March 21, 2019

Rick Keigwin, Director
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U.S. Environmental Protection Agency
1200 Pennsylvania Ave. NW
Washington, DC 20460-0001

Submitted via regulations.gov

RE: Docket # EPA-HQ-2018-0262; Petition Seeking Revised Testing Requirements for Pesticides Prior to Registration, 83 Fed. Reg. 65672 (December 21, 2018)

Dear Mr. Keigwin:

CropLife America (CLA),[1] RISE (Responsible Industry for a Sound Environment)®,[2] the Council of Producers and Distributors of Agrotechnology (CPDA)[3] and the Biological Products Industry Alliance (BPIA)[4] appreciate the opportunity to comment on the petition filed by Center for Food Safety (CFS) "Petition Seeking Revised Testing Requirements of Pesticides Prior to Registration" (Petition). For the reasons explained below, CLA, RISE, CPDA and BPIA encourage the U.S. Environmental Protection Agency (EPA or Agency) to deny CFS's Petition.

[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.
[3] CPDA is the premier advocate for agricultural adjuvant and inert ingredient suppliers. CPDA also provides legislative and regulatory support to formulators, distributors and manufacturers of post-patent pesticide products and biorationals. CPDA members produce and sell tank-mix adjuvants, inert ingredients, pesticides and other agrotechnology products across the United States and range in size from small businesses to large, publicly traded companies. Approximately 80% of the inert ingredients used in agricultural production products throughout the U.S. are provided by CPDA members.
[4] BPIA is the leading organization dedicated to fostering the use of biological technology including biopesticides and biostimulants. Biological products are reduced-risk products based on naturally derived chemistry. BPIA is a growing association with now over 130 member companies around the world ranging from small, innovative sole proprietors to large, international corporations. BPIA's members provide solutions that benefit growers, consumers, and the environment.

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. To register a pesticide product, the registrant must provide EPA with a large amount of data on the product chemistry, health, safety and environmental characteristics. These data must be sufficient to allow EPA to conclude that the product will "perform its intended function without unreasonable adverse effects on the environment" and that "when used in accordance with widespread and commonly recognized practice it will not generally cause unreasonable adverse effects on the environment."[5]

EPA's regulations establish an extensive set of data requirements that must be satisfied before a pesticide can be registered.[6] The specific tests that must be conducted are determined 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 core and conditional testing regime is structured to develop a broad and comprehensive body of health and safety data on active ingredients, and to require more narrowly targeted testing for the formulated products that incorporate those active ingredients.[7] EPA has relied on this testing 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.

The Petition seeks to upend EPA's well-established testing regime, to require that essentially all tests currently required under the Part 158 regulations be conducted on end-use products and tank mixes. Petitioner argues that the current testing requirements are inadequate because EPA cannot predict how the hazard characteristics of a product's active ingredient(s) may be affected by the inert or other ingredients included in a formulated end-use product or tank mixture. In particular, Petitioner suggests that inert ingredients may interact synergistically with active ingredients in ways that EPA cannot predict and that additive effects are not accounted for in risk assessments.[8] Therefore, Petitioner argues, EPA must require that the entirety of testing called

[5] 7 U.S.C. § 136a(c)(5).

[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 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] Petition at 1, 4, 11-16. It is worth clarifying the two types of effects to which Petitioner alludes. An additive effect from combining two or more ingredients is identified by adding together either the separate responses to the separate substances or, if the substances share the same mode of action, adding together the exposures to various substances, adjusted to account for differing potencies. National Research Council, Assessing Risks to Endangered and Threatened Species from Pesticides (2013) at 110. *Available at:* https://doi.org/10.17226/18344. The second type of effect is synergistic, "where the compounds in the mixture interact and the effects are… more than calculated from the [additive] models assuming no interaction." EMJ Verbruggen & PJ van den Brink, Review of Recent Literature Concerning Mixture Toxicity of Pesticides to Aquatic Organisms, RIVM Report 601400001/2010, 9 (2010).

for under the Part 158 regulations be conducted on every end-use product formulation and tank mixture.[9]

CLA, RISE, CPDA and BPIA oppose the unnecessary expansion of testing sought by the Petition. Petitioner is incorrect in asserting that inert ingredients add to the hazards of active ingredients in ways that EPA cannot anticipate and evaluate. EPA requires considerable data on inert ingredients and conducts structure activity modeling (*e.g.*, assessing carcinogenicity with DEREK11) to support tolerance exemptions and the maximum allowable percent of the component in a formulation. Moreover, EPA can request additional information on a case-by-case basis for inert ingredients, formulations and tank mixtures to support safety assessments. In addition, there is scientific consensus that synergistic (significantly greater than additive activity) effects in real-world applications are exceedingly rare.[10] Finally, the Petitioner is incorrect in asserting that Congress intended to require comprehensive testing on each end-use formulated product. In fact, the expanded testing sought by the Petitioner would run counter to Congressional intent, cause substantial harm to pesticide producers and farmers, and result in a massive and needless increase in animal testing.

