UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFETY
AND POLLUTION PREVENTION

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SUBJECT: Center for Food Safety (CFS) Petition to the U.S. Environmental Protection Agency Seeking Revised Testing Requirements of Pesticides Prior to Registration (July 10, 2017)

Dear Ms. Van Saun and Wu:

Thank you for engaging with us on this important topic. The U.S. Environmental Protection Agency (EPA or the Agency) recognizes the need to have the appropriate data necessary to evaluate the potential effects of pesticides on humans and the environment. As such, the Agency has considered your request and concerns, and in response, EPA notes that it has been assessing and will continue to assess the impacts to human health and the environment from exposure to pesticides including the potential impacts from pesticide products and tank mixes.

This letter constitutes the Agency's response to the petition filed on July 10, 2017, by CFS requesting EPA to amend its regulations. In summary, the Petition requests that EPA require testing for whole pesticide formulations to account for the toxicological effects of inert ingredients and additives and the testing of tank mixes to assess the interaction between pesticide ingredients.

To implement that request, the Petition requests that EPA amend its regulations as follows:

I. 40 C.F.R. § 152.3 and 40 C.F.R. § 158.300. Amend the definition of "End-use product" by adding the language in italics:

End-use product means a pesticide product *being registered, including all active and inert ingredients (including adjuvants and surfactants) in the formulation,* whose labeling:

(1) Includes directions for use of the product (as distributed or sold, or after combination by the user with other substances) for controlling pests or defoliating, desiccating, or regulating growth of plants, or as a nitrogen stabilizer, and

(2) does not state that the product may be used to manufacture or formulate other pesticide products.

II. Part 158, Subpart C, 40 C.F.R. §§ 158.200 to 158.270. Amend the test substance requirements from technical grade active ingredient (TGAI[1]) or typical end-use product (TEP) to End-use product (EP[2]).

III. Part 158, Subpart F, 40 C.F.R. § 158.500. Amend the test substance requirements from TGAI or TEP to EP, or End-use product.

IV. Part 158, Subpart F, 40 C.F.R. § 158.510(a). Expand the required data replacing the phrase "active ingredient" with "end-use product."

V. Part 158, Subpart G, 40 C.F.R. § 158.630(d). Amend the test substance requirements from TGAI or TEP to EP, or End-use product.

VI. Add testing requirement for "Combination and tank mixtures" to Part 158, Subparts C, F, and G as "conditionally required" for all categories, with the following testing note: This test is required if, as recommended by the pesticide manufacturer, indicated by the pesticide label, or in common practice, 1) the pesticide product will be mixed prior to application with any recommended vehicles or adjuvants, or 2) if the pesticide product will be mixed prior to application with any other approved pesticide product or active ingredient.

The petition asserts that EPA does not adequately assess the environmental impact from use of pesticide products or tank mixes as most of EPA's data requirements pertain to the pesticide's technical grade active ingredient (TGAI).

Pesticide products include the active ingredient(s) as well as other ingredients (the latter collectively referred to as inerts) that are generally included in the product to improve the efficacy of the active ingredient. Additionally, a user can combine the pesticide product with other ingredients referred to as additives (e.g., surfactants) prior to application (often referring to as tank mixes) as needed for pest control. EPA explains in its response to the petition that the Agency appropriately assesses, as part of its review, the impacts to human health and the environment, and why the additional testing that the petition seeks would not in general provide

[1] Technical grade of active ingredient (TGAI) means a material containing an active ingredient:(1) Which contains no inert ingredient, other than one used for purification of the active ingredient; and (2) Which is produced on a commercial or pilot plant production scale (whether it is ever held for sale). (USEPA 2019. Standard Evaluation Procedure (SEP) for Chemistry and Acute Toxicology Science Advisory Council (CATSAC); SEP No. ADM-03-01 Date Revised 10-29-2019) https://www.epa.gov/sites/default/files/2020-06/documents/sep-adm-03-01-10-29-2019-signed-final.pdf.

[2] End-use product (EP), also referred to as formulated product, means a pesticide product whose labeling:(1) Includes directions for use of the product (as distributed or sold, or after combination by the user with other substances) for controlling pests or defoliating, desiccating or regulating growth of plants, or as a nitrogen stabilizer, and (2) does not state that the product may be used to manufacture or formulate other pesticide products. 40 C.F.R. § 152.3.

a better picture of the risks of a pesticide product. These assessments evaluate relevant exposure routes for the pesticide(s), and the acute and chronic toxicity data EPA currently receives are sufficient for evaluating the potential risk from the registered use of a pesticide product. Furthermore, in addition to the wide-ranging studies the Agency receives from the regulated community regarding potential effects from the TGAI and EP (when appropriate), the Agency also considers other available information from open literature studies and incident reports when assessing risk and making regulatory decisions.

As a result, EPA disagrees with the petitioner's assertion that EPA does not adequately assess risks from formulations or tank mixes and thus is denying the request to amend the regulatory testing requirements. However, EPA recognizes that additional information, beyond data required under 40 CFR part 158, may in some cases have value in evaluating potential effects to humans and the environment. EPA is reiterating the responsibility of the regulated community to report incidents involving pesticides, including with inerts and mixtures, as well as any other information available concerning adverse effects resulting from the use of a pesticide. EPA also recognizes that the science for assessing potential effects to humans and the environment is continuing to evolve and that new approach methodologies (NAMs) may provide additional tools (e.g., high-throughput *in vitro* assays) that could be used to evaluate potential effects from mixtures more efficiently.

If you have any questions regarding this letter, please feel free to contact Amy Blankinship of my staff at (202) 566-1680 or via e-mail at Blankinship.amy@epa.gov.

Sincerely,

Ed Messina

Digitally signed by EDWARD MESSINA
Date: 2023.09.28 09:20:33 -04'00'

Ed Messina, Esq., Director
Office of Pesticide Programs

EPA Response to the 2017 Petition from the Center for Food Safety and Others Relating to the Whole Formulations Testing and Mixtures for Conventional Pesticides

I. Petition Background

On July 10, 2017, EPA received a petition[3] filed by the Center for Food Safety (CFS) seeking revised testing requirements for pesticides prior to registration. The petitioner asserts that EPA "focuses its testing and data collection on active ingredients alone, largely ignoring inerts and adjuvants." The petitioner argues that without testing of the whole pesticide formula to account for the toxicological effects of inert ingredients and additives and the interactions between different pesticide ingredients, EPA cannot determine with accuracy whether a given pesticide formulation will have unreasonable adverse effects to the environment. The petitioner claims EPA has therefore violated the congressional mandates of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), and that the Agency's interpretation of FIFRA and related regulatory actions under FIFRA are unacceptable. The petitioner requests that EPA require testing for whole pesticide formulations to account for the toxicological effects of inert ingredients and additives and the testing of tank mixes to assess the interaction between pesticide ingredients. The petition also claims that the Food Quality Protection Act (FQPA) requires whole formulation and tank mixture testing in that FQPA requires EPA to establish tolerance levels for pesticide residues to ensure a "reasonable certainty that no harm will result" from dietary or other aggregate exposures for which there is reliable information. The petitioner notes that in establishing a tolerance for a pesticide chemical residue, EPA is required to consider all available information concerning cumulative risk or aggregate exposure to the pesticide residue.

Specifically, the petitioner requests the following actions:

1) Revise pesticide registration regulations to account for all pesticide ingredients (active, inert and additives) and their effects on the environment.
2) Revise pesticide registration regulations to require whole pesticide formulation and tank mixture testing to account for synergistic effects.
3) Revise pesticide registration regulations to require inert ingredients and whole pesticide formulations testing for chronic toxicological effects and degradation.
4) Revise pesticide registration regulations to require Endangered Species Act (ESA) consultation on the effects of whole pesticide formulations and tank mixtures on threatened and endangered species.
5) Comply with the above requirements in conducting statutorily mandated registration reviews of pesticides.

To implement requests (1) through (4), the CFS petitions EPA to amend its regulations as follows:

I. 40 C.F.R. § 152.3 and 40 C.F.R. § 158.300. Amend the definition of "End-use product" by adding the language in italics:

[3] Petition Seeking Revised Testing Requirements of Pesticides Prior to Registration; Notice of Availability. December 21, 2018 (83 FR 65672) Regulations.gov.

End-use product means a pesticide product *being registered, including all active and inert ingredients (including adjuvants and surfactants) in the formulation,* whose labeling:

(3) Includes directions for use of the product (as distributed or sold, or after combination by the user with other substances) for controlling pests or defoliating, desiccating, or regulating growth of plants, or as a nitrogen stabilizer, and

(4) does not state that the product may be used to manufacture or formulate other pesticide products.

II. Part 158, Subpart C, 40 C.F.R. §§ 158.200 to 158.270. Amend the test substance requirements from technical grade active ingredient (TGAI[4]) or typical end-use product (TEP) to End-use product (EP[5]).

III. Part 158, Subpart F, 40 C.F.R. § 158.500. Amend the test substance requirements from TGAI or TEP to EP, or End-use product.

IV. Part 158, Subpart F, 40 C.F.R. § 158.510(a). Expand the required data replacing the phrase "active ingredient" with "end-use product."

V. Part 158, Subpart G, 40 C.F.R. § 158.630(d). Amend the test substance requirements from TGAI or TEP to EP, or End-use product.

VI. Add testing requirement for "Combination and tank mixtures" to Part 158, Subparts C, F, and G as "conditionally required" for all categories, with the following testing note:
This test is required if, as recommended by the pesticide manufacturer, indicated by the pesticide label, or in common practice, 1) the pesticide product will be mixed prior to application with any recommended vehicles or adjuvants, or 2) if the pesticide product will be mixed prior to application with any other approved pesticide product or active ingredient.

In December 2018, EPA published a notice in the Federal Register[6] announcing the availability of the petition for a 90-day public comment period and posted the petition in the public docket (EPA-HQ-OPP-2018-0262). In response to the request for comment, EPA received 161 comments. The comments in their entirety can be found in docket EPA-HQ-OPP-2018-0262 at regulations.gov.

The majority (95%) of the 161 comments submitted to the docket supported the request in the Petition that EPA require toxicity testing on end-use products to evaluate potential effects to the environmental and human health. The majority (76%) of the comments in support of the petition are from anonymous

[4] Technical grade of active ingredient (TGAI) means a material containing an active ingredient:(1) Which contains no inert ingredient, other than one used for purification of the active ingredient; and (2) Which is produced on a commercial or pilot plant production scale (whether it is ever held for sale). (USEPA 2019. Standard Evaluation Procedure (SEP) for Chemistry and Acute Toxicology Science Advisory Council (CATSAC); SEP No. ADM-03-01 Date Revised 10-29-2019) https://www.epa.gov/sites/default/files/2020-06/documents/sep-adm-03-01-10-29-2019-signed-final.pdf.

[5] End-use product (EP), also referred to as formulated product, means a pesticide product whose labeling:(1) Includes directions for use of the product (as distributed or sold, or after combination by the user with other substances) for controlling pests or defoliating, desiccating or regulating growth of plants, or as a nitrogen stabilizer, and (2) does not state that the product may be used to manufacture or formulate other pesticide products. 40 C.F.R. § 152.3.

[6] Petition Seeking Revised Testing Requirements of Pesticides Prior to Registration; Notice of Availability. December 21, 2018 (83 FR 65672) Regulations.gov.

sources which cited elements of the petition. One of the submissions from CFS in support of their petition includes 11,149 signatures.

There are eight comments against the petition that assert EPA's data requirements and risk assessment process are adequate to evaluate potential effects. The comments against the petition are generally from organizations including the Pesticide Policy Coalition, California Specialty Crops, Crop Life America, the American Chemistry Council, and the Agricultural Retailers Association. The U.S. Department of Agriculture also submitted comments opposing the requested revisions. Comments against the petition assert that increased testing would be unnecessary and burdensome.

