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Environmental Protection Agency
OPP Docket
Environmental Protection Agency Docket Center (28221T)
1200 Pennsylvania Ave. NW, Washington, DC 20460-0001

**Re: Docket # EPA-HQ-OPP-2018-0262**

These comments are submitted on behalf of Beyond Pesticides. Founded in 1981 as a national, grassroots, membership organization that represents community-based organizations and a range of people seeking to bridge the interests of consumers, farmers, and farmworkers, Beyond Pesticides advances improved protections from pesticides and alternative pest management strategies that reduce or eliminate a reliance on pesticides. Our membership and network span the 50 states and the world.

Beyond Pesticides is writing to support the legally-grounded requests made in the Petition Seeking Revised Testing Requirements of Pesticides Prior to Registration (EPA-HQ-OPP-2018-0262). Beyond Pesticides supports the position of the Center for Food Safety that EPA has failed in its federal mandate to adequately assess and protect against the hazards and risks posed by pesticide products as they are commonly applied.

## Overview: EPA's Mandate

EPA is legally required to regulate a pesticide's use in its entirety. FIFRA states that to be registered, a pesticide must not cause unreasonable adverse effects on the environment, including public health, "when used in accordance with widespread and commonly recognized practice." (7 U.S.C. § 136(c)(5)).

It is neither widespread nor commonly recognized practice to, upon purchasing a pesticide, perform laboratory chemical separations in order to extract only the active ingredient prior to use or to sanitize fields to remove other toxic chemicals. Moreover, it *is* widespread and commonly recognized practice to add pesticide formulations to tanks or containers containing adjuvants and surfactants. Pesticide products as commonly applied in the field are composed of whole pesticide formulations mixed together with their commonly used additives and are applied in a context in which exposure co-occurs with other harmful substances including fertilizers and other pesticides.

Under FIFRA, EPA has the authority to dictate the kinds of information and data registrant applicants must submit, and to propose cancellation at any time if a pesticide is

determined to be in violation of FIFRA. Therefore, it is the legal responsibility of EPA to establish data requirements that capture the material reality of the complete substances that are commonly applied on crops and in homes, find their way into soil and waterways, and enter into the organ systems of wildlife and humans.

**EPA Must Assess Co-Occurring Chemicals to Protect the Environment and Public Health**

People and other organisms predictably encounter pesticides in the environment as co-occurring chemical cocktails. Whether on food, in water, or in the air, a pesticide's active ingredient never occurs in isolation. First, it occurs with other chemicals in the pesticide formulation – so-called "inert" or "other" ingredients or formulants. Second, it occurs with ingredients added to tank mixes, such as adjuvants and surfactants. Third, it is applied to a crop (in the case of an agricultural pesticide) that has received applications of other pesticides and fertilizers. Fourth, these chemicals also predictably co-occur with their own and others' breakdown products and metabolites, yielding a mixture of active ingredients, formulants, tank additives, fertilizers, contaminants, and chemical metabolites on the crop. Finally, all of these chemicals wash off the field into surface waters where they join chemicals from other fields, sewage treatment plants, urban runoff, and industrial discharges. Fish and other animals live in the surface water and may be consumed by humans. Contaminated surface waters may recharge groundwater and/or be used as a source of drinking water.

**Current EPA Testing Requirements Fail to Protect Public Health and the Environment**

EPA currently fails to protect public health and the environment by failing to evaluate pesticides "when used in accordance with widespread and commonly recognized practice." Notably, EPA does not require adequate testing of pesticide products in the following critical regulatory areas.