II. Specific Comments

A. EPA Can And Does Assess Whether Inert Or Other Ingredients Will Add To The Hazards Of Active Ingredients In End-Use Products

The central premise underlying the Petition is that formulated pesticides "are generally more toxic than active ingredient(s)" alone, due to synergistic or additive effects, and that EPA cannot predict the effects of combining an inert or other ingredient with an active ingredient without requiring a complete complement of tests on each formulated product made with the active ingredient(s). This is untrue and additional testing of this scope and nature is unnecessary and inappropriate.

1. There is Scientific Consensus that Synergistic Effects are Very Rare

It is widely accepted among researchers that have studied the issue that "true" synergistic interactions between pesticide ingredients are rare and are generally not predicted to occur under exposure scenarios that are relevant to the lawful use of registered pesticide products.[11] As a

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[9] Petition at 2, 16-19. It should be noted that tank mixing provides practical, economic and agronomic benefits that are critical for farmers. In addition, mixing pesticides that work via different modes of action is an essential component of a comprehensive pest resistance management program.

[10] It is also important to point out that the Petitioner incorrectly defined the term synergy as it is used by EPA and the toxicology community. The Petitioner defines a synergy as "is the interaction of two or more ingredients in a mixture in such a way as to enhance their toxic effects beyond the effects of each individual ingredient." However, a synergistic (greater-than-additive) effect occurs when the combined effects of two chemicals are much greater than the sum of the effects of each component alone (example: 2 + 2 = 20). LJ Casarett, CD Klaassen, MO Amdur, J Doull, Casarett and Doull's Toxicology: The Basic Science of Poisons, McGraw-Hill, Health (1996).

[11] *See, e.g.*, N. Cedergreen, Quantifying Synergy: a Systematic Review of Mixture Toxicity Studies Within Environmental Toxicology, PLoS One 9 (2014); A Kortenkamp, R Evans, M Faust, F Kalberlah, M Scholze, & U Schuhmacher-Wolz,. Investigation of the State of the Science on Combined Actions of Chemicals in Food Through Dissimilar Modes of Action and Proposal for Science-Based Approach for Performing Related Cumulative Risk Assessment, Supporting Publications 2012:EN-232 (2012), *available at* https://doi.org/10.2903/sp.efsa.2012.EN-232; EMJ Verbruggen & PJ van den Brink, Review of Recent Literature Concerning Mixture Toxicity of Pesticides to Aquatic Organisms, RIVM Report 601400001/2010, 9 (2010); National Research Council, Assessing Risks to

result of this scientific consensus, the National Research Council recommended that regulatory agencies assume that synergistic effects are not occurring unless relevant and reliable data indicates otherwise and at concentrations that are relevant to the risk assessment.[12]

Because of this scientific reality, EPA has previously rejected expanded testing of the sort now being sought by Petitioners. For example, until the early 1980s, EPA required the submission of data regarding mixtures of pesticides before it would permit tank mixes, but years' worth of this "data for tank mixes and records of actual field experience" showed that synergistic effects are unlikely to occur. As a result, the Agency revised its policy and decided to approve tank mix label claims without specific data, as long as "[t]he chemical characteristics of all products to be used in the mix are such that no incompatibility or potentiation [i.e. synergy] is likely to occur" although EPA reserved "the right to request appropriate data if it determines that a problem could arise." Thus, EPA decided not to require data on every individual mixture because there was no benefit to this deluge of information which served only as a "data generation burden on registrants as well as [a] review burden on the Agency."[13]

Subsequent experience has not provided a basis for reversing this well-reasoned, evidence-based decision. Decades after finding that testing of tank mixes is unnecessary because synergy is rare, EPA once again considered the need for data on interactions between active ingredients and other substances and determined that "[s]uch testing rarely shows any kind of interaction (synergistic or antagonistic), and there are a nearly infinite number of possible combinations" so "the scientific community believes that exposure to multiple chemicals is best assessed by looking the [sic] effects caused by exposure to each chemical individually." EPA did note, however, that the effects of pesticides that share a common mechanism of toxicity "are expected to be additive," so the Agency assesses combined exposures in cumulative risk assessments.[14]