The Agency has considered all comments in developing this response. The following sections provide a brief discussion of the legal framework around pesticide regulation followed by EPA's response to the petition.

II. Legal Framework

A. Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA)

Generally, FIFRA precludes the distribution and sale of any pesticide that is not registered under FIFRA.[7] Applications for registration of a pesticide may be submitted to EPA but must meet the requirements in FIFRA sections 3(c) and 33.[8] Those requirements include, among other things, submission of complete labeling of the pesticide, including claims made for the pesticide and instructions on use; complete data in support of that registration request; and requisite fees in support of that application.[9]

Before granting a pesticide registration, FIFRA requires EPA to consider, among other things, whether the pesticide poses "unreasonable adverse effects" to human health and the environment.[10] FIFRA section 2(bb) defines "unreasonable adverse effects on the environment" to mean, among other things, "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."[11] This, along with the other requirements in FIFRA section 3(c)(5) concerning composition, labeling, and function, is referred to as the "FIFRA standard", and EPA is required to review each pesticide registration every 15 years to determine whether the pesticide continues to meet the FIFRA standard for registration.[12] The standard for determining whether an application should be granted includes a finding that: (1) a product's composition warrants the proposed claims for it; (2) the product's labeling and other material required to be submitted complies with FIFRA; (3) the product will perform its intended function without causing unreasonable adverse effects on the environment; and (4) when used in accordance with widespread and commonly recognized practice, the product will not cause unreasonable adverse effects on the environment (FIFRA section 3(c)(5)).

[7] 7 U.S.C. § 136a(a).
[8] 7 U.S.C. §§ 136a(c) and 136w-8.
[9] 7 U.S.C. § 136a(c); 7 U.S.C. § 136a(b); and 7 U.S.C. § 136w-8. *See also* 40 C.F.R. part 152 for application procedures and part 158 for data requirements.
[10] 7 U.S.C. § 136a(c)(5)(D).
[11] 7 U.S.C. § 136(bb).
[12] 7 U.S.C. § 136a(g) and 40 C.F.R. part 155, subpart C. "Registration review" is the term used for this process.

To determine whether a pesticide meets the FIFRA standard, EPA considers both the risks and benefits of use of the pesticide. Regarding risk, EPA assesses whether a particular use of a pesticide poses a meaningful risk (often referred to as a "risk of concern"). If a use does not pose a risk of concern and other regulatory and administrative requirements are satisfied, EPA generally finds the use to meet the standard for registration. If the use poses a risk of concern, EPA considers whether that risk may be mitigated in whole or in part, taking into consideration the benefits of the use of the pesticide and the impacts of potential mitigation on the user (*e.g.*, feasibility of the mitigation). Such mitigation may include changes to use instructions to limit application of the pesticide to a lower rate or frequency. Where the Agency determines that the risks associated with a use are justified by the benefits, the use would be found to meet the FIFRA standard for registration. Under Registration Review, the Agency follows a similar process as described above. If the Agency determines that changes to the registration are necessary, or if the risks associated with an existing use are not justified by the benefits associated with that use, the Agency can initiate appropriate administrative action under FIFRA section 6 unless necessary changes (if feasible) are made.[13]

B. Code of Federal Regulations, part 158 (40 CFR part 158) – Data Requirements

Title 40 part 158 of the Code of Federal Regulations ("part 158") specifies the kinds of data and information EPA requires to make regulatory decisions regarding the risks and benefits of pesticide products under FIFRA sections 3, 4, and 5. Further, part 158 specifies the data and information needed to determine the safety of pesticide chemical residues under Section 408 of the Federal Food Drug and Cosmetic Act (FFDCA).[14]

The data requirements laid out in 40 CFR part 158, Subparts C (experimental use permits; EUPs), D (product chemistry), F (toxicology), G (ecological effects), and N (environmental fate) include an array of environmental fate and toxicological tests with which to evaluate potential risks to both human health and other non-target taxa (*e.g.*, wildlife and plants) to support conventional[15] pesticide EUPs or pesticide product registrations. Importantly, based on what is currently stipulated in 40 CFR part 158, EPA receives both acute and chronic toxicity data, which reflect relevant exposure pathways for humans and wildlife to the TGAI, as well as acute toxicity data to EPs (*i.e.*, formulated products) for both humans and wildlife when relevant. For wildlife, studies include acute and chronic toxicity tests with freshwater and estuarine/marine fish and invertebrates and depending on the environmental fate characteristics of the compound, whole sediment toxicity tests with freshwater and estuarine/marine benthic invertebrates. Acute and chronic toxicity tests are also required for birds, mammals, and honey bees (*Apis mellifera*).

While most data for mammals and non-mammalian wildlife are based on TGAI, part 158 stipulates conditions where data on end-use product must be submitted. Acute toxicity data are routinely submitted for mammals for all formulated end-use products representing exposure resulting from ingestion, inhalation, and dermal contact. In addition to testing wildlife, part 158 also identifies data

[13] 7 U.S.C. § 136d.
[14] 21 U.S.C. § 346a.
[15] Conventional pesticides are all active ingredients other than biological pesticides and antimicrobial pesticides. Conventional active ingredients are generally produced synthetically (*i.e.*, are synthetic chemicals that prevent, mitigate, destroy, or repel any pest; or that act as a plant growth regulator, desiccant, defoliant or nitrogen stabilizer.

needed for aquatic (vascular and non-vascular) and terrestrial (monocotyledonous and dicotyledonous) plants. These studies are typically conducted with end-use product, as are colony-level exposure and effect studies with honey bees. Depending on the use (*e.g.*, direct application to water), data for EP may also be required for freshwater and estuarine/marine fish and invertebrates. These data enable EPA to determine whether TGAI and formulated end-use products meet the FIFRA standard.

In most cases the data already required under part 158 enable the Agency to have a reasonable understanding of both exposure and effects with which to estimate potential risk from a pesticide registration. In situations where there are lines of evidence to suggest that additional data may be needed or additional refinements to EPA's assessments may be needed, part 158 discusses the flexibility EPA has in requiring data for pesticide registrations. Under 40 CFR part 158.30, EPA may modify the data requirements on a case-by-case basis to fully characterize the effects of a pesticide product. However, as will be described later in this response, the information typically required is adequate in most cases for an assessment of the environmental fate properties and effects of the pesticide on humans and plants/wildlife. The Agency encourages each applicant to consult with EPA to discuss the data requirements particular to their product(s) prior to and during the registration process as well as during registration review, to better ensure that the data submitted will be adequate to evaluate the likelihood of adverse effects from exposure.

C. FIFRA Definition of Pesticide and other Terms as Mentioned in the Petition

Under FIFRA, the term "pesticide" is defined as:

> (1) any substance or mixture of substances intended for preventing, destroying, repelling, or mitigating any pest;
> (2) any substance or mixture of substances intended for use as a plant regulator, defoliant, or desiccant; and,
> (3) any nitrogen stabilizer, except that the term "pesticide" shall not include any article that is a "new animal drug" within the meaning of section 321(w)[16] of title 21, that has been determined by the Secretary of Health and Human Services not to be a new animal drug by a regulation establishing conditions of use for the article, or that is an animal feed within the meaning of section 321(x)[17] of title 21 bearing or containing a new animal drug.[18]

EPA's regulations differentiate between a pesticide and a "pesticide product." The latter is defined as "a pesticide in the particular form (including composition, packaging, and labeling) in which the pesticide is, or is intended to be, distributed or sold" (40 CFR 152.3). The term includes any physical apparatus used to deliver or apply the pesticide if distributed or sold with the pesticide and is frequently referred to as the "end-use product (EP) or "formulation".

With respect to pesticides, FIFRA defines the term "active ingredient" as:

> (1) in the case of a pesticide other than a plant regulator, defoliant, desiccant, or nitrogen stabilizer, an ingredient which will prevent, destroy, repel, or mitigate any pest;

[16] See https://uscode.house.gov/view.xhtml?req=(title:7%20section:136%20edition:prelim)#136_1_target.
[17] See https://uscode.house.gov/view.xhtml?req=(title:7%20section:136%20edition:prelim)#136_1_target.
[18] 7 U.S.C. § 136(u).

(2) in the case of a plant regulator, an ingredient which, through physiological action, will accelerate or retard the rate of growth or rate of maturation or otherwise alter the behavior of ornamental or crop plants or the product thereof;
(3) in the case of a defoliant, an ingredient which will cause the leaves or foliage to drop from a plant;
(4) in the case of a desiccant, an ingredient which will artificially accelerate the drying of plant tissue; and,
(5) in the case of a nitrogen stabilizer, an ingredient which will prevent or hinder the process of nitrification, denitrification, ammonia volatilization, or urease production through action affecting soil bacteria.[19]

Pesticide products can contain active ingredient(s), inert ingredients (sometimes referred to as "other ingredients" which can be used in lieu of "inert ingredients" on product labels per PR Notice 97-(6), and impurities. The term "inert ingredient" is defined in FIFRA Section 2(m) as "an ingredient which is not active". 40 CFR 152.3 defines inert ingredient as "... any substance (or group of structurally similar substances if designated by the Agency), other than an active ingredient, which is intentionally included in a **pesticide product**..." (emphasis added). Examples of inert ingredients include emulsifiers, solvents, carries, aerosol propellants, fragrances, and dyes[20]. EPA defines "impurity" as "any substance (or group of structurally similar substances if specified by the Agency), in a pesticide product other than an active ingredient or an inert ingredient, including unreacted starting materials, side reaction products, contaminants, and degradation products."[21]

The term "ingredient statement" means a statement which contains the following:

(1) the name and percentage of each active ingredient, and the total percentage of all inert ingredients, in the pesticide; and,
(2) if the pesticide contains arsenic in any form, a statement of the percentages of total and water-soluble arsenic, calculated as elementary arsenic.[22]

For pesticide regulation, the Agency generally considers "adjuvants" as chemicals added to the pesticide by users to improve the pesticide's efficacy but are not part of the "pesticide" as defined above. Additionally, adjuvants are not necessarily included among the ingredients that make up the composition of the registered product (but can be at times) and thus may not be part of the registered pesticide product formulation. Rather, agricultural chemical adjuvants are typically grouped according to their intended purpose in a tank mix[23]. The Agency primarily uses the term "adjuvant" when describing products applied to crops in conjunction with pesticide applications and are typically referred to as agricultural tank mix adjuvants (*e.g.*, spray adjuvants).

According to the EPA Pesticide Label Review Manual[24], the criteria for determining an ingredient's active or inert status are in 40 C.F.R. § 153.125. Generally speaking, an ingredient will be considered an active ingredient if, by itself and when used as directed at the proposed use dilution, it has the capability to

[19] 7 U.S.C. § 136(a).
[20] Inert Ingredients Overview and Guidance | US EPA.
[21] 40 C.F.R. 158.300.
[22] 7 U.S.C. § 136(n).
[23] US EPA - Label Review Manual - Complete Manual.
[24] US EPA - Label Review Manual - Complete Manual.

function as a pesticide or has the ability to elicit or enhance the pesticidal effect of another compound whose pesticidal activity is substantially increased due to the interaction of the compounds. Ingredients such as stickers and other adjuvants which function simply to enhance or prolong the activity of an active ingredient by physical action are not generally considered to be active ingredients. *See* 40 C.F.R. § 153.125(a).