**1. Toxicology/ Human Health (40 C.F.R § 158.500):**

EPA currently requires or conditionally requires 27 types of tests to fulfill toxicology data requirements across food and nonfood uses, intended to ensure protection of human health. Of these 27 tests, 19 use only the active ingredient. Included among these 19 active-ingredient-only tests are all required tests of chronic toxicity, carcinogenicity, mutagenicity, developmental toxicity and reproduction, in addition to 70% of all subchronic tests. What this means is that EPA may have no knowledge of the effect of pesticide products, as commonly applied, on chronic toxicity, mutagenicity, developmental toxicity and reproduction, or subchronic oral toxicity, inhalation toxicity, and neurotoxicity, when registering pesticide products.

**2. Terrestrial and aquatic nontarget organisms/ Ecological Effects (40 C.F.R. § 158.630):**

EPA currently requires nine and conditionally requires an additional 12 tests for toxicity to terrestrial and aquatic nontarget organisms across terrestrial, aquatic, forestry, and residential outdoor uses, intended to protect against unreasonable ecological damage. Of the nine required tests, six require only the active ingredient, including tests for: avian oral toxicity, avian dietary toxicity, avian reproduction, freshwater aquatic invertebrate life cycle, freshwater

fish early-life stage, and honeybee acute contact toxicity. The remaining three require the active ingredient or typical end-use product (TEP) only under certain conditions.

**3. Conditional Requirements (40 C.F.R § 158.500-660):**

Several tests prescribed by EPA are conditionally required (CR). In many cases, even when a test is listed as required (R), EPA requires tests for toxicity only under certain conditions. Several of the conditional terms for testing are based on active ingredient properties alone, and thus are incapable of accurately capturing actual hazards given end-use product environmental fate and toxicity. For instance, "environmental fate characteristics that indicate potential exposure" are among the conditions indicating that toxicity to wild mammals must be tested; the substance used in environmental fate testing is not specified and therefore may be the active ingredient alone. Given that "inert" ingredients impact environmental fate (as detailed in this comment), the decision to forgo testing requirements based on environmental fate parameters of the active ingredient or other intermediary products further exacerbates unacceptable data gaps. Further examples of conditions that are based on properties that vary between the active ingredient and end-use product are listed in Appendix A, reformatted for ease of comprehension. In order to comply with FIFRA, these conditions must specify use of the whole formulation and whole pesticide mixture, as commonly applied.

**EPA Must Assess Whole Formulations and Mixtures to Fulfill its Federal Mandate**

FIFRA dictates that in order to be registered, pesticide products as they are commonly applied in the field must be shown not to cause unreasonable adverse effects on the environment and public health. Active ingredients co-occur with the other chemicals used in the pesticide formulation and prescribed tank mix, including adjuvants and surfactants. These multiple chemicals influence the mobility, stability, environmental fate, exposure potential, and toxicity of the pesticide as it is commonly applied. As commonly practiced, the use of a given pesticide product leaves a mixture of active ingredients, formulants, and their metabolites in soil, on crops, in water, in air, and in homes; this end-use product, as it is applied, must be regulated in its entirety to ensure no unreasonable adverse effects on the environment and human health.

In order to fulfill its federal mandate to protect public health and the environment, EPA must evaluate each whole pesticide formulation and commonly applied tank mixture, including adjuvants, surfactants, and all other additives, for the following reasons.

**1. "Inert" Ingredients are Toxic by Themselves.**

Despite their name, "inert" ingredients are neither chemically, biologically, nor toxicologically inert. Many "inert" ingredients are known to state, federal, and international agencies to be hazardous to human health. According to a peer-reviewed study, as of 2006,

more than 500 ingredients that were listed as "inert" in some products served as the active ingredient in other products.[1]

Some "inert" ingredients are even more toxic than the active ingredients in their formulations. One of the most hazardous ingredients in common formulations of the popular herbicide Roundup is a surfactant, which is classified as an "inert", and therefore not listed on the label. A 2003 study found that the surfactant POEA accounted for more than 86% of Roundup's toxicity to bacteria, microalgae, protozoa and crustaceans.[2] Similarly, a 2013 study found that the Roundup adjuvants POE-15 and Genamin, by themselves, are 9,661 times more toxic to human cells than the active ingredient glyphosate.[3] POE-15 levels as low as 1 to 3 ppm caused toxic effects on cellular respiration and membrane integrity.