Like EPA, the National Research Council has reviewed the data regarding the potential for synergistic effects of pesticides to wildlife. After concluding that synergistic effects are unlikely to occur as a result of the lawful use of registered pesticide products, the Council concluded that "[i]n the absence of any data that would support the hypothesis of a synergistic interaction between the pesticide active ingredient and other mixture components" the assessment of a mixture's hazards "should proceed on the assumption that the components have additive [not synergistic] effects."[15] Based on its review of the pertinent data, EPA also considers true synergism among ingredients in pesticides to be rare. Consequently, the Agency has decided to

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Endangered and Threatened Species from Pesticides (2013) at 112-118, *available at* https://doi.org/10.17226/18344; P Price, Synergy: A Risk Management Perspective, in Principles and Practice of Mixtures Toxicology 371-388 (M. Mumtaz, ed., 2010); P Kudsk, HR Andersen, N Cedergreen, SK Mathiassen, F Møhlenberg, JC Streibig, & AM Vinggaard, Combined Effects of Pesticides, Pesticide Research from the Danish Environmental Protection Agency No. 98 (2005).

[12] National Research Council, Assessing Risks to Endangered and Threatened Species from Pesticides (2013) at 134. Available at: https://doi.org/10.17226/18344.

[13] Pesticide Registration Notice 82-1, available at https://www.epa.gov/pesticide-registration/prn-82-1-revised-policy-label-claims-tank-mixing.

[14] 72 Fed. Reg. 11784 (March 14, 2007) at 11788.

[15] National Research Council, Assessing Risks to Endangered and Threatened Species from Pesticides (2013) at 112-118; 134. Available at: https://doi.org/10.17226/18344.

follow the National Research Council's recommendation and estimate potential mixture effects from the effects of each component, *unless* the Agency has specific reason to believe there may be synergistic effects.[16]

Petitioner attempts to support its position by arguing that synergistic effects are "often the subject of chemical company patents."[17] However, patent claims for synergy are not necessarily a reliable indicator of effects that would impact regulatory assessments and decision making under FIFRA. In part, this is because the data supplied with a patent application for a pesticide (i) do not necessarily reflect registered uses of the pesticide (ii) are typically not generated at application rates that are ultimately approved for the FIFRA-registered product; (iii) do not necessarily reflect the composition of the commercial formulation(s) that is registered; and (iv) may not have sufficient replication. In addition, the test methods used in the patent typically do not follow established regulatory testing methods and endpoints that are applicable to a regulatory risk assessment. It has also been well established that synergy relies upon the exceedance of an "interaction threshold," and exposure levels that are below an effect threshold will not result in synergistic effects even if synergy is observed in the laboratory at high concentrations.[18] Consequently, the data submitted to support a pesticide patent based on a claim of synergy conducted at levels that exceed environmentally relevant exposure levels may be of limited, if any, relevance to the regulation of that pesticide product under FIFRA. Extrapolation of synergistic effects observed at higher doses to lower doses is not justified on either a theoretical or an empirical basis.

Moreover, in response to concerns regarding the potential for synergism, EPA implemented "a screening process to determine whether or not information supporting" claims of synergy in a granted patent is relevant to EPA's ecological risk assessments. Based on the results of the screening process for the active ingredients that had been evaluated to date, EPA concluded that data contained in patents supporting a claim of synergy are "of little value" for risk assessment purposes.[19] As of May 2017, EPA had looked at eight active ingredients where patent applications included synergy claims for an applicant's pesticide. In two of those cases, the registrants provided guideline tests conducted with the formulation as the most expedient way to support the assessment.[20] Ultimately, the additional testing did not result in changes to EPA's risk conclusions based on the risk assessment of the individual components in the formulations.[21] Thus, claims of synergy in those two granted patents do not contradict the established fact that synergy is very rare under the conditions of use regulated by EPA.

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[16] *See, e.g.*, USEPA, Final Registration Decision of the New Active Ingredient Halauxifen-methyl (July 28, 2016) at p. 8, available at https://www.regulations.gov/document?D=EPA-HQ-OPP-2012-0919-0024.

[17] Petition at 12.

[18] P Price, Synergy: A Risk Management Perspective, in Principles and Practice of Mixtures Toxicology 371-388 (M. Mumtaz, ed, 2010); SL Levine & CJ Borgert, Review and Recommendations on Criteria to Evaluate the Relevance of Pesticide Interaction Data for Ecological Risk Assessments, 12 Chemosphere 124-136 (doi: 10.1016/j).