Although the petition uses the term *adjuvant* consistent with the way the term is used in EPA's Pesticide Registration Manual (*i.e*., adjuvants are chemicals added to a pesticide by users to improve the pesticide's efficacy), the term is often used more broadly to include chemicals added to products to help the pesticide do its job and stay on target. In this broader usage, adjuvants may be in a formulated product when it is purchased (*i.e*., as an inert ingredient), or they may be added to a mixture before it is applied (tank-mixed). For purposes of clarity in this document, EPA will use the term "additive" to refer to substances that are added to products by users either on site or in a tank mix; any other substance that may fit the broader definition of "adjuvant" but is included within a pesticide formulation will be considered an "inert" ingredient for purposes of this document.

Tank-mixing of pesticides is an important practice often used to meet multiple agronomic objectives, including:

- Effective and timely management of co-occurring insect, pathogen and weed pests as biological monitoring, weather, local conditions, and predictive biological and weather models advise;
- Effectively performing other farm operations (*e.g*., mowing, pruning, pest scouting) in between spray applications, each with re-entry interval restrictions);
- Broadening the spectrum of pests controlled and/or increasing the duration of control;
- Reducing application costs (*e.g*., fuel, labor, equipment wear);
- Reducing environmental impacts from increased use of application equipment (*e.g*., emissions, fuel consumption);
- 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).

The Agency defines "mixtures" as any combination of two or more chemical substances regardless of spatial or temporal proximity (USEPA 1986[25]); however, more frequently than not, data regarding the components of the mixture are limited particularly with respect to their adsorption, distribution, metabolism, excretion (ADME) and activity at receptor sites(s) in large part due the limited time that the various components are expected to remain together.

In the absence of data to the contrary, chemicals with the same mode of action and resulting in similar effects in mammals are assumed to exhibit dose addition. However, an assumption of dose addition for

[25] USEPA 1986. Guidelines for the Health Risk Assessment of Chemical Mixtures. Risk Assessment Forum. FRN 51(185):34014-34025 https://ordspub.epa.gov/ords/eims/eimscomm.getfile?p_download_id=4488.

chemicals exhibiting dissimilar effects is not well supported.[26,27,28,29] For chemicals with the same mode of action, the combined effects of these chemicals on human health are evaluated; however, since a mode of action may not be conserved across taxa and ADME may vary widely, similar assessments are not conducted for wildlife.

D. Endangered Species Act ("ESA")

Congress enacted the ESA in 1973 to, among other things, conserve species deemed to be endangered or threatened.[30] The ESA imposes certain legal requirements protecting federally listed threatened or endangered ("listed") species, including that federal agencies—in consultation with the Services[31]—must "insure that any action authorized, funded, or carried out by such agency . . . is not likely to jeopardize the continued existence of any [listed] species or result in the destruction or adverse modification" of designated critical habitat.[32]

Prior to initiating consultation with the Services, the action agency must determine whether its action "may affect" a listed species or its designated critical habitat.[33] If the action agency determines that the action will have "no effect" on any listed species or designated critical habitat, then it need not "consult" with the Services.[34] If, however, the action agency determines that the action "may affect" one or more listed species or designated critical habitat, then it must pursue consultation with the appropriate Service(s).[35]

For FIFRA actions, including pesticide registration actions, EPA's determinations under the ESA are called "effects determinations."[36] Where EPA determines that the FIFRA action "may affect, but is not likely to adversely affect" one or more listed species or designated critical habitat, EPA initiates informal consultation with the appropriate Service(s).[37] Where EPA determines that the FIFRA action "may affect, and is likely to adversely affect" one or more listed species or designated critical habitat, EPA initiates formal consultation with the appropriate Service(s).[38] If formal consultation is necessary, EPA typically prepares a Biological Evaluation (BE), which contains EPA's analyses of the potential effects of the

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[26] *Ibid* USEPA 1986.
[27] Borgert, C.J., T. F. Quill, L. S. McCarty, and A. M. Mason. 2004. Can mode of action predict mixture toxicity for risk assessment? Toxicology and Applied Pharmacology 201(2): 85 – 96 https://doi.org/10.1016/j.taap.2004.05.005.
[28] Lydy, M., J. Beldon, C. Wheelock, B. Hammock, and D. Denton. 2004. Challenges in Regulating Pesticide Mixtures. Ecology ad Society 9(6): [online] URL: http://www.ecologyandsociety.org/vol9/iss6/art1/.
[29] Beldon, J. B., R. J. Gilliom, and M. J. Lydy. 2007a. How well can we predict the toxicity of pesticide mixtures to aquatic life? Integrated Environmental Assessment and Management 3(3): 364 – 372 https://doi.org/10.1002/ieam.5630030307.
[30] *See* 16 U.S.C. §§ 1531 (b), 1532(6), 1532(20), 1533.
[31] U.S. Fish and Wildlife Service (FWS) and National Marine Fisheries Service (NMFS).
[32] 16 U.S.C. § 1536(a)(2).
[33] 50 C.F.R. § 402.14.
[34] *See* 50 C.F.R. § 402.12.
[35] *See* 50 C.F.R. §§ 402.13-402.14; and 50 C.F.R. part 402, subpart D.
[36] 50 C.F.R. § 402.40(b).
[37] *See* 50 C.F.R. § 402.13.
[38] *See* 50 C.F.R. §§ 402.14, 402.46.

pesticide on listed species and their designated critical habitat and EPA's effects determinations, and uses the BE to initiate formal consultation with the appropriate Service(s).[39]

When EPA initiates formal consultation, the Service(s) review the information provided in the BE and develop their Biological Opinions (BiOps). In their BiOps, the Services document their determination of whether a pesticide is likely to jeopardize the continued existence of the species and whether there will be adverse modification to designated critical habitat.[40] The BiOps also include any reasonable and prudent alternatives (RPAs) and reasonable and prudent measures (RPMs) that the Service(s) determine are appropriate. Once a BiOp is finalized, EPA is responsible for ensuring that the BiOp is implemented.

III. Petition Response

In the following section, the relevant portion of the petition is summarized and is then followed by the Agency's response. Section III.A summarizes and responds to CFS's requests to amend the definition of an end-use product. Section III.B summarizes and responds to the request that EPA revise pesticide registration regulations by requiring toxicity testing for whole formulations and mixtures to account for all pesticide ingredients (*e.g.*, active ingredient, inerts and additives). Section III.C summarizes and responds to requests to require whole pesticide formulation and tank mixture testing to account for synergistic effects.

Section III.A Petition Requests to Amend the Definition of an End-Use Product.

Summary of Petition: The petitioner asserts that FIFRA's definition of "pesticide" supports whole formula and tank mixture testing and that it does not refer exclusively to active ingredients. The petition is also requesting that EPA amend the definition of "End-use product" at 40 C.F.R. § 152.3 and 40 C.F.R. § 158.300 by adding the language in italics:

> End-use product means a pesticide product *being registered*, *including all active and inert ingredients (including adjuvants and surfactants) in the formulation*.

The petition states that FIFRA's definition of a "pesticide" is "any substance or mixture of substances intended for preventing, destroying, repelling, or mitigating any pest," and does not refer exclusively to active ingredients, and that the specific words "any substance or mixture of substances" indicate that whole formulations are the "pesticides" and not merely those ingredients deemed "active" (see CFS Petition, p. 16). Furthermore, the petitioner also argues that while FIFRA does not explicitly mandate specific ingredient testing or testing of whole formulations and tank mixtures, it does so implicitly through the requirements for registering a pesticide (see CFS Petition, p. 19)[41].

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[39] *Cf.* 50 C.F.R. §§ 402.12; 402.40(b).

[40] "The Services [may] also authorize any "take" (unintended injury or killing of individual listed species) that would otherwise be prohibited, as long as measures to minimize take are implemented." *See* Assessing Pesticides under the Endangered Species Act found at https://www.epa.gov/endangered-species/assessing-pesticides-underendangered-species-act.

[41] The petition also points to the FFDCA, which references both active and inert ingredients in its definition of "pesticide chemical" [21 U.S.C. 321(q).] but is not relevant for this response.

EPA Response:

EPA is denying the petitioner's request to amend the definition of end-use product because EPA concludes that such a change is not necessary or appropriate. First, an end-use product represents the whole formulation of the product as registered with the Agency, which includes both active and inert ingredients. The composition of the end-use product must be reflected on the confidential statement of formula,[42] and the ingredient statement for the registered product must reflect all the ingredients that are in the product.[43] It is not necessary to repeat that phrasing, since it is already included. Second, regarding the phrase "including adjuvants and surfactants", EPA contends that surfactants are already considered inert ingredients and therefore already part of the EP and including such language would be superfluous. Moreover, to the extent CFS is using the term "adjuvants" to refer to ingredients that are part of the registered pesticide formulation, those are also considered inert ingredients and including them here would be redundant. But for "adjuvants" that are considered "additives" and are included by the pesticide user later (*e.g.*, at the time of application in a tank mix), they do not comprise part of the end-use product and thus including them in this definition would be inconsistent with the definition of a pesticide product.

Additionally, it is not clear from the petitioner's request what the additional phrasing "*being registered*" is intended to accomplish, and EPA asserts that this additional language should not be included in the definition. There are examples of initial pesticide formulations being modified (*i.e.*, reformulated) at some point (*e.g.*, prior to submission to the Agency or even during the registration process), but not necessarily triggering additional testing. In these case, the initial proposed formulation does not ultimately get registered by the Agency, and it is unclear how that would impact the petitioner's request regarding the additional ecological and human health testing for an EP. Additionally, a pesticide formulation may be reformulated for several reasons after it is registered (*e.g.*, different source of material, substitutions to the inert ingredients), but may not be substantially different with regards to the composition or intent of the formulation. If these modifications are substantial enough, though, they can trigger the need for additional data required for the EP (*e.g.*, acute mammalian toxicity); however, requiring all the additional testing the petitioner is requesting would be burdensome and unnecessary. Given that the components of the formulation dissipate at varying rates soon after application and that the primary focus is on the active ingredient itself, requiring chronic toxicity tests on formulations would not be particularly informative and would be costly in terms of the resources needed to conduct and review the studies.

Therefore, for the reasons herein, EPA concludes that it is inappropriate and unnecessary to amend the current definition of an end-use product as requested by the petitioner.

[42] See 40 CFR 158.320; see also https://www.epa.gov/sites/default/files/2013-07/documents/8570-4_0.pdf.
[43] See 7 U.S.C. 136(n).

Section III.B Petitioner's Claims Relating to Sufficiency of EPA Assessments to consider All Pesticide Ingredients and to Amend 40 CFR part 158 to Include End-Use Requirements.

Summary of Petition: The petitioner asserts that most EPA requirements for toxicological data pertain to a pesticide's active ingredients in isolation, and thus do not adequately consider the environmental impact of the whole pesticide formulation. The petitioner also asserts that EPA's data requirements largely ignore inert ingredients in each formulation and the additives that may be used along with each formulation in practice. According to the petitioner, FIFRA's definition of "pesticide" supports whole formula and tank mixture testing and does not refer exclusively to active ingredients. The petitioner is requesting that the Agency amend FIFRA part 158, Subpart C (experimental use permits), F (toxicology) and G (ecological effects) testing requirements from TGAI or TEP to end-use product. Specifically, they request that EPA amends:

- Part 158, Subpart C, 40 C.F.R. §§ 158.200 to 158.270. Amend the test substance requirements from technical grade active ingredient (TGAI) or typical end-use product (TEP) to End-use product (EP).
- Part 158, Subpart F, 40 C.F.R. § 158.500. Amend the test substance requirements from TGAI or TEP to EP, or End-use product.
- Part 158, Subpart F, 40 C.F.R. § 158.510(a). Expand the required data replacing the phrase "active ingredient" with "end-use product."
- Part 158, Subpart G, 40 C.F.R. § 158.630(d). Amend the test substance requirements from TGAI or TEP to EP, or End-use product.