Whether "inerts" are synergists or not, their presence in whole formulations can increase toxicity of the whole formulation. Toxicity testing on embryonic, placental and hepatic human cells revealed that eight out of nine tested formulations of insecticides, fungicides, and herbicides are significantly more toxic than their active ingredients, by an average of several hundred times and up to over one thousand times.[4] In the one exception, no adjuvants were present in the formulation. The greatest levels of currently underregulated toxicity appear to hide in fungicide formulations. Fungicide formulations were found to be the most toxic to human cells, followed by herbicide and insecticide formulations. A tebuconazole formulation was found to be a full 1,053 times more toxic to human cells than its active ingredient alone. Among herbicides and insecticides, the herbicide Roundup was found to be the most toxic, with a human cellular toxicity level 125 times higher than that of glyphosate alone.

Common "inert" ingredients have also been shown to cause harm to valuable crop pollinators. A 2017 study published in Nature reveals that "inert" organosilicone surfactant (OSS) adjuvants commonly used in tank mixes applied to grapes, tree nuts, and tree fruits compromise the immune system of honey bee larvae, inducing viral pathogenicity and mortality.[5] Even in the absence of chemical synergy, toxins included in tank mixes adversely impact pollinators. When synergy is added to the mix, the overall effects are even more damning.

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[1] Cox, C. and Surgan, M., 2006. Unidentified inert ingredients in pesticides: implications for human and environmental health. *Environmental health perspectives*, *114*(12), pp.1803-1806.

[2] Tsui, M.T. and Chu, L.M., 2003. Aquatic toxicity of glyphosate-based formulations: comparison between different organisms and the effects of environmental factors. *Chemosphere*, *52*(7), pp.1189-1197.

[3] Mesnage, R., Clair, E., Gress, S., Then, C., Székács, A. and Séralini, G.E., 2013. Cytotoxicity on human cells of Cry1Ab and Cry1Ac Bt insecticidal toxins alone or with a glyphosate-based herbicide. *Journal of Applied Toxicology*, *33*(7), pp.695-699.

[4] Mesnage, R., Defarge, N., Spiroux de Vendômois, J. and Séralini, G.E., 2014. Major pesticides are more toxic to human cells than their declared active principles. *BioMed research international*, *2014*.

[5] Fine, J.D., Cox-Foster, D.L. and Mullin, C.A., 2017. An inert pesticide adjuvant synergizes viral pathogenicity and mortality in honey bee larvae. *Scientific reports*, *7*, p.40499.

## 2. Synergistic Effects Mean that Pesticide Products are More Toxic Than Their Ingredients Alone "When Used in Accordance with Widespread and Commonly Recognized Practice."

All ingredients included in the applied pesticide product interact at the chemical level, organismal level, and environmental level to influence mobility, stability, exposure, and toxicity of the active ingredient. A 2016 Center for Biological Diversity (CBD) Investigative report found that 69% of recently approved pesticide patent applications claimed or demonstrated synergy between ingredients in the product.[6] Of these, 72% involved highly used pesticides. A 2017 report by EPA's Office of the Inspector General acknowledged that the agency must collect and assess information on chemical mixtures and potential synergistic effects in order to adequately protect the environment.[7]

### *Chemical Synergy*

Chemical synergy results when the mixture of chemicals creates effects greater than the aggregation of individual effects, leading to underestimated toxic impacts on human and environmental health.

"Inert" ingredients as well as active ingredients can interact synergistically. "Inert" ingredients are specifically designed to promote the pesticidal action of active ingredients. Additives are selected, or 'optimized', for their ability to make the active ingredient more potent. Surfactants and adjuvants are used to increase the spreading ability and cell penetration of active ingredients, thereby increasing toxicity of formulations to target and non-target organisms.[8] Synergistic toxicity of whole mixtures have a profound negative impact on beneficial and non-target species, beyond that caused by active or "inert" ingredients alone.