[19] Pesticide Program Dialogue Committee Meeting Day One – May 3, 2017 at 163. Available at: https://www.epa.gov/sites/production/files/2017-07/documents/may-3-2017-ppdc-meeting-transcript.pdf.

[20] *Id.* at 164.

[21] *Id*. at 158.

2. *EPA Can Accurately Assess the Risks Associated with Formulated Products Based on Data Collected on the Individual Components of the Formulation*

Petitioner incorrectly contends that EPA cannot anticipate the effects of inert and other ingredients in formulated products and that, therefore, a complete battery of testing of all end-use formulations is required. The reality is that: (i) as discussed above, synergy is rare and most chemical mixture effects are additive; (ii) there are reliable models for understanding the additive effects of multiple ingredients; and (iii) EPA effectively applies these models when it registers formulated pesticide products.

When appropriate toxicity data for the individual ingredients in a formulation exist and there is no evidence of synergistic interactions, a model that assumes additive effects either the "response addition" model or the "concentration addition" model can be used to accurately predict mixture toxicity.[22] Concentration addition predicts mixture effects based on the assumption that each chemical in the mixture behaves as a form of the same component of the mixture, and is best utilized with respect to chemicals that share a common mode of action.[23] Concentration addition is often selected as the default additivity model, because it often provides more conservative estimates of combined toxicity.[24]

The response addition model (also known as the independence model) assumes that the joint effect of multiple components can be calculated from the response of the test system to each individual mixture component. An underlying principle of the response addition model is that the components of a mixture elicit their effects independently.[25] Response addition has typically been the model of choice for predicting the effects of mixtures of components with different modes of action (i.e. compounds that act mechanistically independently). Under the tenets of the response addition model, components present at concentrations below their no-effect levels will not contribute to the joint effect of the mixture, and so combined effects are not predicted.[26] The predictability of this model is reflected in the studies of Feron, Groten, van Zorge, Cassee, Jonker, van Bladeren, Könemann and Pieters, which found that exposure to non-toxic low doses of mixtures of substances with different modes of action do not represent an increased risk

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[22] US EPA, Guidelines for the Health Risk Assessment of Chemical Mixtures (Sept. 24, 1986), Fed. Reg. 51;34014; Committee of Toxicity; Risk assessment of mixtures of pesticides and similar substances (2002), available at https://cot.food.gov.uk/sites/default/files/cot/reportindexed.pdf; National Research Council, Assessing Risks to Endangered and Threatened Species from Pesticides (2013), available at https://doi.org/10.17226/18344.

[23] N Cedergreen, Quantifying Synergy: a Systematic Review of Mixture Toxicity Studies Within Environmental Toxicology, 9(5) PLoS One e96580 (2014), *available at* https://doi.org/10.1371/journal.pone.0096580; MC Berenbaum, What is Synergy?, 41 Pharmacol Rev. 93-141 (1989). *See also* VJ Feron, JP Groten, JA van Zorge, FR Cassee, D Jonker, & PJ van Bladeren, Toxicity Studies in Rats of Simple Mixtures of Chemicals With the Same or Different Target Organs, 82-83 Toxicol Lett. 505-12 (1995).

[24] US EPA, Guidelines for the Health Risk Assessment of Chemical Mixtures (Sept. 24, 1986), Fed. Reg. 51:34014.

[25] *Id.*

[26] VJ Feron, JP Groten, JA van Zorge, FR Cassee, D Jonker, & PJ van Bladeren, Toxicity Studies in Rats of Simple Mixtures of Chemicals With the Same or Different Target Organs, 82-83 Toxicol Lett. 505-12 (1995); Committee of Toxicity, Risk Assessment of Mixtures of Pesticides and Similar Substances (2002), *available at* https://cot.food.gov.uk/sites/default/files/cot/reportindexed.pdf. *See also*, National Research Council, Assessing Risks to Endangered and Threatened Species from Pesticides (2013) p. 97, *available at* https://doi.org/10.17226/18344.

compared with exposure to single substances in low doses.[27] It is important to point out that EPA's risk management practices limit chronic exposures of mixture components to levels that are below chronic no-observed-adverse-effect-levels (NOAELs) from animal studies. In addition, human safety assessment safety factors are further placed on NOAELs, which greatly reduces the likelihood of combined effects.