The petition specifically highlights potential risks to the environment, including those to amphibians and listed species from exposure to glyphosate formulations. The petition discusses potential risks to bees from exposure to organosilicone additives and cites potential effects to human health.

EPA Response:

EPA is denying the petitioner's request to amend the above-mentioned regulatory provisions by removing the requirement to obtain data on the TGAI and instead to require data on the end-use product. First, foregoing studies using the TGAI and replacing them with studies using the EP would not provide the Agency the most useful data with which to assess potential effects. This is primarily because in the real world, humans and non-target organisms are not typically exposed to the intact formulation in a long-term, repeated exposure (*e.g.*, chronic) scenario, except in a few situations. Thus, requiring that end-use product data instead of active ingredient alone (*i.e.*, TGAI) data would likely be less helpful for assessing risk and provide a misleading basis for risk assessment as the potential effects observed from repeated exposure to an intact formulation in long-term toxicity testing is not expected in the real world and would be misrepresenting the potential risks. Moreover, EPA does not need to require these EP data in its regulations as the petitioner requests because EPA already considers multiple lines of evidence when evaluating the potential effects of pesticide active ingredients and formulations. Of these, consideration of the relevant route of exposure to humans and other non-target organisms (wildlife and plants) is a major factor in whether it is appropriate or necessary to conduct toxicity testing

using a whole formulation. Taking exposure into consideration (*e.g.*, whether the formulated product is applied directly to water), the Agency has requirements for formulation testing in addition to testing with TGAI (see 40 CFR 158 Subpart G), where the potential acute exposure to the intact pesticide product is most relevant. Furthermore, in addition to the numerous and wide-ranging studies the Agency receives regarding potential effects from the TGAI and EP (when appropriate), the Agency also considers other lines of evidence, including information from open literature and incident reports, when assessing risk and making regulatory decisions. Each of these points are discussed below as well as the practicality/feasibility and burden of testing each formulation as requested by the petition.

Exposure Potential to Humans and Wildlife from Pesticide Formulations and Inert Ingredients/Additives/Tank Mixes

As the petition indicates, pesticide formulations can be comprised of several different types of chemicals or substances. Usually, the pesticide formulation consists of the active ingredients and inert ingredients. Sometimes there is a higher percentage of inert ingredients than active ingredients. Sometimes the pesticide formulation is comprised of the active ingredient and mainly water, and some product labels require that the pesticide product must be watered-in soon after application, resulting in further dilution of the product. Additionally, for conventional food use pesticide products, there is often a dilution of the products using water prior to application, which further reduces the exposure concentrations of the intact formulation. These different substances in a formulation can and often do have vastly different physico-chemical properties (*e.g.*, water solubility) from the active ingredient and from each other. It is expected that given these differential properties, the individual components in a formulation will dissipate in the environment at different rates and through different environmental processes (in water, soil, air).[44]

Except for direct applications to water and spray drift, most exposure scenarios involving the potential movement of a chemical to surface water are through runoff. The extent to which the active ingredient alone is vulnerable to runoff is strongly influenced by the chemical/physical characteristics/properties of that chemical. Based on these properties, the chemical may be dissolved in the runoff water, it may be bound (sorbed) to sediment suspended in runoff (*i.e.*, erosion), or it may be present in both. The same would hold true for other constituents of the formulation or the tank mix that may contain additives where each is moving at differential rates such that what reaches the surface water (*i.e.*, is transported off-site) is not reasonably expected to represent the same ratio of compounds as was in the original formulation applied to a use site. Even with respect to sprays and dusts moving via atmospheric transport, the volatility of the various components, their octanol-air coefficients and hydroscopicity[45] and their susceptibility to reacting with light are likely to vary, which will result in different dissipation rates and exposure as particles move off-site from the application area. Each component of a formulation and/or tank mix has differing environmental fate characteristics, and hence each component dissipates differentially soon after the formulation is applied. Therefore, EPA does not expect that the formulation or the other components in the tank mix will remain intact such that chronic

[44] An overview on common aspects influencing the dissipation pattern of pesticides: a review | SpringerLink.

[45] Hygroscopicity is the amount of water taken up by carbonaceous particles in the atmosphere, depends the relative humidity, the particle size (*e.g.*, spray droplet or dust particle) and the chemical mixture within the particle and the extent to which they can absorb and scatter light (Russell 2014).

exposure studies would be warranted or even meaningful. The Agency concludes, based on its understanding of the physico-chemical properties of the active ingredient and other ingredients and supported by the references in this petition, that chronic exposures to intact formulations (or tank mixes) are not likely to occur even in situations in which a product is applied directly to water or moves off-site via spray drift.

While the differential properties of the various constituents of a formulation and the other additives that may be used make chronic exposure to the intact product unlikely, these same properties affect the extent to which off-site transport through spray drift and/or runoff of the intact formulation and/or tank mix may occur. Although several inerts and additives are typically thought of in terms of enhancing (potentiating) the toxicity of an active ingredient, they are typically directed at increasing the efficacy of the product in controlling a pest through more targeted delivery (*e.g.*, increasing the ability of the pesticide to remain on a plant surface). This targeted delivery also affects exposure by influencing how the chemical moves in the environment and in doing so can reduce the potential for non-target exposure (*e.g.*, increased penetration of plant leaf cuticles) and hence reduce the likelihood of adverse effects from such exposure (*e.g.*, tank mix additives to reduce off-site drift).[46,47,48,49,50,] Evolving technologies also include formulations intended to reduce environmental loading.[51] In determining sensitivity of a non-target organism to a chemical stressor, EPA considers exposure to be a key determinant.[52,53] Even in these situations, based on the available information cited in the petition and for the reasons discussed in this response, EPA considers exposure to the intact formulation or tank mixture as an acute (*i.e.*, short-term) event and unlikely to occur through chronic or repeated exposure via direct contact via runoff or through routine dietary exposures.

Additionally, formulated product tests are frequently conducted under static conditions (*i.e.*, exposure solution is not renewed over the duration of the test). Therefore, the pesticide active ingredient as well as the inert ingredients are allowed to degrade, and therefore the test organisms are allowed to be

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[46] Miller, P.C.H., J. Hewitt, and W. E. Bagley. 2001. Adjuvant effects on spray characteristics and drift potential. In *Pesticide Formulations and Application Systems: Twenty First Volume* ASTM Special Technical Publication 1414 (2001): 175-184.

[47] Wang, C. J., Z. Q. Liu. 2006. Foliar uptake of pesticides – present status and future challenge. Pesticide Biochemistry and Physiology 87: 1 – 8 https://doi.org/10.1016/j.pestbp.2006.04.004 .

[48] Green, J.M, G. B. Beestman. 2007. Recently patented and commercialized formulation and adjuvant technology. Crop Protection 26(3): 320 – 327 https://doi.org/10.1016/j.cropro.2005.04.018.

[49] Hewittt, A. J. 2008. Spray optimization through application and liquid physical property variables-I. The Environmentalist 28: 25 – 30.

[50] Wang, S., X Li, A. Zeng, J. Song, T. Xu, X. Lv and X. He. 2022. Effects of adjuvants on spraying characteristics and control efficacy in unmanned aerial application. Agriculture 12(2): 138 https://doi.org/10.3390/agriculture12020138.

[51] Ohkouchi, T. and K Tsuji. 2022. Basic technology and recent trends in agrichemical formulation and application technology. Journal of Pesticide Science 47(4): 155 – 171 https://www.jstage.jst.go.jp/article/jpestics/47/4/47_D22-055/_pdf/-char/ja.

[52] USEPA. 1998. Guidelines for Ecological Risk Assessment. EPA/630/R-95/002F. April 1998. Published May 14, 1998, Federal Register 63(93): 26846-26924 https://www.epa.gov/sites/default/files/2014-11/documents/eco_risk_assessment1998.pdf

[53] USEPA 2004. Overview of the Ecological Risk Assessment Process in the Office of Pesticide Programs, U.S. Environmental Protection Agency. Endangered and Threatened Effects Determinations. Office of Prevention, Pesticides and Toxic Substances, Office of Pesticide Programs, Washington DC. January 23, 2004. https://www.epa.gov/sites/default/files/2014-11/documents/ecorisk-overview.pdf.

exposed to both the intact formulation as well as any degradates that would form under such test conditions.

As such, humans and wildlife are not expected to be exposed to the intact formulations over extended durations. Chronic toxicity testing with a whole intact formulation is neither necessary nor typically conducted to support a pesticide registration because repeated exposure (either by ingestion or direct contact) to an intact formulation or even components in a tank mix over long durations is not expected. This approach is consistent with other regulatory authorities as described in the European Commission working document Guidance on Aquatic Ecotoxicology (SANCO/3268/2001 rev.4 (final)) and the *Evaluation Manual for the Authorisation of Plant Protection Products* according to Regulation (EC) No 1107/2009[54] wherein ecotoxicity and human toxicity testing generally focuses on the pesticide active ingredient particularly with respect to chronic toxicity testing.[55,56] Given the differential environmental fate properties of inerts and TGAI and that the toxicity is largely associated with TGAI, current data requirements for TGAI are important for assessing potential acute and chronic risks associated with specific uses of the active ingredient. While existing data requirements for EP provide a means of determining the extent to which the acute toxicity of the EP may differ from TGAI, the Agency would be remiss if it were to forego testing of TGAI in preference to EP.

In ecological risk assessments for conventional pesticides, EPA assumes, consistent with guidance issued by the European Commission,[27] that non-target organisms could be exposed to an intact formulation via spray drift or through direct application of a product to water. It is anticipated that acute exposure to an intact formulation could occur through spray drift and not through runoff since the latter renders the various constituents of a formulation more vulnerable to soil/aquatic metabolism and opportunities to sorb/partition to sediments, thereby limiting their persistence and mobility. If there are toxicity data for a formulation (based on registrant-submitted data, open literature, or incident reports) suggesting that a product is potentially more toxic than the active ingredient alone, EPA conducts an analysis to estimate the exposure from the spray drift event from a liquid pesticide application and compares this estimate to that toxicity endpoint; appropriate actions are then taken based on the findings of that analysis.

Furthermore, the National Academy of Sciences issued a report on assessing risks to endangered and threatened species from pesticides.[57] The report discusses chronic toxicity testing using formulations, as well as environmental partitioning and the applicability of formulation testing. The report also acknowledges that the active ingredient and inerts in a formulation seldom have the same physico-chemical properties and will partition at different rates in the environment. The report concludes that while longer-term (*i.e.,* chronic) studies conducted on pesticide formulations could be useful in

[54] CTGB. 2017. Chapter 4 Human toxicology; mammalian toxicity dossier. In Evaluation Manual for the Authorisation of plant protection products according to Regulation (EC) No 1107/2009. EU Part Plant Protection Products. Version 2.2; March 2017. https://rvs.rivm.nl/sites/default/files/2021-10/Regulation_EC_No_11072009_ch_4_human_tox.pdf

[55] Guidance on Aquatic Ecotoxicology (SANCO/3268/2001 rev.4 (final)).

[56] Kienzler *et al*. 2016. Regulatory assessment of chemical mixtures: requirements, current approaches and future perspectives. Regulatory Toxicology and Pharmacology 80: 321 – 334 https://doi.org/10.1016/j.yrtph.2016.05.020.

[57] https://nap.nationalacademies.org/read/18344/chapter/1.

evaluating the long-term effects of a formulation, they likely have little relevance to exposures that occur in the environment as partitioning occurs.