Several independent scientific studies have confirmed that "inert" ingredients often significantly increase the toxicity of formulations relative to their active ingredients alone. A recent review of "pesticide cocktail effects" studied from 2000 to 2014 found that 36% of studies reported interactions between compounds, leading "mainly to synergic effects," with only "few examples of potentiating and antagonistic interactions."[9]

Additives have been found to change not only the toxic effects but the toxic mode of action of pesticides. Researchers found that a glyphosate formulation was twice as toxic to human placental cells as glyphosate alone. Glyphosate formulation, but not glyphosate alone, was found to interfere with the normal process of conversion of androgens into estrogens by inhibiting the activity of the enzyme aromatase in human placental cells (Richard et al. 2005, cited in Cox & Surgan 2006). Adding to these findings, Walsh et al. reported that glyphosate

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[6] Donley, N. 2016. Toxic Concoctions: How the EPA Ignores the Dangers of Pesticide Cocktails. *Center for Biological Diversity*.

[7] U.S. EPA Office of Inspector General, 2017. EPA Can Strengthen its Oversight of Herbicide Resistance with Better Management Controls.

[8] Castro, Mariano & Ojeda, Carlos & Cirelli, Alicia. (2014). Advances in surfactants for agrochemicals. Environmental Chemistry Letters. 12. 10.1007/s10311-013-0432-4.

[9] Rizzati, V., Briand, O., Guillou, H. and Gamet-Payrastre, L., 2016. Effects of pesticide mixtures in human and animal models: an update of the recent literature. *Chemico-biological interactions*, *254*, pp.231-246.

formulation, but not glyphosate alone, inhibited the production of progesterone in mouse Leydig cells.[10]

An independently conducted 2017 study found that Roundup was significantly more toxic to damselfly larvae than that the active ingredient glyphosate alone[11]. "Our results consistently indicate that at similar levels of the active compound, Roundup was more toxic than glyphosate with negative effects on survival, behavior and most of the physiological traits being present at lower concentrations (food intake, escape swimming speed) or even only present (survival, sugar and energy content and muscle mass)." These findings add to growing body of work corroborating that Roundup has greater toxicity to aquatic animals than glyphosate alone (Howe et al. 2004; Moore et al., 2012; Tsui and Chu, 2003).

Similar studies of other active ingredients and formulations strengthen the case for individualized formulation testing. 2,4-D formulations, but not 2,4-D alone, were found to cause breast cancer cells to proliferate in vitro (Lin and Garry, 2000, cited in Cox & Surgan, 2006). When "inerts" were included in the formulation of herbicides containing 2,4-D and picloram, the solution became 136 times more potent (136 times lower amounts caused the same toxic effects on mitochondrial oxidative activity). Zeljezic et al. 2006 found that atrazine by itself did not exert any genotoxic effects in human lymphocytes, but formulation containing atrazine caused DNA damage in human lymphocytes.[12]

In a 2017 study by Takacs et al., three neonicotinoid-based pesticides and their active ingredients were tested for acute immobilization toxicity to the indicator species *Daphnia magna*. The sulfonic acid surfactants included in the clothianidin-based formulation Apache 50 WG was found to cause a 46.5-fold increase in toxicity over the active ingredient alone.[13] In the two other insecticides tested, the formulation was found to be 2-3 times less toxic than the active ingredients thiacloprid and thiamethoxam alone. Such heterogeneous results indicate that both synergistic and antagonistic interactions can occur in neonicotinoid insecticides, and each unique formulation requires its own set of testing to understand the full range of toxic effects to non-target organisms. These findings have massive implications for assessing

