pesticides, and Toxic Substances 850 test guideline must be followed.
- Exposure method, route, and frequency of administration and length of the treatment period should be reported. The total volume of material administered (test substance plus carrier) to each organism or in feed or water each time administration is made must be reported. In addition, the frequency of administration and duration of the exposure must be reported. For all studies, the exposure conditions must be clearly described and documented. Where measured concentrations are not available, and/or they fluctuate markedly during the study period, it is difficult to characterize exposure to the extent that a dose-response (cause/effect) relationship can be documented. Typically, EPA rejects studies where measured concentrations deviate more than 20% and/or variability between treatment group-measured concentrations is renders treatment means statistically indistinguishable. Where only nominal concentrations are reported, the EPA reviewer must consider whether the test compound is subject to degradation, volatilization, and/or partitioning, such that exposure levels may be considerably different than the reported nominal values. Additionally, the EPA reviewer must consider whether test conditions may not adequately preclude exposure to other potentially confounding chemicals.

In such cases, the reviewer should consider the variability associated with the measured endpoints from the controls.

- Normal development times for the test species should be achieved. Where the development time for the control animals differs substantially from normal reported values, the reviewer must determine whether study conditions have impaired the animals' ability to thrive. In cases where development time is substantially different than what is typically observed for the test organisms, the study should be invalidated as the study's ability to distinguish treatment effects is uncertain.
- Guideline studies establish conditions under which the test organisms are most likely to thrive and where husbandry conditions will not confound the interpretation of the study. Reviewers must verify whether the environmental conditions of the study are adequately described and/or addressed to ensure that the test organisms are not adversely affected. This description should include: dimensions of the test container, the number of test organisms per cage or test container (i.e., biological loading rate); ambient temperature and humidity; photoperiod; description of the diet; source of the animal feed; source of the dilution water and a description of its chemical characteristics; and description of the toxicant delivery system and flow rate expressed as the average water volume of test solution passing through each test chamber in 24 hours. Loading rate of the study must ensure adequate husbandry conditions. Control performance and the variability associated with these measures will indicate suitability of the test environment.
- Studies should provide descriptive statistics that report measures of central tendency (e.g., means, medians) and measures of dispersion (e.g., standard deviations, standard errors) along with associated sample sizes (N values). The report should state which methods of statistical comparison (e.g., t-test, ANOVA, chi square) were used and the presumed nature of the data (parametric versus nonparametric).
- Analytical confirmations for treatments are required. Many journals in the field of environmental toxicology will not publish articles unless analytical confirmations are performed and reported.
- Although not required, inclusion of a positive control will help assess whether the test system can detect adverse effects. This adds tremendous validity to a study by showing that the test system is capable of detecting adverse effects.

Guidance on the design, analysis and interpretation of mixture data that can be used to inform an ERA should follow the recommendation outlined by Levine and Borgert (2018).[41] These recommended criteria reflect the consensus of the literature on interaction analysis from decades of research in pharmacology and toxicology and are broadly applicable to mixtures of drugs, pesticides, industrial chemicals and food additives. They are useful for researchers who design

[41] Levine SL and Borgert CJ. 2018. Criteria to Evaluate Pesticide Interaction Data for Relevance and Reliability to an Ecological Risk Assessment. Chemosphere. 209:124-136.

and analyze interaction studies, for risk assessors who use interaction data in risk assessments, and for those who make risk management decisions pertaining to pesticides.

- Dose-response curves for each active ingredient should include concentrations relevant to the ecological assessment, identify maxima, minima, inflection points (NOAEL), and regions of linearity for assessing parallelism of dose-responses.
- Each component and the mixture should be assessed in head-to-head assays to correctly interpret the results.
- An appropriate "no-interaction" hypothesis (e.g., concentration addition or response addition) should be explicitly stated and used as the basis for evaluating and interpreting interactions.
- Combinations of active ingredients should be evaluated at rates or concentrations and ratios that are relevant to the ecological assessment and across a sufficient range to support the goals of the assessment.
- An acceptable visual assessment of the response pattern in the context of biological variability, biological significance, statistical significance, and/or defined benchmark should be used to distinguish whether the response produced by a dose combination differs from that predicted by the "no-interaction" hypothesis.
- Potential interactions should be assessed at levels of biological organization relevant to the protection goals and the risk management objectives, using appropriate species, protocols, and quantitative endpoints.