Therefore, given that formulations and other chemicals in a tank mix can and will likely behave differently in the environment after application and not stay as an intact mixture, humans and wildlife will not be exposed to that initial mixture under long-term durations and thus chronic exposure testing of an intact formulation is not likely to provide meaningful results for EPA's risk assessments and could be misleading as to the potential for real-world exposures. Therefore, EPA concludes that amendments to 40 CFR part 158 to require chronic toxicity on an *a priori* basis for end-use product formulations is not warranted. Where the available data indicate a need for additional chronic exposure data, EPA can require that data under its current regulations. See 40 CFR 158.75. For example, with the fungicide Pristine™ (EPA Reg. No. 7969-199), which is a co-formulation of boscalid and pyraclostrobin, commercial beekeepers had raised concerns regarding the use of the compound on almonds during bloom when roughly 70% of the nation's managed honey bee colonies are providing pollination services in the orchards. In this case, EPA required data on the formulation including the nonionic wetter/spreader adjuvant Induce™, which had been identified as being used in combination with the formulated product.[58] As noted earlier, when there is potential for acute exposure to more intact formulations (*i.e.*, direct contact), the Agency has data requirements to obtain that information (see below for specific situations).

40 CFR part 158 Requirements and Other Lines of Evidence

The burden of demonstrating that a product meets the standards for registration rests fully on the registrant or applicant for registration. This applies to the registration review of currently registered pesticides as well. To obtain or maintain registration of a pesticide, applicants are responsible for satisfying all applicable data requirements, which often involves generating or citing specific data contained in EPA's regulations at 40 CFR part 158. The standard for determining whether an application should be granted includes that when used in accordance with widespread and commonly recognized practice, the product will not cause unreasonable adverse effects on the environment. As noted above, FIFRA defines "unreasonable adverse effects" as, among other things, "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." In addition to these data requirements, the Agency also evaluates other lines of evidence (e.g., open literature and incident reports) to evaluate potential effects and risk to both humans and non-target organisms.

The data requirements laid out in 40 CFR part 158, Subparts C, F, and G include an array of toxicological tests to evaluate potential risks for both human health and other non-target taxa (*e.g.*, wildlife and plants) to support the experimental use or registration of a conventional pesticide[59] product. The types of data needed may vary depending on where and how the pesticide is used.

FIFRA's implementing regulations at 40 CFR sections 158.200 to 158.270 describe the data requirements for an Experimental Use Permit for a particular pesticide product. These sections require a range of

[58] Lawrence, J. and M. Riley. 2012. Determination of residues of Pristine fungicide (Pyraclostrobin + Boscalid) in royal jelly and pollen in almond trees in central California (MRID 490093-04).

[59] Conventional pesticides are all active ingredients other than biological pesticides and antimicrobial pesticides. Conventional active ingredients are generally produced synthetically.

information, including product chemistry, product performance, toxicology (human health), ecological effects, and environmental fate. Within these requirements, data using the EP as opposed to testing on the individual components separately are already required for product chemistry (158.210) and product performance (158.220). Additionally, for the toxicological section (158.230), testing with EP is required for the acute toxicity studies with mammals. Furthermore, for the ecological effects, there are conditions described for when testing with an EP or Typical end-use product ("TEP") are required (see below for discussion under 40 CFR part 158: Subpart G). Ecological effects testing of EP is triggered when exposure to a specific product is expected (*e.g.*, direct application to water); testing of TEP is required when there are multiple formulations of an active ingredient and testing is required on a typical formulation of the active ingredient rather than a specific formulation.

Regarding the potential for acute exposure to a formulation, EPA currently requires a suite of mammalian acute toxicity data (referred to as the "six-pack"[60]) on end-use products with which to gauge the toxicity of the products relative to the TGAI. In addition to the formulated product data provided through the six-pack, EPA routinely requires testing of TEP for terrestrial and aquatic plants, and in situations where there is direct application to water, the Agency requires a broader suite of acute toxicity tests of formulated product with both freshwater and estuarine/marine fish and invertebrates. There are also cases where, because of limited solubility of TGAI, the Agency has recommended additional acute toxicity tests with formulated product to ensure exposure of test organisms to the active ingredient. These acute toxicity data on the formulated product in combination with other lines of evidence inform the Agency's understanding of the toxicity of the formulated products relative to TGAI alone. EPA can compare the results of the acute toxicity studies for the formulated product and the TGAI and assess whether the toxicity endpoints for the EP are of similar magnitude as those for the TGAI, and these data can help EPA determine whether additional data should be required. This approach represents an evidence-based means of determining whether more targeted testing is needed and serves as a more effective means of leveraging EPA resources and reducing both unnecessary testing costs and unnecessary animal testing.

FIFRA's implementing regulations at 40 CFR sections 158.500 to 158.510 specify the data that EPA may require to determine the risks of a conventional pesticide to human health. These data requirements are intended to enable EPA to evaluate potential human health risks ranging from acute and short-term toxicity to long-term effects such as cancer and reproductive system disorders. Regarding toxicology testing to evaluate potential effects to human health, as noted in the petition, the Agency does require acute toxicity testing of mammals for each formulation proposed for registration. For acute toxicity, testing requirements (*i.e.*, acute oral, acute dermal, acute inhalation, primary eye irritation, primary dermal irritation, dermal sensitization) apply for the EP and not the TEP. Additionally, dermal penetration studies are commonly performed with EPs and, under particular circumstances as outlined in 158.500, the subchronic requirements for the 21/28 and 90-day dermal toxicity studies may also be performed with the EP. Other subchronic requirements as well as chronic, genotoxicity, developmental toxicity, and reproduction toxicity are not tested using an EP (or TEP). The rationale for these specific

[60] The 40 CFR Part 158 Subpart F identifies the acute mammalian "six-pack" which includes mammalian acute oral toxicity, acute dermal toxicity, acute inhalation toxicity, primary eye irritation, primary dermal irritation, and dermal sensitization studies and serve as a basis of hazard classification and precautionary labeling.

testing requirements is described below in the discussion regarding exposure potential to an intact formulation.

FIFRA's implementing regulations at 40 CFR sections 158.630 and 158.660 specify the data that EPA may require to determine the risks of a conventional pesticide to non-target terrestrial and aquatic animals and plants (including birds, wild mammals, fish, aquatic and terrestrial invertebrates, plants). To evaluate potential risks to wildlife and plants, EPA requires submission of data intended to evaluate everything from short-term toxicity (*e.g.*, acute mortality) to potential longer-term effects on survival, growth, and reproduction.

While many of the ecological tests required to support pesticide registrations are conducted for the technical grade of the active ingredient (TGAI),[61] there are several situations specified in 40 CFR part 158 in which EP (also referred to as the "formulated product') testing is required. Testing of EP or TEP is required for any product that meets any of the following conditions:

i. The end-use pesticide will be introduced directly into an aquatic environment (*e.g.*, aquatic herbicides and mosquito larvicides) when used as directed.

ii. The maximum expected environmental concentration (MEEC) or the estimated environmental concentration (EEC) in the aquatic environment is less than or equal to one-half the LC_{50}[62] or EC_{50}[63] of the TGAI when the EP is used as directed.

iii. An ingredient in the end-use formulation other than the active ingredient is expected to enhance the toxicity of the active ingredient or to cause toxicity to aquatic organisms.

Based on EPA's Guidance on Exposure and Effects Testing for Assessing Risks to Bees, testing of TEP is also required for Tier 2 (enclosure studies and residue monitoring studies) and Tier 3 (full-field pollinator study) colony-level studies with honey bees. Testing of formulated product is typically reserved for situations in which it is likely that the non-target organisms may come in direct contact with the intact formulation (*e.g.*, via direct application to water) rather than to the active ingredient alone. However, these situations are limited in scope based on the exposure potential described above. For the direct application to water, since the EP is being directly applied this represents a relevant exposure route. Although even in that situation, once the EP is applied to the water, it too will begin to dissipate and the different components will move through the aquatic environment at different rates, in which case organisms are likely only exposed to the intact formulation for a short duration. For the other conditions described above, exposure through spray drift, and not runoff/erosion, is the likely pathway based on the exposure potential described above. And this exposure route, just like direct application, will also undergo dissipation in the aquatic environment. Regarding the third requirement, as an example, the surfactant polyethoxylated tallow amine (POEA), which is known to cause potential toxicity in some aquatic organisms, resulted in the registrant submitting aquatic toxicity studies of the surfactant.

[61] Technical Grade Active Ingredient (TGAI) is the pesticide chemical in pure form (with impurities) as it is manufactured by a chemical company prior to being formulated into other pesticide products.
[62] The LC_{50} is the concentration resulting in 50% lethality of the organisms tested.
[63] The EC_{50} is the concentration resulting in 50% effect of the organisms.

The 2004 Overview of the Ecological Risk Assessment Process in the Office of Pesticide Programs discusses situations in which there may be evidence that a pesticide formulation may be more toxic to aquatic organisms than indicated by active ingredient testing and where it may be necessary to consider aquatic exposure to the formulation (see Special Aquatic Exposure Methods for Pesticide Formulations). Such considerations though are typically limited to direct applications of the product to water (*e.g.*, rice production) or to incidental exposure from spray drift. As noted in the Overview document:

> [T]he ability to quantify exposure to intact formulations is limited by the expectation that the varying physical-chemical characteristics of the individual components of the pesticide formulation will result in progressively different formulation constituents in the environmental media over time. As the proportions of formulation components in environmental media differ from the proportions in the tested formulation, the assumption that environmental residues are toxicologically equivalent to tested formulations cannot be supported beyond the time period immediately following product application. This assumption is especially important in the case of runoff from treated areas to surface waters. In this case, partitioning and degradation properties for each formulation component suggest that the final proportion of the residues of these components in the receiving surface waters would not represent what was introduced and what was tested in an aquatic organism toxicity study using the formulated product."

In other words, given that the different components in a formulation are anticipated to dissipate at different rates and be present in the environment in different proportions after application, conducting toxicity testing on all pesticide formulations, as the petitioner requests, especially under longer duration exposures (*i.e.*, chronic), is not expected to reflect actual exposures of non-target organisms in the real world from pesticides applied in the environment.

Regarding acute formulation testing with aquatic organisms (*e.g.*, fish, invertebrates, vascular and non-vascular aquatic plants), when a pesticide product is proposed to be directly applied to water, it is assumed that the organisms are exposed to the intact formulation before it dissipates differentially in the aquatic environment. Additionally, toxicity testing for terrestrial plants is routinely conducted using pesticide products (*i.e.*, EP) rather than the TGAI alone, which is consistent with the requests of the petition. This is because it is recognized that plants may be directly exposed to the intact formulation from a pesticide spray application. However, these tests do not include additives, as such combinations are influenced by multiple factors (*e.g.*, pest pressure, crop, weather, equipment type, method of application, *etc*.) and would likely vary both spatially and temporally and be difficult to anticipate.

Additionally, as ecological effects testing moves from laboratory-based testing to higher-tiered testing to better reflect more environmentally realistic testing conditions, those studies are typically conducted using a formulated product. For example, testing with a formulation is common when the Agency requests testing for higher-tiered pollinator testing (Tiers II and III[64]). Regarding pollinator testing, when moving to a higher-tier analysis, EPA may require studies designed to reflect real-world exposures and effects on the whole colony more closely, especially with respect to how the pesticide is applied in the environment, and how the pesticide active ingredient may then move through the environment in terms of its persistence and mobility. While laboratory-based acute and chronic toxicity studies of individual

[64] How We Assess Risks to Pollinators | US EPA.

bees are conducted with technical grade active ingredient, the Tier II and III field-based colony-level studies are routinely conducted with formulated end-use product. At the highest level of refinement (*i.e*., Tier III full field pollinator testing; OCSPP 850.3040), the studies are with formulated product and the colonies are exposed just as they would be under actual use conditions. As such, they are exposed to multiple chemicals which may be in use within the broad foraging distance (*i.e*., 5 – 8 miles) of honey bees. As discussed in the Agency's 2014 Guidance for Assessing Pesticide Risks to Bees,[65] the decision to transition to higher-tier testing is based, in part, on the Tier I laboratory-based assays with individual bees using TGAI and whether risks of concern are identified. Since higher-tier studies require considerable resources to conduct and review, the Agency reserves such studies for situations in which tests with TGAI indicate the need for further refinement.