EPA has a long history of successfully applying these models to assess additive effects of multiple components.[28] When considering tank mixtures, EPA frequently applies the response addition model and bases risk assessments on this model's principle that "as long as the applicator/handler follows the most restrictive use directions for all chemical partners in the tank mix, there are no unidentified or additional risks with use of tank mixes." The Agency uses the concentration addition model when conducting cumulative risk assessments, first "identifying the chemicals that belong in" a common mechanism group, and then using "dose addition" as the default assumption, unless there is evidence of synergism or antagonism.[29] EPA's long history of successfully using these models demonstrates that the Agency can determine the likely effects of formulated pesticides without requiring duplicative testing to support its conclusions.

B. EPA Already Sufficiently Accounts for Potential Risks from Formulations

Contrary to Petitioner's assertions, when EPA reviews an application to register an end-use pesticide product, the Agency considers the hazard characteristics of the product's inert ingredient(s) as well as the active ingredient(s) and the likely effects of the formulated product.

1. EPA Acquires Robust Information on Inert Ingredients Before Allowing Them to Be Used in Formulations

EPA has assessed the likelihood of harm from inert ingredients since the mid-1980s, when the Agency announced it would require data to approve the use of inerts.[30] From 2006 to 2009, EPA conducted tolerance reassessments on all inert ingredients then approved EPA reviews and approves every single inert ingredient before it can be used in any formulated product.[31] If the inert will be used in a food use pesticide, EPA must also determine and codify a specific tolerance or tolerance exemption.[32] To review the inert and decide whether to approve its use and, if applicable, its tolerance, EPA requires that an applicant provide "sufficient data to make a

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[27] VJ Feron, JP Groten, JA van Zorge, FR Cassee, D Jonker, & PJ van Bladeren, Toxicity Studies in Rats of Simple Mixtures of Chemicals With the Same or Different Target Organs, 82-83 Toxicol Lett. 505-12 (1995); FR Cassee, JP Groten, PJ van Bladeren, & VJ Feron, Toxicological Evaluation and Risk Assessment of Chemical Mixtures, 28 Critical Reviews in Toxicology 73-101 (1998); VJ Feron & JP Groten, Toxicological Evaluation of Chemical Mixtures, 40 Food and Chemical Toxicology 825-839 (2002); JP Groten, Mixtures and Interactions, 38 (Suppl.) Food Chem. Toxicol. S65-71 (2000); WH Könemann & MN Pieters, Confusion of Concepts in Mixture Toxicology, 34 Food Chem. Toxicol. 1025-31 (1996).

[28] *See, e.g.*, USEPA, Final Registration Decision of the New Active Ingredient Halauxifen-methyl (July 28, 2016) at p. 7, available at https://www.regulations.gov/document?D=EPA-HQ-OPP-2012-0919-0024.

[29] EPA, Guidance on Cumulative Risk Assessment of Pesticide Chemicals That Have a Common Mechanism of Toxicity, p. iii, 31 available at https://www.epa.gov/sites/production/files/2015-07/documents/guidance_on_common_mechanism.pdf.

[30] 49 Fed. Reg. 42862 (Oct. 24, 1984).

[31] EPA, Inert Ingredient Frequently Asked Questions, p. 2, available at https://www.epa.gov/sites/production/files/2015-12/documents/faqs.pdf.

[32] *Id.*

safety determination regarding human dietary risk under the [Federal Food, Drug, and Cosmetic Act] FFDCA … and to determine that […] the ingredient will not present unreasonable adverse effects to the environment."[33] To make these determinations, EPA requires submission of data on physical and chemical properties, the specific purpose of the inert ingredient in formulations, and the intended use patterns. EPA also typically requires the applicant to provide information on acute toxicity, chronic toxicity, reproductive and developmental toxicity, as well as modeling mutagenicity and carcinogenicity, and considering animal metabolism, routes of exposure, environmental fate and effects, and ecotoxicity.[34] For food-use inerts, a petition for a tolerance or tolerance exemption must be submitted, providing even more extensive information than that required for non-food use applications.[35] Based on the submitted information, EPA conducts a risk assessment before deciding on the safety of the inert, and will reject the application if the supporting data are insufficient.[36]

It should also be noted that inert ingredients (unlike active ingredients) are regulated and subject to EPA review under the Toxic Substances Control Act (TSCA).[37] Under TSCA, before a new inert can be manufactured, EPA must review the data regarding the substance and affirmatively determine that the reasonably foreseen uses of the inert are "not likely to present an unreasonable risk of injury to health or the environment including an unreasonable risk to a potentially exposed or susceptible subpopulation."[38] If EPA does not have sufficient data to make such a finding, it can order the development of additional data.[39] Thus, EPA will review data regarding a new inert ingredient under two different regulatory programs, both of which grant the Agency the power to prohibit use, absent sufficient data to demonstrate the safety of the ingredient.