[10] Walsh LP, McCormick C, Martin C, Stocco DM. 2000. Roundup inhibits steroidogenesis by disrupting steroidogenic acute regulatory (StAR) protein expression. *Environ Health Perspect* 108:769–776.
[11] Janssens, L. and Stoks, R., 2017. Stronger effects of Roundup than its active ingredient glyphosate in damselfly larvae. *Aquatic Toxicology*, *193*, pp.210-216.
[12] Zeljezic D, Garaj-Vrhovac V, Perkovic P. 2006. Evaluation of DNA damage induced by atrazine and atrazine-based herbicide in human lymphocytes in vitro using a comet and DNA diffusion assay. *Toxicol In Vitro* 20(6):923–35.
[13] Takács, E., Klátyik, S., Mörtl, M., Rácz, G., Kovács, K., Darvas, B. and Székács, A., 2017. Effects of neonicotinoid insecticide formulations and their components on Daphnia magna–the role of active ingredients and co-formulants. *International Journal of Environmental Analytical Chemistry*, *97*(9), pp.885-900.

ecological risk, given the widespread use of neonicotinoids and their known harms to vital pollinators and nontarget organisms.[14]

Honey bees and native pollinators are further threatened by EPA's failure to adequately assess whole mixtures in multiple classes of commonly used pesticides. Results from standard acute oral toxicity testing reveal that formulations of common fungicides can be just as toxic to honey bees as some of the most bee-toxic insecticides on the market. In a study by agrochemical regulators in China, a tebuconazole formulation was found to be more than 25,600 times as toxic as the active ingredient alone, exceeding the toxicity of the potent insecticide enamectin benzoate.[15] These serious threats to pollinator health are masked behind low-toxicity reports based on partial testing.

***Organismal and Ecological Synergy***

Even when chemicals do not interact to produce direct synergistic effects, the effects of multiple co-occurring exposures in a given individual body can act to increase toxicity of any given ingredient in the mix. Similarly, ecological systems interact such that when one organism is compromised by a given toxin, other organisms can be indirectly adversely impacted.

Chemical 'Body Burden' refers to the accumulation of synthetic chemicals found in pesticides, cosmetics, industrial solvents, heavy metals, etc. in human bodies. At any given time, hundreds of chemicals can be found in the blood, urine, breast milk and even umbilical cord blood of a given individual. The consequences of multiple interacting chemicals can far outweigh the individual consequences of any one substance. A 2017 study of multiple exposure toxicity found, for example, that a mixture of six pesticides caused decreased birth weight in rats at dose levels "well below the no-observed adverse effect levels (NOAELs) of the individual pesticides."[16]

These body burden effects are especially relevant given the ubiquitous presence of multiple co-occurring pesticides in the environment and in drinking water. According to data from the U.S. Geological Survey (USGS) and the Environmental Protection Agency (EPA), of the over 300 food production pesticides with registered tolerances, 52 are known surface or groundwater contaminants. The overwhelming majority of the most popular pesticides used in the U.S. have been detected in surface and groundwater, including the popular herbicides atrazine, glyphosate, and 2,4-D.[17]

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[14] van Lexmond, M.B., Bonmatin, JM., Goulson, D. et al. 2015. Worldwide integrated assessment on systemic pesticides. Global collapse of the entomofauna: exploring the role of systemic insecticides. *Environ Sci Pollut Res* 22: 1. doi: 10.1007/s11356-014-3220-1.

[15] Mullin, C.A., 2015. Effects of 'inactive'ingredients on bees. *Current Opinion in Insect Science*, *10*, pp.194-200.

[16] Hass, U., Christiansen, S., Axelstad, M., Scholze, M. and Boberg, J., 2017. Combined exposure to low doses of pesticides causes decreased birth weights in rats. *Reproductive Toxicology*, *72*, pp.97-105.

[17] USEPA. Pesticide Industry Sales and Usage, 2006-2007. Office of Pesticide Programs. Washington DC.