Furthermore, consistent with 40 CFR part 158, testing using a formulation instead of TGAI alone can be requested for other terrestrial and aquatic organisms under semi-field or field conditions. Conducting formulated product testing on only these types of tests is generally consistent with other international regulatory authorities, such as those in Canada and Europe. As discussed in the Agency's 2004 Overview of the Ecological Risk Assessment Process in the Office of Pesticide Programs[66] and as described in the European Commission working document Guidance on Aquatic Ecotoxicology (SANCO/3268/2001 rev.4 (final)) formulated product testing is typically confined to acute studies given the uncertainty associated with chronic toxicity testing of a formulation. In situations where chronic toxicity testing of a formulation might be required to support registrations in the European Union, measurement endpoints would have to be expressed relative to the initial concentration as the expectation is that the constituents are dissipating at variable rates over the duration of the study.

In addition to the eco(toxicology) testing conducted with a formulation, terrestrial field (OCSPP 835.6100) and aquatic dissipation studies (OCSPP 835.6200) are conducted with a formulation (see 40 CFR part 158: Subpart N). These studies are conducted to better understand how a pesticide moves through the environment under actual use conditions at representative field sites and how those results compare to those environmental fate data from laboratory-based studies of the TGAI. The need to request or conduct these studies depends on the results of the risk assessment that is typically conducted using laboratory-based studies, considering whether sufficient information is available to support the regulatory decision process or whether additional information is needed to understand the potential risk. The 40 CFR part 158 subpart G stipulates conditions that may trigger additional toxicity testing and the nature of the test material (*i.e*., TGAI; EP; TEP) based on the persistence and mobility of the chemical, estimated exposure values, and toxicity. In addition to studies identified in 40 CFR part 158, over the years the Agency has published guidance (*e.g*., Guidance on Exposure and Effects Testing for Assessing Risks to Bees) identifying additional exposure and toxicity tests needed to inform regulatory decisions.

When assessing the potential for adverse effects from exposure to pesticides proposed for registration or undergoing registration review, in addition to registrant-submitted data, EPA may use toxicity

[65] USEPA *et al*. 2014. Guidance for Assessing Pesticide Risks to Bee. Office of Pesticide Programs, USEPA; Health Canada Pest Management Regulatory Agency, California Department of Pesticide Regulation. June 14, 2014. https://www.epa.gov/sites/default/files/2014-06/documents/pollinator_risk_assessment_guidance_06_19_14.pdf.

[66] https://www.epa.gov/sites/default/files/2014-11/documents/ecorisk-overview.pdf.

endpoints (from TGAI, formulations, or inert ingredients) found in publicly available literature for human health and ecological risk assessments. Open literature studies considered for use in a human health and ecological risk assessment are evaluated using agency guidance.[67, 68] While the guidance on human health open literature focuses on mammalian *in vivo* toxicity studies, its general principles and criteria also apply to pharmacokinetic/metabolism, mechanism of toxicity and *in vitro* studies. Additionally, the Agency considers human epidemiology and human incident data using an OPP framework.[69] Consideration of this type of data represents real-world exposures and conditions that can be considered when evaluating a pesticide.

To identify open literature studies that may potentially be incorporated into the Agency's ecological risk assessments, EPA uses the ECOTOXicology ("ECOTOX") Knowledgebase. ECOTOX is a comprehensive knowledgebase providing single chemical environmental toxicity data on aquatic and terrestrial species. While ECOTOX indicates that it contains references to single chemical exposure, it contains papers that evaluate pure active ingredients as well as formulated products. During Registration Review, EPA systematically reviews open literature for more sensitive toxicity endpoints, which can include data on formulated products provided that the study is found to be reliable and represents a relevant route of exposure. For example, open literature indicating effects from the surfactant POEA, which is in several formulations of glyphosate, were included as additional lines of evidence along with studies containing POEA submitted by the registrant in the ecological risk assessment written in support of the registration review of glyphosate.[70] Similarly, EPA also reviews and considers ecological incident data for plants and animals and these data provide another line of evidence regarding the effects of pesticides under actual use conditions.

While the data required through 40 CFR part 158 provide EPA with an understanding of the potential effects on humans and the environment from exposure to TGAI and EP, these studies are largely conducted under controlled conditions and consider the relevant exposure routes. However, there are mechanisms in place to ensure that the Agency is alerted to unanticipated adverse effects (*i.e.*, incidents) should they occur under actual use conditions. Under FIFRA Section 6(a)(2) and pursuant to 40 CFR 152.125 and part 159, subpart D, registrants have a continuing obligation to report to EPA factual information on unreasonable adverse effects to human health or the environment of the pesticide. Failing to provide the necessary information about the pesticide to the EPA is a violation of FIFRA and can result in civil or criminal penalties for the responsible party (7 U.S.C. §§ 136j(a)(2)(B)(ii), 136). In addition to data provided by registrants, adverse effect data may also be available through reports provided by the public and by state and tribal authorities responsible for pesticide enforcement.

Furthermore, as described earlier, EPA has the authority to call in additional data as it deems appropriate to adequately evaluate potential risks (see 40 CFR 158.75). For example, because of targeted testing of the surfactant POEA, EPA determined, based on existing part 158 data requirements for products intended as direct applications to water, that the substance is more toxic than the active ingredient (glyphosate) to aquatic organisms and took action to ban the direct application of the

[67] Guidance for Considering and Using Open Literature Toxicity Studies to Support Human Health Risk Assessment (epa.gov).
[68] 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.
[69] https://www3.epa.gov/pesticides/EPA-HQ-OPP-2008-0316-DRAFT-0075.pdf.
[70] Glyphosate registration review public docket (EPA-HQ-OPP-2009-0361) at https://www.regulations.gov.

formulations to water. Additionally, the Agency considered the effects of POEA in isolation, as well as its inclusion in formulations allowed on terrestrial use sites, during the glyphosate registration review.[71]

EPA's Analysis of Inert Ingredients in Pesticide Formulations

40 CFR 158.300 defines inert ingredients as any substance (or group of structurally similar substances if designated by the Agency), other than an active ingredient, which is intentionally included in a pesticide product. All new inert ingredients (food use and nonfood use) are subject to Agency review under FFDCA/FQPA and Pesticide Registration Improvement Act (currently as PRIA 5[72]). Most approved inert ingredients can be found in 40 CFR 180.910-180.960; part 158 also contains sections that include tolerances/ tolerance exemptions for specific inert ingredients. An online searchable database (InertFinder[73]) allows pesticide formulators and other interested parties to easily identify chemicals approved for use as inert ingredients in pesticide products.

Inert ingredients and additives can play a key role in the effectiveness of a pesticidal product. For example, inert ingredients may serve as a surfactant and/or wetting agent allowing the pesticide's active ingredient to penetrate a plant's outer surface. In some instances, inert ingredients are added to extend the pesticide product's shelf-life or to protect the pesticide from degradation due to exposure to sunlight. Pesticide products may contain more than one inert ingredient.

Federal law does not require that these ingredients be identified by name or individual percentage on the label, although this information must be provided to EPA as part of the confidential statement of formula. In general, only the total percentage of inert ingredients is required to be on the pesticide product label, with limited exceptions. However, registrants provide to the Agency for review the complete summary (identity and percentage) of all ingredients, including inert ingredients, in the pesticide formulation.

EPA's evaluation considers potential risks of the inert ingredient to human health and the environment as part of the evaluation of pesticide products under FIFRA. In the case of food use inert ingredients, the approval of the use of the inert ingredient must also meet the FFDCA safety standard that ''there is a reasonable certainty that no harm will result from aggregate exposure to the [inert ingredient] residue, including all anticipated dietary exposures." The data used to make these determinations include toxicity data to address risks to humans and domestic animals as well as to non-target organisms, residue data/information, and exposure and fate data. Under the tolerance reassessment provisions of FQPA, all inert ingredient tolerances/tolerance exemptions in effect as of 1996 were reassessed using the FQPA safety standard.

The Burden of Testing Every Formulation Product

Currently, there are over 18,000 pesticide formulations registered. Conducting testing on the entire toxicity (40 CFR part 158 subparts: Subparts F and G) testing battery (acute and chronic), as requested by the petitioner, for every formulation represents a significant cost for the applicant and/or registrant. Although the petitioner's request is to substitute the end-use product formulation testing for any TGAI testing, the fact remains that imposing any such requirement at this time would add to the already high

[71] https://www.regulations.gov/document/EPA-HQ-OPP-2009-0361-0077.
[72] Pesticide Registration Improvement Act of 2022 (PRIA 5) | US EPA.
[73] https://ordspub.epa.gov/ords/pesticides/f?p=INERTFINDER:1:0::NO:1::.

costs for producing data that have already been incurred to support those registrations. Moreover, because end-use product data alone would not be sufficient for assessing risks (*i.e.*, EPA would still need TGAI data to support registration actions since, as described above, understanding the toxicity potential of the TGAI alone is a critical component of evaluating potential risk and is the relevant chemical in most cases), the costs for requiring end-use product data would be in addition to the costs for producing TGAI data. Using the cost estimates for studies[74] required for pesticide registration by taking into consideration the data requirements for human health and ecological (acute and chronic), it is estimated that it would cost well over an additional $8 million per formulated product to implement the petitioner's requests. It is estimated that the human health toxicity testing costs between $8-16 million alone.[75]

In addition to the financial costs, there are costs associated with use of animals for toxicity testing. It is estimated that the testing battery would result in testing on approximately 5,000-7,000 animals per formulation for the requested human health toxicity testing,[76] and around 9,000 animals for both human health and ecological toxicity testing.[77] As such, the costs in terms of resources needed for generating data for each formulated product are significant; however, these costs are not limited to the regulated community, as reviewing these relatively complex studies requires substantial EPA resources as well. Additional testing requirements (*e.g.*, on every formulated product) would further increase Agency resources needed to review data and increase the time required for assessing registration applications. Because the petitioner has not provided evidence that increased testing would substantially affect the Agency's understanding of whether the use of a compound would result in unreasonable effects on human health or the environment, EPA opposes such a burden on the regulated industry. Moreover, if EPA were to propose additional testing requirements as the petitioner has suggested, it is unclear whether the benefits of obtaining those studies would outweigh the costs associated with requiring those studies. Under Executive Order 12866,[78] EPA would likely need to submit any rule proposing to require the data suggested by the petitioner to the Office of Management and Budget (OMB) for review, including a justification that the benefits of obtaining the new data outweighed the costs of that rule. EPA would be unable to provide such justification for that increased burden since it does not believe that requiring that information, as a general matter, is necessary for all FIFRA assessments.

EPA has committed to reducing reliance on whole animal testing and is pivoting toward new approach methodologies (NAMs[79]) and/or is relying on more targeted hypothesis-based testing to avoid unnecessary use of limited resources and animals.[80] While it is not possible at this time to test all

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[74] US EPA - Cost Estimates of Studies Required for Pesticide Registration.

[75] Craig, E., K. Lowe, G. Akerman, J. Dawson, B. May, E. Reaves, and A. Lowit. 2019. Reducing the need for animal testing while increasing efficiency in a pesticide regulatory setting: Lessons from the EPA Office of Pesticide Programs' Hazard and Science Policy Council. Regulatory Toxicology and Pharmacology 108 https://doi.org/10.1016/j.yrtph.2019.104481

[76] Id. 37

[77] epa_nam_work_plan.pdf (2020).