2. EPA Specifically Assesses the Effects of the Complete Formulation, Including Inert Ingredients, As Well As Tank Mixes

When registering an end-use pesticide product, EPA considers both the additive effects of the inert ingredient(s) in the formulated product as well as potential synergistic effects with the active ingredient(s). EPA maintains a list of approved inert ingredients for which the Agency

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[33] EPA, Inert Ingredient Frequently Asked Questions, p. 4, available at https://www.epa.gov/sites/production/files/2015-12/documents/faqs.pdf.

[34] EPA, General Guidance for Requesting the Approval of a New Nonfood Use Inert Ingredient or Amending a Currently Approved Nonfood Use Inert Ingredient under PRIA 3, p. 3-4, *available at* https://www.epa.gov/sites/production/files/documents/nonfood_inert.pdf; EPA, General Guidance for Petitioning the Agency for the Establishment of a New/Amended Food Use Inert Ingredient Tolerance or Tolerance Exemption under PRIA 3, p. 4-5, *available at* https://www.epa.gov/sites/production/files/2015-12/documents/inertpetition.pdf.

[35] EPA, General Guidance for Petitioning the Agency for the Establishment of a New/Amended Food Use Inert Ingredient Tolerance or Tolerance Exemption under PRIA 3, p. 2-5, *available at* https://www.epa.gov/sites/production/files/2015-12/documents/inertpetition.pdf.

[36] EPA, General Guidance for Requesting the Approval of a New Nonfood Use Inert Ingredient or Amending a Currently Approved Nonfood Use Inert Ingredient under PRIA 3, p. 6, *available at* https://www.epa.gov/sites/production/files/documents/nonfood_inert.pdf; EPA, General Guidance for Petitioning the Agency for the Establishment of a New/Amended Food Use Inert Ingredient Tolerance or Tolerance Exemption under PRIA 3, p. 7, *available at* https://www.epa.gov/sites/production/files/2015-12/documents/inertpetition.pdf.

[37] EPA, Questions & Answers for the New Chemicals Program, p. 2-18, *available at* https://www.epa.gov/sites/production/files/2015-09/documents/qanda-newchems_new.pdf.

[38] 15 U.S.C. § 2604(a)(3)(C).

[39] 15 U.S.C. § 2604(e)(1).

has reviewed data and determined the substance's safety for use in formulated products.[40] When EPA receives an application for registration for an end-use product, the Agency reviews the confidential statement of formula to "ensure that all inert ingredients are either approved or pending with the Agency for the labeled use of the pesticide formulation."[41] Despite having previously reviewed and approved the inert ingredient when it was added to the list of approved inert ingredients, EPA again considers the safety of the inert ingredient in the proposed pesticide formulation by "requir[ing] acute toxicity data for end-use products, i.e., formulations containing active and inert ingredients." Among other things, these studies allow EPA to assess "potential synergistic effects of mixtures of active and inert ingredients in a pesticide product."[42]

In addition to evaluating the safety data for the inert ingredient and acute toxicity data for the complete formulation as part of the human safety assessment, EPA also considers all anticipated effects from the formulated product, including possible synergistic effects. EPA has considered the possibility of synergism since the mid-1980s, when the Agency stated it would require testing of formulations if it had reason to believe synergism might occur.[43,44] For example with herbicidal formulations, where adjuvants are added to the formulation to increase the uptake of the active ingredient, non-target plant testing with a typical end-use product is required under the Part 158 regulations to account for this interaction. Thus, even though EPA does not require all tests on all formulated end-use products, the Agency adequately considers the effects of formulated products and tank mixes, and requires whatever tests are justified based on its reasoned analysis of the combined risks from pesticide products' ingredients.