Pesticides as well as nutrients from fertilizers can find their way into finished drinking water and well water, especially in rural and agricultural communities. One USGS survey (2008) analyzed water from nine selected rivers that are used as a source for public water systems and found that low levels of certain synthetic chemicals remain in the finished drinking after being subject to treatment by community water facilities.[18] A study (2010) in Iowa shows a nearly three-fold increase in thyroid cancer risk for women with more than five year's use of public water supplies contaminated with nitrates at levels of five milligrams per liter (mg/L) or above.[19]

When exposed to these chemical cocktails, the body's organ systems interact such that when one organ is compromised by a given toxin, other organs become more susceptible to impact by all toxins in the mix. Of particular note, low dose pesticide mixtures can impair the liver's ability to perform its normal detox functions, thus opening the gates for increased chronic exposure to other chemical contaminants.[20] In nontarget insects, too, the consequences of multiple exposures can be devastating. Common systemic neurotoxic insecticides have been shown to impair pollinators' ability to defend against other toxic exposures, possibly by interfering with normal cellular mechanisms of pathogen detection, digestion, and encapsulation.[21]

On the level of the ecosystem or ecological community, exposure to one chemical can initiate a trophic cascade that makes species more susceptible to other chemicals. In a 2008 aquatic mesocosm study, both acute and chronic exposures to the organophosphate insecticide malathion were found to cause a trophic cascade among phytoplankton, periphyton, zooplankton, and leopard frog tadpoles.[22] By depressing the zooplankton population, malathion exposure caused phytoplankton to flourish. The increase in free-floating algae clouded water, decreased light penetration, and led to reduced periphyton growth. Decreases in periphyton algae, the primary food source for tadpoles, retarded growth and development in leopard frogs, which prevented many from metamorphosing before the vernal pool in which they resided dried up. While zooplankton in the single-application mesocosm eventually experienced a population rebound, it took nearly a month and a half before this occurred. Overall, frogs in single-application mesocosms fared slightly better than those in chronically exposed tanks, which experienced an ongoing state of disruption that never permitted zooplankton

[18] Kingsbury, J.A., Delzer, G.C., and Hopple, J.A., 2008, Anthropogenic organic compounds in source water of nine community water systems that withdraw from streams, 2002–05: U.S. Geological Survey Scientific Investigations Report 2008.
[19] Ward MH, Kilfoy BA, Weyer PJ, et al. 2010. Nitrate intake and the risk of thyroid cancer and thyroid disease. Epidemiology. 21(3):389-9.
[20] Rouimi, P., Zucchini-Pascal, N., Dupont, G., Razpotnik, A., Fouché, E., De Sousa, G. and Rahmani, R., 2012. Impacts of low doses of pesticide mixtures on liver cell defence systems. *Toxicology in Vitro*, *26*(5), pp.718-726.
[21] Pamminger, T., Botías, C., Goulson, D. and Hughes, W.O., 2018. A mechanistic framework to explain the immunosuppressive effects of neurotoxic pesticides on bees. *Functional Ecology*, *32*(8), pp.1921-1930.
[22] Relyea, R.A. and Diecks, N., 2008. An unforeseen chain of events: lethal effects of pesticides on frogs at sublethal concentrations. *Ecological Applications*, *18*(7), pp.1728-1742.

populations to bounce back. The lesson is clear: unregulated effects of whole pesticide mixtures can have devastating consequences for entire ecological communities.

***Environmental Stability***

"Inerts" can increase exposure to pesticides by causing longer retention times, resistance to washing, greater absorbance through materials and skin, and greater stability in the environment. The ecological and human health impacts of widespread use of pesticides are vastly underestimated when environmental fate of the whole pesticide mixture is not accounted for.