Each of these five criteria should be considered when evaluating mixture data for GTA activity for risk assessment. Borgert et al. proposed a simple scoring algorithm as a means of evaluating interaction studies in a consistent fashion and comparing the strength of the evidence provided by different studies.[42] For each criterion, a study is assigned a score of zero if it fails, 0.5 if it partially satisfies, and 1 if it fully satisfies the criterion. A composite score can be calculated for any study by dividing the sum of the scores for all the criteria by five; hence, a composite score of zero is the lowest score that can be attained and one the highest.

This simple scoring algorithm does not attempt to weight the criteria, although it could be argued that some criteria are more important than others. Nonetheless, the criteria can be used to define the limits of interpretation of the data and to assess the ecological relevance of data regardless of the goals of the study. In addition, the criteria can be used to inform a weight of evidence evaluation, particularly when there are multiple data sets that reach contradictory conclusions for a specific type of interaction. Although one could set a particular score (e.g., at least 0.5) as a selection criterion for using interaction studies in a specific risk assessment, it is difficult to set a general cut-off score below which one should not use the data without knowing the goals of the assessment. A weight of evidence evaluation might include all the data weighted by the composite score for each study. It might also be appropriate to set a cut-off (e.g., 0.4) for using a

[42] Borgert CJ, Borgert SA, Findley KC. 2005. Synergism, antagonism, or additivity of dietary supplements: application of theory to case studies. Thromb Res, 117:123-132.

body of literature in which all the studies have low composite scores. Several studies have been evaluated that illustrate the use of the five criteria and this simple scoring algorithm (Levine and Borgert, 2018).

2. Should EPA consider standardizing a more detailed search and reporting approach, and how should EPA do that?

Yes, to improve standardization and efficiency of the interim process, EPA should adopt a standardized template to document Steps 1 (U.S. Patent Search and Identification) and 2 (i.e., relevancy assessment). Documentation of Steps 3 and 4 can be easily provided to EPA with screen shots in a standard format using the EPA calculator for assessing statistically significant deviations from additivity. An example template has been provided to help move towards standardization for Step 2 and is provided in Appendix 2. Specific comments on aspects of the statistical analysis are provided below, in the final section which addresses Question 4 (burdens).

3. Should EPA continue the interim evaluation process as described in this document? If so, what performance metrics should EPA consider before deciding the utility of this approach?

Yes, CLA and RISE fundamentally support continued use of the interim process, incorporating the refinements and suggestions included in these comments. As experience with the interim process accumulates, EPA may conclude that GTA claims in patents are irrelevant to FIFRA ERAs. At that point, it would be appropriate to discontinue implementation of the interim process. Against that backdrop, we understand EPA's question about performance metrics to mean: "how many additional reviews should EPA perform and how should the results be used to assess the utility of the interim process with a reasonable level of certainty."

CLA and RISE have conducted initial analyses to address the question of performance metrics, focusing on the number of patents that would need to be evaluated to test the hypothesis that assertions of GTA effects in granted patents would impact ERAs for pesticide active ingredients. Scenarios were developed to characterize the degree of confidence on the estimated proportion of impactful patents to ERAs making assumptions about the number of patents per active ingredient with GTA claims and the number of potentially impactful patents to the ERA. A strength of this approach is that it does not ignore the number of patents with GTA assertions for each active ingredient.

For example, with this scenario-based approach, the number of active ingredients that would need to be evaluated considering 95% confidence of ≤1% likelihood of a patent being impactful to an ERA can be estimated. Under the scenario where 20 active ingredients are evaluated, with each active ingredient having 20 granted patents with assertions of GTA effects and zero impactful patents discovered, the 95% upper bound on the proportion of impactful patents is <1%. In other words, to conclude with 95% confidence that the percent of impactful patents is

<1% with this scenario, one would need to evaluate 20 active ingredients and not find any patent with data or claims that are relevant to the ecological risk assessment.

Using this approach, or a similar approach, EPA can conduct an analysis to evaluate the utility of the interim process with an appropriate level of confidence. Although EPA has already completed 24 active ingredient reviews, some of these reviews were performed before the interim process was entirely developed. Consequently, the number of active ingredients (n = 3) that required guideline testing to inform the ERA is artificially inflated and should not be considered as failing the process because ultimately those assertions, through direct testing of GTA activity, did not impact the ERA for those active ingredients. Therefore, applying the existing interim process to a defined number of additional active ingredients will give EPA the ability to assess the utility for continuing the interim process.