More recently, EPA has been screening pesticide patents, as well as the publicly available scientific literature, to determine whether a pesticide under consideration may have synergistic interactions or if an adjuvant in the formulation exerts toxicity to aquatic organisms in a way that would impact the Agency's risk assessment. EPA also considers whether it knows of any possible mechanism of interaction or if the Agency would benefit from additional data.[45] Where EPA finds possible effects from synergism, the Agency requires additional guideline studies on the formulated product.[46] EPA routinely undertakes this assessment for potential tank mix partners to a new active ingredient, and has prohibited the use of specific tank mix partners for which a claim of synergism exists in patents, unless additional testing is performed to address potential synergy or if the claim is concluded not be relevant to a safety assessment.[47]

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[40] See, e.g. https://www.epa.gov/pesticide-registration/pesticide-registration-manual-chapter-1-overview-requirements-pesticide#products (stating that "the [adjuvant] ingredient is reviewed during registration and any necessary tolerances or exemptions from the requirement of a tolerance are established.").

[41] https://www.epa.gov/sites/production/files/2014-05/documents/faqs.pdf.

[42] 49 Fed. Reg. 42862 (Oct. 24, 1984).

[43] *Id.*

[44] 71 Fed. Reg. 45726 (Aug. 9, 2006).

[45] Pesticide Program Dialogue Committee Meeting Day One – November 1, 2017 at 165. *Available at* https://www.epa.gov/sites/production/files/2018-01/documents/november-1-2017-ppdc-meeting-transcript.pdf.

[46] *Id.* at 157, 160.

[47] *See, e.g.*, USEPA, Final Registration Decision of the New Active Ingredient Florpyrauxifen-benzyl (Sept. 8, 2017) at p. 10-11, *available at* https://www.regulations.gov/document?D=EPA-HQ-OPP-2016-0560-0065, USEPA, Final Registration Decision of the New Active Ingredient Halauxifen-methyl (July 28, 2016) at p. 9, *available at* https://www.regulations.gov/document?D=EPA-HQ-OPP-2012-0919-0024; USEPA, Registration Decision of

EPA has developed a comprehensive process to evaluate the relevance of synergy claims in granted patents to environmental risk assessments and if necessary can require additional studies on the mixtures to inform regulatory decision making.[48] In two registration cases, patent information was used to evaluate pesticide interaction for formulations with multiple active ingredients. In both cases, the EPA and the registrant determined that the most direct and efficient way to address the observed effects was testing of the end-product formulations to inform the ecological risk assessment. In all the other cases, patent data claiming a synergy has not been relevant for the ecological risk assessment. In the near term, EPA will continue to evaluate specific cases of synergy claims in granted patents. As EPA gains more experience with these evaluations, the Agency can eventually conclude if there is long-term value by continuing to review synergy claims in granted patents. However, in the near term, EPA should consider implementing a self-reporting process for patent reviews that would document whether a patent claiming synergy is relevant to an ecological risk assessment. Under this process, registrants would be responsible for following EPA's interim evaluation process. This self-evaluation process would enable an efficient and predictable outcome when determining the relevance of given patents claiming synergy to an EPA ecological risk assessment. If the established review process concludes that a patent could be potentially impactful, then EPA would take a hard look at the data in the patent and make the final determination if there is an impact to a risk assessment.

C. In addition to Being Unnecessary, the Testing Sought by the Petition is Contrary to Congressional Intent and Impractical

Petitioner is wrong in suggesting that, to comply with FIFRA, EPA must require a full battery of testing on every end-use product formulation it registers. First, as discussed above, EPA can use its scientific expertise and the extensive data required for active and inert ingredients to determine if a particular formulation satisfies FIFRA's statutory standard, and if EPA concludes that the available data are inadequate, the Agency can require additional data on the formulated product or refuse to register the product. Thus, EPA is able to successfully fulfill its duty to analyze and address potential adverse effects of formulated products *without* requiring expansive testing of each and every end-use product and tank mixture.

Furthermore, EPA's decision not to require a complete battery of tests on all formulated products is consistent with Congressional intent. As the Senate made clear when amending FIFRA in 1978, Congress "authoriz[ed] the Administrator to make one safety finding on a basic ingredient that would apply to all pesticides using that ingredient."[49] Congress specifically found that "once the Administrator made a finding that there were no unreasonable adverse effects to the environment caused by a basic ingredient, or 'generic' chemical, it would be a waste of resources to review that decision each time an application was received for the registration of an end-use product containing the generic chemical."[50] Congress's goal in amending FIFRA in 1978 was to

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Sulfoxaflor for Use on Agricultural Crops, Ornamentals and Turf (Oct. 14, 2016) at p. 10, *available at* https://www.regulations.gov/document?D=EPA-HQ-OPP-2010-0889-0563.

[48] *See* Pesticide Program Dialogue Committee Meeting, November 1-2, 2017, EPA Synergy presentation, *available at* https://www.epa.gov/sites/production/files/2017-11/documents/session-4-pesticide-synergy.pdf.