Additives increase the dermal absorption of pesticide products, as detailed in a 2006 review by Cox and Surgan, published in the journal *Environmental Health Perspectives*:

> *"Some inert ingredients can increase dermal absorption or penetration of the active ingredient. In a comparison of the penetration of three formulated herbicidal products through hairless mouse skill with their respective active ingredients, Brand and Mueller (2002) found that dermal penetration of the formulation was 3-30 times greater than the penetration of the active ingredients alone. Similar results were obtained in studies of the absorption of the insecticide lindane and the wood preservative pentachlorophenol through human and porcine skin, respectively (Baynes et al. 2002; Dicks et al. 1997a, 1997b). In all three of these studies, solvents used as inert ingredients increased the dermal absorption of the active ingredient."*

Furthermore, these increased exposure risks wrought by "inert" ingredients cannot be adequately prevented through use of protective clothing, as "inert" ingredients also impact the efficacy of common laundry detergents. For example, emulsifiable concentrate formulations of the insecticides methyl parathion, cyfluthrin, and cypermethrin have been found to be more difficult to remove from clothing by washing than encapsulated and wettable powder formulations.[23]

The impact of "inerts" on environmental stability has massive consequences for ecological as well as human exposures. For example, honey bees and other pollinators face far greater exposure potential to systemic insecticides due to their additives in formulations and mixtures. Copolymers are intentionally added to systemic insecticides, such as fipronil, to increase their solubility and systemic activity. [24] A study by Gupta et al. (2002) found that formulations of imidacloprid have greater leaching potential than the active ingredient alone. Taken together, unregulated synergies and unregulated environmental fate spell wholly inadequate protection against unreasonable hazards and risks to humans and nontarget

[23] Cox, C. and Surgan, M., 2006. Unidentified inert ingredients in pesticides: implications for human and environmental health. *Environmental health perspectives*, *114*(12), pp.1803-1806.
[24] Bonmatin, J.M., Giorio, C., Girolami, V., Goulson, D., Kreutzweiser, D.P., Krupke, C., Liess, M., Long, E., Marzaro, M., Mitchell, E.A. and Noome, D.A., 2015. Environmental fate and exposure; neonicotinoids and fipronil. *Environmental Science and Pollution Research*, *22*(1), pp.35-67.

organisms. Pesticide toxicity and exposure potential must both be studied in the context in which they are commonly applied, as whole formulations and mixtures.

## EPA Must Assess the Combined Impacts of All Pesticide Ingredients, Their Metabolites, and Chemicals That Co-Occur in the Environment as a Result of the Pesticide's Use.

### *Other pesticides*

A single field is often the target of herbicide, insecticide, and fungicide applications. Combined pesticides may have additive or interacting effects.[25] The use of multiple pesticides on one site is "widespread and commonly recognized practice." This aspect of pesticide use must be included in pesticide risk assessment. Hence, every pesticide must be tested in combination with all other pesticides and fertilizers that may be used on the same site.

A 2016 report published out of the UCLA Fielding School of Public Health found that three commonly applied fumigants interact to increase the health risk for California farm workers and residents.[26] The fumigants, chloropicrin, Telone (also known as 1,3-D), and metam salts, are commonly applied together in California on high value crops, such as strawberries, tomatoes, tree nuts, and stone fruits. Workers and residents are regularly exposed to two or more of these pesticides simultaneously. Researchers found that the combined effect of the multiple pesticides is greater than the sum of their effects because the pesticides interact to increase damage to cells, leading to an increased risk of cancer. The report notes that the fumigants analyzed in the study can reduce the body's ability to remove or neutralize toxic substances. The California Department of Pesticide Regulation does not regulate the application of multiple pesticides to prevent or decrease risks to human health, despite having authority to do so.