While CLA and RISE agree that the interim process is sound and should be continued, we also believe the process could be substantially improved by allowing for self-evaluation and self-certification when assertions of GTA effects are shown not to be relevant or significant for ERA purposes (in Steps 2-4). To date, the interim process has primarily been used as part of the registration process for new active ingredients and to enable a limited number of specific combinations for use on specific herbicide tolerant (HT) crops. For these uses on HT crops, the interim process must be followed, along with a wind-tunnel assessment that examines spray droplet size, to enable approval of a mixing partner. To speed up the review process and quickly allow agronomically important tank mixtures, registrants should be given the ability to enable additional combinations once the mixing partner has been shown to pass the wind-tunnel requirements and has been shown to not be relevant in Step 2 or statistically significant in Step 4. Similarly, when a mixing partner does not have a single granted patent with an assertion of GTA effects, self-certification should be allowed.

We envision the self-certification process to work as follows for mixing partners that have satisfactory wind tunnel data: if a registrant documents the search methodology and the outcome of the search indicating that there are no granted patents with an assertion of GTA effects, the mixing partner would be allowed to tank mix via a self-certification process. Similarly, if granted patents with an assertion of GTA effects are identified in Step 1, and those assertions of GTA effects are shown not to be relevant to the ERA with the relevancy criteria in Step 2, the mixing partner should be enabled through self-certification. Finally, if granted patents with an assertion of GTA effects are shown to be relevant in Step 2, however, the data used to claim GTA effects is shown not to be statistically significant in Step 4, the mixing partner should be enabled through self-certification.

CLA is requesting that EPA consider implementing self-certification for the interim process as it relates to mixing partners for products intended for use on HT crops though either Step 1, Step 2 or Step 4 with a conclusion of non-significance.

4. **What applicant burden is associated with the activities described in this memorandum, including compiling, analyzing, and submitting the information? Does an estimate of 80 – 240 hours of burden per applicant cover the respondent burden associated with the interim process?**

Generally, the applicant burden associated with the activities described in the interim process, including compiling, analyzing, and submitting the required information is likely to fall within the range of 80 – 240 hours per active ingredient assessment. However, in some cases, particularly those with large patent portfolios, the burden could be as high as 500 hours.

IV. Conclusions

EPA's process for evaluating acute and chronic ecological risks for pesticides primarily relies on toxicity information from studies conducted with single active ingredients. This approach has historically enabled EPA to conduct assessments that are protective of the environment and human health. These assessments are protective because EPA uses "no adverse effect" thresholds in ERAs to protect against chronic effects and uses safety factors with acute endpoints so that there is a low probability of acute effects at environmental exposure levels. This approach is consistent with guidance on mixtures assessment from the NRC. In addition, EPA understands, consistent with the broad consensus of the scientific community, that interactions between pesticides are rare at environmentally relevant concentrations and unless there is scientifically relevant information indicating that an interaction could impact an ERA, the base assumption is one of no interaction. However, because of granted patents with assertions of GTA effects, EPA has developed the interim process.

CLA and RISE fundamentally support continuing the interim process as described in this document, and comments provided here are aimed at improving the efficiency and effectiveness of the interim process.

To date, EPA has used the interim process to evaluate 24 new active ingredient registrations. None of these reviews have ultimately impacted an existing EPA ERA. The results from the analysis of the first two dozen active ingredients indicate that there is a low probability that patent claims asserting GTA effects will impact ERAs for pesticide active ingredients. Therefore, CLA and RISE support EPA's plans to evaluate the results of the interim process, and once a sufficient number of reviews are completed, to decide whether continuing the process has utility in evaluating ecological risk associated with product use. If the outcome of EPA's future evaluation demonstrates that granted claims asserting GTA effects are not relevant to ERAs under FIFRA, CLA and RISE agree that registrants and EPA should not waste time and resources and should discontinue such evaluations. However, while the interim process is still being used several efficiencies can be recognized, as recommended within, to further standardize the process and make it even more effective. An important area where efficiencies can be

recognized would be for EPA to permit self-certifications for specific combinations that would be used with products registered for use on HT crops. The interim process is amenable to self-certification in cases where there are no GTA claims for those combinations (Step 1), where all identified patents with assertions of GTA effects are concluded to not be relevant (Step 2) and where the assertion of GTA effects in the patent are not statistically significant (Step 4). Under the self-certification process EPA would have the ability to audit the documented evaluations that would be submitted for accuracy and compliance with the interim process.

Thank you for reviewing these comments. Please contact us if you have any questions or require additional information.