[78] https://www.archives.gov/files/federal-register/executive-orders/pdf/12866.pdf.

[79] EPA defines NAMs as any technology, methodology, approach, or combination that can provide information on chemical hazard and risk assessment to avoid the use of animal testing https://www.epa.gov/system/files/documents/2021-11/nams-work-plan_11_15_21_508-tagged.pdf.

[80] USEPA. 2021. New Approach Methods Work Plan. USEPA Office of Research and Development Office of Chemical Safety and Pollution Prevention December 2021. EPA 600/X-21/209 https://www.epa.gov/system/files/documents/2021-11/nams-work-plan_11_15_21_508-tagged.pdf.

combinations that may result from tank mixing, the use of NAMs involving *in vitro* high-throughput screening (HTS) assays may in the future provide a means of testing such permutations. EPA has prioritized the development of NAMs to accelerate the pace of screening/testing and decrease reliance on more resource intensive methods of testing and assessment, thereby rendering such analyses more practical and economically feasible. As part of this effort, EPA is working with multiple stakeholders to establish scientific confidence in NAMs and to demonstrate their application to regulatory decisions. EPA has identified the near- and long-term goals in its New Approach Methods Work Plan and through the EPA Office of Research and Development's Strategic Research Action Plans and is providing funding through its Science to Achieve Results (STAR) program to reduce, refine, and/or replace vertebrate animal testing in chemical hazard assessment.[81] The Agency remains committed to taking into consideration and utilizing the best available science to support our assessments and regulatory decisions as the science evolves.

In sum, the Agency believes that there are multiple reasons not to expand the current testing requirements. These include: 1) the current data requirements already include formulation testing for relevant exposure routes; 2) exposure to intact formulations is not anticipated over long durations given dissipation in environment; and 3) the burden of imposing these requirements is not outweighed by the benefit to the Agency's risk assessment process; and, 4) current testing is consistent with EPA's international regulatory counterparts.

Section IV.C. Petition Asserts that the Agency is Required to Evaluate Synergy and Tank Mixtures

Summary of Petition: The petition discusses evaluating the potential for harm resulting when pesticides and other chemicals are combined and create synergistic effects. For example, the petition highlights risks from organosilicone adjuvants (which the Agency is referring to as "additives" since they are added to pesticides in the field) and asserts that these additives have been found to have synergistic effects combined with insecticides and fungicides, including neonicotinoids.

EPA Response:

Tank mixing pesticides can reduce the number of times growers or agricultural workers need to enter a field. In situations where a grower intends to apply a specific regimen of pesticides [and possibly fertilizer] within a narrow time frame, they have the option of either sequentially treating the field with each product or simply mixing the products together and making a single application. Sequential applications of pesticides to a field may not be substantially different in terms of exposure than a combined application (*i.e.*, tank mix). If EPA has data indicating that specific combinations enhance the toxicity of some pesticides or are chemically incompatible (*e.g.*, may result in an emulsion which cannot be readily applied by equipment), then the label may restrict such combinations. For example, the fungicide formulated end-use product Pristine™ contains the following restriction on the label:[82]
"**DO NOT** apply Pristine to blueberries as a tank mix with other pesticide products except fungicide products that contain captan (N-trichloromethythio-4-cyclohexene-1,2-dicarboxamide) as the ONLY active ingredient. **DO NOT** apply Pristine as a tank mix with adjuvants, liquid fertilizers, nutrients, or other additives. Only use water as the spray carrier."

[81] *Ibid* USEPA 2021.
[82] US EPA, Pesticide Product Label, PRISTINE FUNGICIDE,11/30/2022.

In some situations, the user may be warned about potential tank mixes. For example, the insect growth regulator Dimilin 2L (EPA Reg No. 400-461) contains the following information: "*it is known that many components, including crop protection products, fertilizers, micronutrients, and spray adjuvants, may be present in a tank mix combination. There is potential for adverse chemical reactions. It is impossible to determine the physical, biological, and plant compatibility for all scenarios that may be encountered; therefore, it is recommended that the users determine the chemical, physical, biological and plant compatibility of such mixes prior to making applications on a broad commercial scale. Whenever preparing a new tank mix, always conduct a compatibility test by mixing proportional amounts of all spray ingredients in a test vessel (jar) . . .*"

Several commenters (0151; 0157) cited Pesticide Registration Notice (PRN) 82-1 Revised Policy on Label Claims for Tank Mixing, in which EPA revised its policy for approving tank mix claims on pesticide label. Prior to this revised policy, EPA received compatibility data to support such claims. These data consisted of residue data demonstrating that the mixture would not result in residues higher than the tolerance established for each active. The Agency's review of data which had been provided demonstrated that potentiation is not likely to occur and that the resulting residues were within established tolerances. As noted in the PRN, EPA also further clarified recommendations made under FIFRA Section 2(ee)(4) to allow any person to make tank mix recommendations for use on crops or sites listed on the labels of both pesticide products regardless of whether or not the label contains tank mix claims; however, in no case may tank mix recommendations be made for products containing label prohibitions against such claims.[83]

As noted earlier, EPA relies on multiple lines of evidence to assess the toxicity of pesticides both as TGAI and as formulated end-use products. These laboratory and field-based data are responsive to data requirements specified in the FIFRA regulations at 40 CFR part 158 and are supplemented by suitable studies published in the open literature and by adverse effect (incident data) reported by both the public and the regulated community. When uncertainties regarding the potential for adverse effects from exposure to a compound are identified, FIFRA authorizes EPA to require data to address uncertainties if it deems the additional information is necessary. At this time, EPA has no compelling data, nor did the petitioner provide any such data, to suggest that current lines of evidence used by the Agency are insufficient to inform EPA's understanding of potential risks associated with active ingredients undergoing review such that a wholesale shift in the scope of data which should be required.

EPA acknowledges that pesticides are combined in tank mixes and that, while each of the individual pesticide active ingredients and end-use products have been evaluated as appropriate, in many cases, the effects when combined are not tested. But based on the evidence discussed below, there is an absence of compelling data demonstrating the need for such data. Additionally, anticipating and requiring data on all possible combinations is not feasible and would require resources well beyond those currently available, which is especially relevant considering the lack of information indicating that need. The current suite of registrant-submitted tests with TGAI and EP, combined with information gleaned from other lines of evidence (*e.g.*, open literature) have proven effective in estimating human and environmental risks from the prescribed use of pesticides. In the absence of incident data and/or open literature to support concerns regarding such combinations, it would be unreasonable and unnecessary to require such data. In situations where products are combined or tank-mixed in the field,

[83] https://www.epa.gov/pesticide-registration/prn-82-1-revised-policy-label-claims-tank-mixing.

the applicator is required to follow the most restrictive or protective use directions and precautions, as described on the product label; to do otherwise would result in violations of the more restrictive pesticide label language.

Further, attempting to identify all possible combinations of pesticides at a national level would likely be a significant drain on limited resources and impossible. Based on California Pesticide Use report data collected between 2014 to 2015 for pesticides applied to almonds during bloom in California alone, there were 2,537 tank mixes of varying pesticides combinations. Therefore, determining specific ratios of the constituent products to test would be daunting, if not impossible, as these ratios can vary both spatially and temporally even for a single crop and are influenced by multiple factors (*e.g.*, pest pressure, weather).

When chemicals are combined and interact, their toxicity may be additive (*i.e.*, their overall effect equals sum of each individual effect), greater than additive (*i.e.*, their overall effect is greater than the activity of each component), or less than additive (*i.e.*, their overall effect is less than the activity of each component). The extent to which an interaction results in greater than additive effects and represents a synergistic effect or conversely is less than additive and represents and antagonistic effect varies.[84,85] As noted earlier, once sufficiently vetted, NAMs could provide a means of high-throughput screening that will make it more feasible/practical to evaluate various combinations.

While the petition uses the term "synergy," the Agency uses the term greater than additive (GTA). To evaluate for potential greater than additive (GTA) situations for new active conventional pesticide ingredients, EPA has developed an interim process to evaluate effects of mixtures of active ingredients based on patents granted by the U.S. Patent and Trademark Office (PTO) on the basis of patent applicant statements asserting that the combined effects of the mixture are synergistic (*i.e.*, the effect of a mixture of pesticides is greater than the sum of the individual effects). In 2019, the Agency released its GTA Interim Policy[86] and such assessments are routinely conducted for new chemical registrations. To ensure that effects data of the mixture relevant to ecological risk assessments are considered, EPA has requested that registrants of new chemicals submit toxicity data that were provided to the U.S. PTO in support of patent claims for mixtures. EPA provided guidance to assist registrants in identifying relevant data for submission. The Agency then reviews the information submitted by the registrants to determine if there are any findings of GTA effects that could impact the conclusions of the ecological risk assessment, risk mitigation efforts, or registration decision. The Agency could also decide that additional mixture toxicity data are needed to better evaluate for any potential GTA effect.

Based on the EPA's evaluation of open literature and data from our new AI GTA patent search process, any instances of true synergy between active ingredients are rare, which is consistent with analyses

[84] Hertzberg, R. C. and M. M. MacDonell. 2002. Synergy and other ineffective mixture risk definitions. Science of the Total Environment 288: 31 – 42. https://doi.org/10.1016/S0048-9697(01)01113-5.

[85] Liess, M., S. Henz and N. Shahid. 2020. Modeling the synergistic effects of toxicant mixtures. Environmental Science Europe 32 https://doi.org/10.1186/s12302-020-00394-7.

[86] EPA-HQ-OPP-2017-0433-0002.

reported in the open literature.[87,88,89,90] When such interactions do occur, it is at relatively high concentrations.[91,92] As discussed in the Agency's GTA interim policy, pesticide ecological risk assessments conducted by EPA have focused on the likelihood of exposure and effects (*i.e.,* risks) from the use of individual pesticide active ingredients. The following are some of the reasons why the Agency has focused on single active ingredients:

- Open literature indicates that toxicological interactions between active ingredients that produce significant GTA effects across a variety of taxa are rare occurrences.[93,94,95] For example, Belden *et al*. (2007a) report that GTA effects across a variety of taxa that were above a 5-fold increase in effect occurred in less than 1% of mixture studies evaluated.
- Analysis of environmental monitoring information and associated pesticide toxicological endpoints (*e.g.,* U.S. Geological Survey's ambient water monitoring as discussed in Belden *et al*. 2007b)[96] indicates that the potential ecological risk of environmental mixtures of pesticides is often predominantly attributable to one or a few dominant active ingredients in the mixture;
- The National Research Council (NRC), in its review of OPP's ecological risk assessment methods (NRC 2013), stated that, in general, toxicological interactions between pesticide active ingredients that produce GTA effects are rare.
- EPA's focus on chronic, no effect thresholds (*e.g.,* no observed adverse effect concentration values (NOAEC)) and the low probability of individual acute effects levels is protective at the low concentrations associated with these thresholds. The theory of independent action suggests that mixtures of ingredients of diverse modes of action should not yield a combination effect when components are present at levels associated with zero responses. This expectation is similar to the European Food Safety Authority (EFSA) conclusion reached by a limited review of the available literature by the Panel on Plant Protection Products and their Residues (PPR) (EFSA 2008), which states that significant toxic interactions between chemicals are "*…much less likely*

[87] Coors, A. and T. Frische. 2011. Predicting the aquatic toxicity of commercial pesticide mixtures. Environmental Sciences Europe 23. https://doi.org/10.1186/2190-4715-23-22.