[49] S. Rep. No. 95-334, at 8 (1977).

[50] *Id.* at 9.

"enable EPA to use a generic approach to pesticide registrations [which] will mean that the agency will devote more attention to basic or technical materials."[51] Not only is EPA permitted to base its decisions about formulated products on data generated on the "basic ingredients," Congress specifically intended that EPA focus on those "basic ingredients" and apply the Agency's findings to its evaluation of end-use product formulations.

Congress adopted this approach in order to reduce the burden on both the companies that would be required to generate the data and EPA, and to avoid "duplicative data development and, thus, unnecessary costs to producers and consumers."[52] To accomplish its goal of avoiding unnecessary testing, Congress permitted applicants to rely on the data generated by registrants of "a similar pesticide," so long as the applicant compensated the original registrant.[53] This scheme whereby data regarding one product is used to support the registration of another is codified at 7 U.S.C. § 136a(c)(1)(F)(iii). If, as Petitioner suggests, every single test must be conducted on every single end use product, this data use and compensation program would never be used an illogical result that runs counter to Congress's clear intent and would render nearly meaningless the data use and compensation provisions of FIFRA.

Based on Congress's intent that EPA utilize its resources and the resources of pesticide companies efficiently and reduce data duplication where possible, the Agency's current Part 158 testing requirements, and its specification that the majority of tests be conducted on the technical grade active ingredient, reflect the Agency's reasonable exercise of its discretion. EPA currently requires approximately 100 studies for the typical agricultural pesticide, and the average cost of these studies is approximately $150 million.[54] To conduct virtually all such tests on every end-use pesticide would be economically prohibitive, and there is scant evidence that it would better inform EPA of a pesticide's risks. The massive expansion of testing contemplated by the Petition would not only result in a counterproductive diversion of Agency resources and a large, unnecessary expense, but it would also imply a huge and unwarranted increase in animal testing – which is antithetical to EPA's goal of reducing the amount of animal testing that is required under FIFRA.[55]

D. Petitioner's Remaining Statutory Arguments Lack Merit

The Petition raises two other statutory arguments to support expanded testing. First, Petitioner makes the conclusory statement that "EPA cannot effectively establish tolerance levels per FQPA [the Food Quality Protection Act] because it fails to consider information on all potentially toxic substances and actual residues on food." This is incorrect. For both active and inert ingredients, EPA requires the submission of sufficient data to allow the Agency to promulgate a tolerance or tolerance exemption before the ingredient can be included in the formulation of a food use pesticide. Thus, EPA does consider information on all ingredients and potential residues from end-use products. Second, Petitioner makes a similarly conclusory

[51] *Id.* at 27.

[52] *Id.* at 7, 28.

[53] *Id.* at 2.

[54] *See* Phillips McDougall, The Cost of New Agrochemical Product Discovery, Development and Registration in 1995, 200, 2005-8 and 2010 to 2014 (March 2016).

[55] *See* https://www.epa.gov/pesticides/epa-releases-draft-policy-reduce-animal-testing-skin-sensitization.

statement regarding the Endangered Species Act (ESA), declaring that unless EPA requires the full panoply of tests to be conducted on each and every end-use product and tank mix, the Agency "cannot properly determine whether a pesticide as used 'may affect' endangered species or critical habitat." However, as outlined in detail above, EPA collects extensive data on active and inert ingredients and utilizes its technical expertise as well as widely-accepted models and information on potential synergistic effects to assess the risks associated with end-use products. This robust analysis is sufficient to allow EPA to determine whether an end-use formulated pesticide "may affect" endangered species or critical habitat.

III. Conclusion

Petitioner's proposal that EPA require virtually all tests to be performed on all end-use products is not only unnecessary, but harmful and contrary to Congressional intent. EPA thoroughly evaluates the potential risks associated with all active and inert ingredients that are used in registered pesticides, and before registering an end-use product, EPA assesses the possible additive and synergistic effects from the mixture of ingredients in the product formulation. If, in any particular case, EPA concludes that the data are insufficient to support a conclusion of no unreasonable adverse effects, the Agency can either require the submission of additional data or decline to register the end-use product. EPA has adopted a similar approach to tank mix partners, requiring the submission of additional data or prohibiting a particular tank mix partner, where evidence exists of potential greater-than-additive effects from the tank mixture. For all of the foregoing reasons CLA, RISE, CPDA and BPIA encourage EPA to deny the Petition.

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

Respectfully submitted,

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