Respectfully submitted,

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Appendix 1

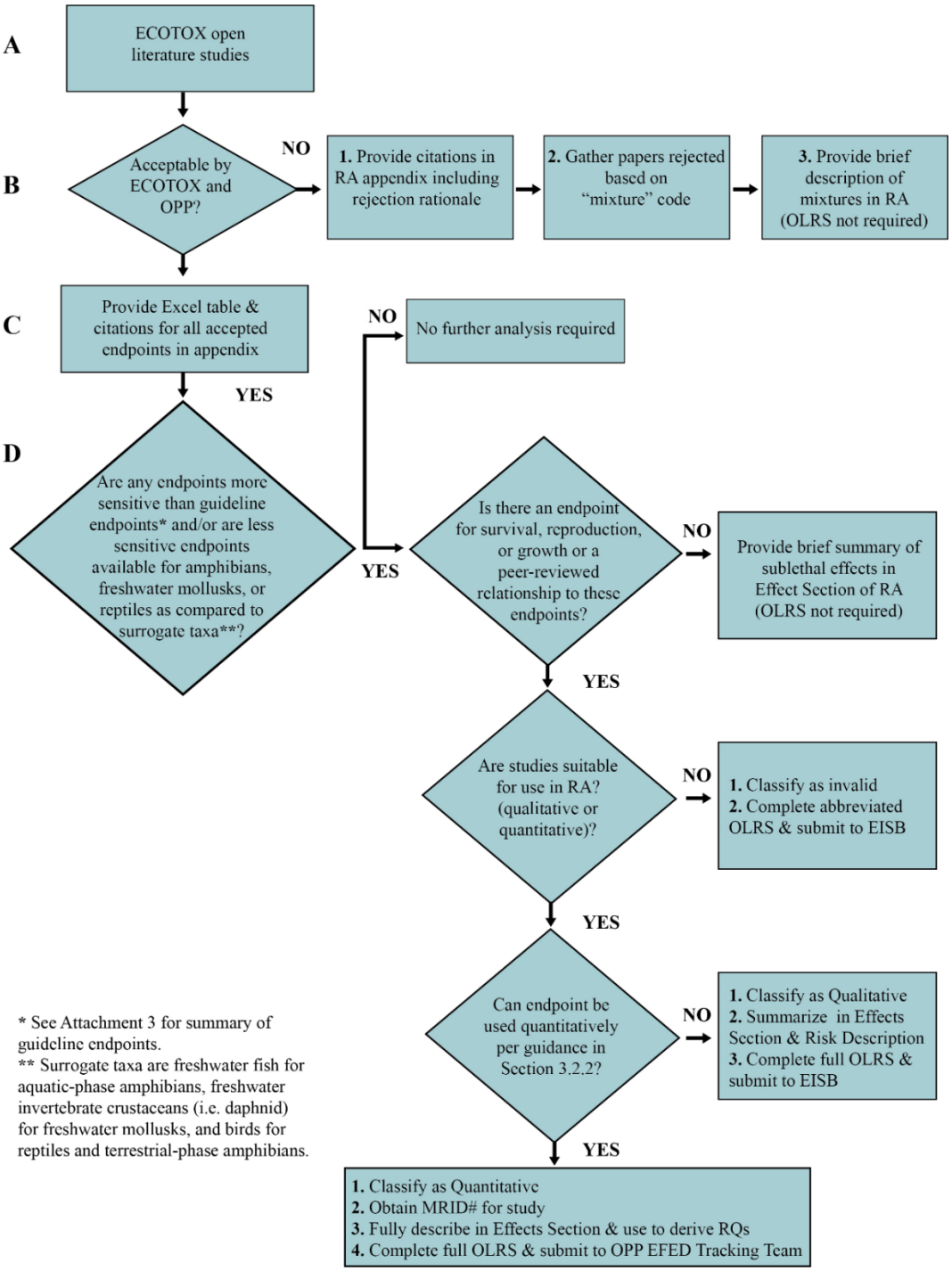

Figure 1: Screening, Review, and Documentation Process for ECOTOX Open Literature used by EPA.