[88] Beldon, J. B., R. J. Gilliom, and M. J. Lydy. 2007a. How well can we predict the toxicity of pesticide mixtures to aquatic life? Integ. Environ. Assess. Manage. 3(3): 364 – 372 https://doi.org/10.1002/ieam.5630030307.

[89] Cedergreeen, N. 2014. Quantifying Synergy: A Systemic Review of Mixture Toxicity Studies within Environmental Toxicology. PLoS ONE 9(5): e96580. doi:10.1371/journal.pone.0096580 https://doi.org/10.1371/journal.pone.0096580.

[90] Martin, O., M. Scholze, S. Ermler, J. McPhie, S. K., Bopp, A., Kienzler, N. Parissis and A. Kortenkamp. 2020. Ten Years of research on synergisms and antagonisms in chemical mixtures: a systematic review and quantitative reappraisal of mixture studies. Enviro Int. DOI: 10.1016/j.envint.2020.106206.

[91] *Ibid* Cedergreeen 2014.

[92] Hernández, A.F., G. Fernando and M. Lacasaña. 2017. Toxicological interactions of pesticides mixtures: an update. Arch. Toxicol 91: 3211 – 3223. DOI: 10.1007/s00204-017-2043-5.

[93] Carpy, S. A., W. Kobel, and J. Doe. 2000. Health Risk of Low-dose pesticide mixtures: a review of the 1987 – 1998 literature on combination toxicology and health risk assessment. Journal of Toxicology and Environmental Health, Part B 3: 1 – 25 https://doi.org/10.1080/109374000281122.

[94] *Ibid* Beldon *et al*. 2007a.

[95] *Ibid* Cedergreen. 2014.

[96] Beldon, J. B., R. J. Gillion, J. D. Martin, M. J. Lydy. 2007b. Relative toxicity and occurrence patterns of pesticide mixtures in streams draining agricultural watersheds dominated by corn and soybean production. Integ. Environ. Assess. Manag. 3: 90 – 100 https://doi.org/10.1002/ieam.5630030108

to occur at doses below the effect levels for individual component compounds than at higher doses."

Although the GTA interim policy is geared towards ecological risk assessments, for human health evaluation, the Agency already has a greater understanding of the potential effects of exposure to formulated products because applicants must submit end-use product toxicity testing for certain study types (*i.e*., acute toxicity).

Furthermore, the National Research Council (NRC) report[97] on assessing risks to endangered and threatened species from pesticides also considered synergy and mixture toxicity. The report acknowledged that a quantitative mixture assessment requires extensive data and that there are challenges in assessing potential risk, which include having the necessary data as well as a lack of understanding of the interactions in the mixture components. The NRC report notes that the toxicity of chemical mixtures probably would not be known and that it is "not feasible to measure the toxicity of all pesticide formulations, tank mixtures, and environmental mixtures."[98] The NRC recommend that in the absence of this information, the effects analysis for a risk assessment should proceed on the assumption that the components have additive effects.

The Agency is aware of chemicals that are intended to act in a GTA manner based on information provided through registrant-submitted studies, patent searches, open literature and incident reports. Piperonyl butoxides (PBOs) are such an example. These chemicals are registered as pesticide active ingredients themselves and are often co-formulated with other pesticide active ingredients such as pyrethroids. EPA has required registrants to conduct specific toxicity testing with PBOs and other chemicals to better understand the extent of the GTA effects when combined at different rates.

While additives are frequently recommended to enhance the efficacy/performance of a pesticide, the increased efficacy does not always result in increased toxicity of the active ingredient. Rather, the increase in efficacy may be the result of more targeted applications where the additive increases surface contact (*e.g*., stickers; wetting agents), decreasing surface tension and reducing runoff. Additives can also modify the physical characteristics of spray solutions to increase droplet size and reduce spray drift. As such, it would be inaccurate to characterize additives as simply potentiating the toxicity of the active ingredient, and in some cases the additives can serve as a means of reducing environmental exposure through more targeted treatments (*e.g*., increased rain fastness limiting the extent to which the pesticide may be vulnerable to wash-off following rain events soon after application).[99]

Current Practices for Consideration of Whole Formulation and Tank Mixes in EPA's Risk Assessments

There can be any number of combinations of pesticides used in and around a particular use site (*e.g.*, one field application may have a certain combination whereas another adjacent field may use another). Attempting to conduct the analyses that would be needed to support restrictions of tank mix combinations goes beyond the scope of the current risk assessment process. That process is focused on

[97] National Research Council. 2013. Assessing Risks to Endangered and Threatened Species from Pesticides. Washington DC: The National Academies Press https://doi.org/10.17226/18344.
[98] *Ibid* National Research Council. 2013.
[99] Krogh, K.S, B. Halling-Sørensen, B.B. Mogensen, K.V. Vejrup. 2003. Environmental properties and effects of nonionic surfactant adjuvants in pesticides: a review. Chemosphere 50(7): 871-901. ISSN 0045-6535, https://doi.org/10.1016/S0045-6535(02)00648-3.

a single active ingredient, and when products are mixed, the required application restrictions are based on the most protective or conservative label instruction from each FIFRA label. Beyond tank mixes, exposure to coincidental mixtures in the environment is complicated by how these mixtures can vary in space and time due to differential environmental fate properties and environmental conditions. Additionally, there is significant uncertainty in assigning causality to specific chemicals where interactions may be occuring. For example, if there was an effect observed in a toxicity test involving the whole formulation, it may be difficult to ascertain the specific constituent responsible for that effect and that should be removed or replaced in the formulation.

Additionally, there is a practical difference in understanding the environmental relevance of testing tank mixtures when, as discussed previously, it would be possible for a user to apply formulations sequentially over the course of a day or other relatively short timeframe as opposed to applying formulations simultaneously in a single application through a "tank mix." Getting information on specific tank mixes may be of limited utility for assessing risks, since users may not apply the formulations in a single application. It is unknown whether exposure would be the same or substantially different if compounds were applied simultaneously or in rapid sequence individually, and the petitioner has not provided any data to suggest that tank mix data would be relevant for anything other than tank mixing, which could be of limited utility for situations in which pesticides are applied sequentially.

In response to a Government Accountability Office (GAO) recommendation, EPA explored potential effects of mixtures to honey bees (https://www.gao.gov/products/gao-16-220). EPA conducted a case study evaluating tank mixes commonly used in almond production due to data showing that 60-75% of the nation's commercial honey bee colonies provide pollination services to almond crop in California. Through this effort, fungicides were used in conjunction with insect growth regulators and other insecticides; however, it is noted that these combinations were sometimes applied during the dormant period of the crop when bees would not be actively foraging on the trees. Based on data obtained from the California Department of Pesticide Regulations Pesticide Use Reporting Database (PUR), there were 2,537 tank mixes of varying pesticide combinations applied to almond orchards in California during bloom in 2014 and 2015. With respect to this issue, the Agency notes that several programs are underway to continue to monitor and address potential issues of tank mixes, including engagement on managed pollinator protection plans intended to enhance communication between growers/applicators and beekeepers; the registration review program, involving review of incident data and open literature; and working with state lead agencies on enhanced investigation and enforcement efforts.

Furthermore, the Agency has considered tank mixing in the past, particularly where it was concerned with potential compatibility issues or potential for higher residues, which could impact tolerances. EPA has since then reviewed compatibility and residue data for tank mixes and records of actual field experience, which shows that potentiation is not likely to occur and that residues are within established tolerances. Therefore, the Agency revised its policy with respect to tank mixes claims on labels and issued a revised policy addressing this (PRN-82-1).[100]

With regard to the Petition's request to revise pesticide registration regulations to require Endangered Species Act (ESA) consultation on the effects of whole pesticide formulations and tank mixtures on threatened and endangered species, as well as comply with the requested requirements in conducting

[100] Pesticide Registration Notice (PRN) 82-1: Revised Policy on Label Claims for Tank Mixing https://www.epa.gov/pesticide-registration/prn-82-1-revised-policy-label-claims-tank-mixing.

statutorily mandated registration reviews of pesticides, EPA considers the current risk and ESA assessment policies and frameworks and testing requirements sufficient to meet the statutory requirements, as supported by the rationale provided in this response, and the petition did not provide compelling information to alter the EPA's process. The Agency takes into consideration multiple lines of evidence when considering both the pesticide active ingredient(s), as well as other ingredients present in pesticide end-use products, and adequately evaluates both the toxicity as well as potential exposure. This conclusion is based on the following: 1) data requirements are already in place for formulation testing for relevant exposure routes; 2) exposure to intact formulations is not anticipated over long durations given dissipation in environment; 3) synergy (or GTA) is a rare occurrence, as supported by existing data; and 4) even considering all the other lines of evidence, evaluating all possible tank mixtures for registered pesticides is not feasible.

IV. Conclusion

EPA is denying the petition. The information provided in the petition is insufficient to compel any change to EPA's current understanding of the science. In addition, the information provided in the petition is insufficient to support any change to the Agency's risk assessment approach or amendments to EPA's regulations to include data identified in the petition.

EPA currently receives toxicity data across multiple taxa (*i.e.*, acute mammalian 6 pack; terrestrial and aquatic plants; colony-level honey bee studies) on all formulations for which direct exposure to a pesticide may be likely. Additional acute ecotoxicity data on formulations are submitted (*i.e.*, freshwater and estuarine/marine fish and invertebrate studies) for uses involving direct application to water. Other lines of evidence (*i.e.*, incident data and studies reported through the open literature) are also available to further inform the Agency's understanding of the potential for formulated products to be more toxic than the TGAI. Furthermore, since the formulations are not expected to remain intact in the environment after application, and the components in the formulation will dissipate differently in the environment, the likelihood of exposure to the whole formulation under long-term durations is considered low.

Therefore, EPA has determined that amending 40 CFR part 158 to require chronic toxicity testing on all formulations would likely not provide a more meaningful understanding of how pesticide formulations—or more specifically, the individual components of those formulations—impact humans and wildlife when applied.

EPA acknowledges that formulations may be combined with additives for a variety of reasons and that these combinations are frequently intended to enhance the exposure potential, and thereby the potential efficacy, of the active ingredient toward controlling the target pest. However, such combinations can enhance the efficacy of the product by keeping the product on the intended use site and reducing potential off-site movement, thereby reducing non-target exposure, which the Agency considers a positive impact.

EPA acknowledges that there are combinations of formulations and additives due to tank mixing for which data are not available. However, these combinations are influenced by multiple factors, (including but not limited to weather, target pest, field condition) and the potential number of such permutations would be difficult to predict. Therefore, the Agency finds that testing beyond the formulations to include all possible tank mixes is not feasible and would result in a substantial increase in the resources needed to conduct/review such additional studies. There is also no clear evidence that applying a single

tank mix to a site is substantially different than sequential applications of individual products nor is there much evidence of tank mixes or combined products resulting in greater than additive effects on humans or the environment. Therefore, requiring data on all tank mixes or prohibiting such practices is neither practical nor is it supported by the available data.

EPA acknowledges that there is uncertainty regarding the number of combinations which are likely across agricultural and non-agriculture uses of pesticides; however, there are mechanisms in place (*e.g.*, incident reporting requirements) that serve as a means of alerting the Agency to adverse effects that may occur under actual use conditions.

Recognizing the value of incident reports as a line of evidence regarding the extent to which pesticides applied under actual use conditions may lead to unanticipated adverse effects (*i.e.*, incidents), EPA is reiterating the responsibility of the regulated community to report incidents as well as any other information available concerning adverse effects resulting from the use of a pesticide.

Additionally, EPA believes that NAMs (*e.g.*, *in vitro* HTS assays) may provide an opportunity in the future to screen possible combinations more effectively without reversing progress made on reducing resource-intensive animal testing.