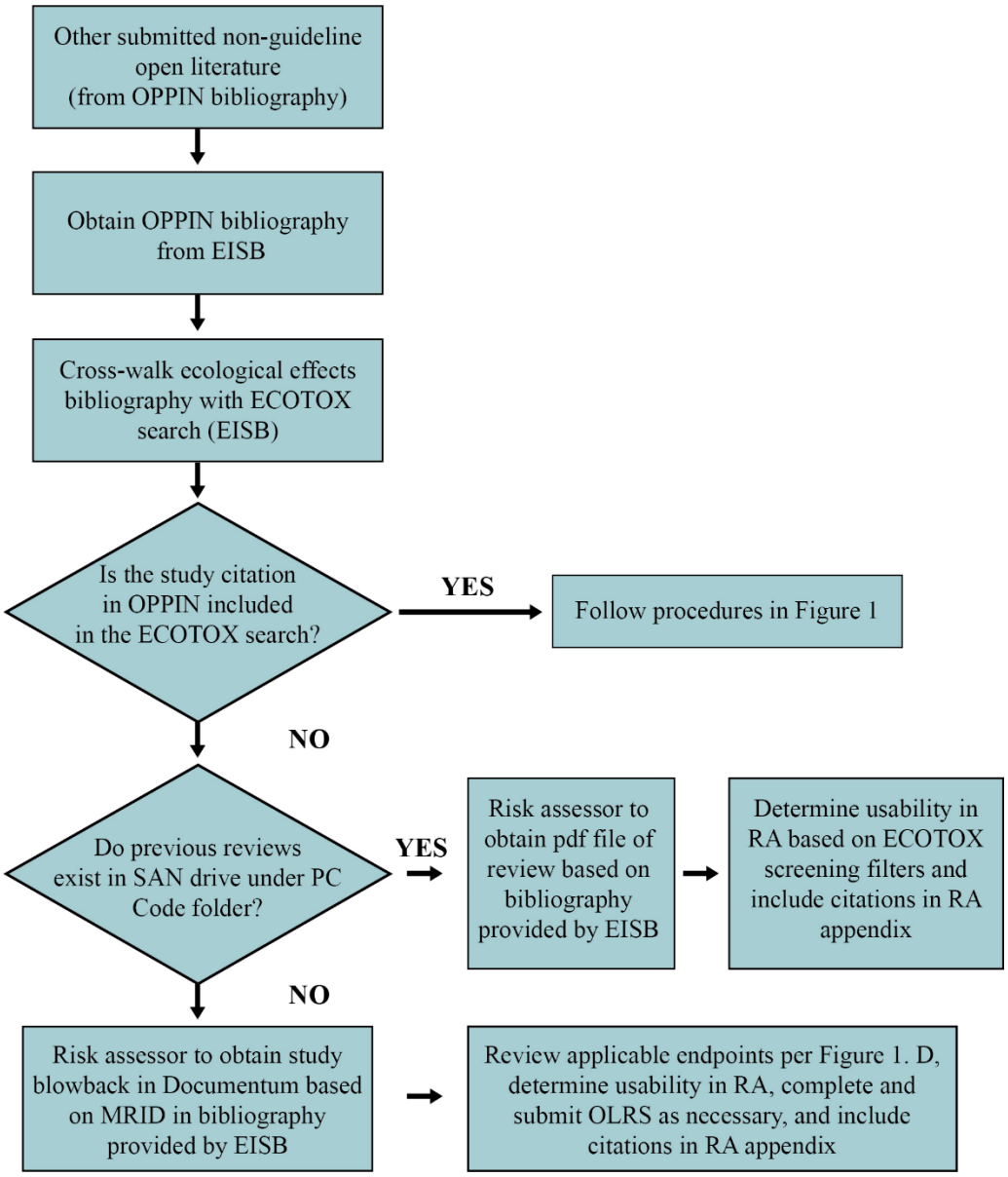

Figure 2: Screening, Review, and Documentation Process used by EPA for Other Submitted Non-Guideline Open Literature Data Cited in OPPIN.

Appendix 2

US Synergy Patent Data Search for [active ingredient]
EPA Registration Number:

Chemical Identifiers:	**[chemical name], [chemical analogue name], [IUPAC name], [CAS Name], etc.**
Relevant search terms:	synergy, synergistic, synergism, excess **toxicity, interaction, and Colby**
Databases searched:	**US PTO, etc.**
Number of Relevant patents(s)	

Relevancy assessment of patent Search Results with claims of greater than additive (GTA) effects for active ingredient under review:

Patent Number(s):	Mixing Partner(s):	(Criteria 1) Mixing partner registered in US (yes or no)	(Criteria 2) Claim contains empirical effects comparison (yes or no)	(Criteria 3) Claim cites direct effects on tested taxa (yes or no)	(Criteria 4) Tested taxa are relevant to ERA (yes or no)	(Criteria 5) Test data available for chemical under review (yes or no)	Data determined statistically significant (N/A, yes or no)

Note:

- If response is "yes" for criteria 1-5, registrant must evaluate statistical significance of available data using the most recent version of the established EPA templates. The results of the statistical analysis will be summarized and reported.