### *Fertilizers*

Chemical fertilizers are used in chemical-intensive land management and animal agriculture, resulting in fine particulate pollution (nitrate and ammonia) that is carried deep into the lungs. Fine particulates have been identified as the most dangerous particles because they penetrate most deeply, affecting gas exchange within the lungs. Pesticides may be adsorbed onto fine particles, increasing their toxicity to humans[27] and to aquatic organisms.[28]

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[25] Hernández, A.F., Parrón, T., Tsatsakis, A.M., Requena, M., Alarcón, R. and López-Guarnido, O., 2013. Toxic effects of pesticide mixtures at a molecular level: their relevance to human health. *Toxicology*, *307*, pp.136-145.
[26] Zaunbrecher, V. et al. 2016. Exposure and Interaction: The Potential Health Impacts of Using Multiple Pesticides. http://stpp.ucla.edu/sites/default/files/Exposure_and_Interaction_2016_Web_0.pdf.
[27] Socorro, J., Durand, A., Temime-Roussel, B., Gligorovski, S., Wortham, H. and Quivet, E., 2016. The persistence of pesticides in atmospheric particulate phase: An emerging air quality issue. *Scientific reports*, *6*, p.33456.
[28] Magbanua, F.S., Townsend, C.R., Hageman, K.J., Lange, K., Lear, G., Lewis, G.D. and Matthaei, C.D., 2013. Understanding the combined influence of fine sediment and glyphosate herbicide on stream periphyton communities. *Water research*, *47*(14), pp.5110-5120.

### *Metabolites*

In addition to multiple pesticides and fertilizer chemicals, metabolites –breakdown products that form when a pesticide is used in the environment and mixes with air, water, soil or living organisms—also co-occur with pesticides in a treated field and on treated articles as a result of "widespread and commonly recognized practice." The metabolite may be more hazardous than the parent pesticide.[29] A recent study by researchers at the University of Iowa detected imidacloprid metabolites in drinking water that have potential for high toxicity to humans, due to a loss of chemical insect-specificity.[30] To protect against unreasonable harms, the co-occurrence of pesticide metabolites and pesticide parent compounds must be included in a pesticide risk assessment. Every pesticide must be tested in combination with all other pesticides, pesticide metabolites, and fertilizers that may be used on the same site.

## Conclusion: EPA Must Alter Data Requirements to Comply with the Law and Adequately Protect the Environment and Public Health

EPA's current policies and practices do not adequately protect against unreasonable harms from pesticides as they are commonly applied. To comply with FIFRA, EPA must make the amendments proposed in the CFS petition, in addition to changes in the language of conditional requirements, including but not limited to those detailed in Appendix A. All requirements and conditions for tests of toxicity as well as environmental fate must explicitly mandate the use of the whole pesticide formulation and its commonly used tank mixture additives. Additionally, further testing must be required to adequately assess the environmental and public health consequences of pesticides as commonly applied in combination.

To fulfill these additional testing requirements, both registrants and EPA will need to invest new resources into the assessment process. However, meeting these additional resource requirements is achievable, and claims to the counter cannot lawfully be put forward as justification for failing to abide by the law under FIFRA. There exists no clause within FIFRA stating that economic concerns can be used to justify a failure to determine whether pesticides cause unreasonable adverse effects on the environment and public health, "when used in accordance with widespread and commonly recognized practice." (7 U.S.C. § 136(c)(5)). Regardless of financial considerations and registrant interests, EPA must fulfill its mandate under FIFRA to protect the lives of nontarget organisms and nontarget humans.

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[29] Roberts, J.R. and Reigart, J.R., 2013. Recognition and management of pesticide poisonings.

[30] Wong, K.L.K., Webb, D.T., Nagorzanski, M.R., Kolpin, D.W., Hladik, M.L., Cwiertny, D.M. and LeFevre, G.H., 2019. Chlorinated byproducts of neonicotinoids and their metabolites: An unrecognized human exposure potential? *Environmental Science & Technology Letters*.

Please consider the real cost to the American people and to our ecosystem and amend all data requirements to specify the use of the whole end-use pesticide product mixture, in the context in which it is commonly applied in the field.

Thank you for your consideration of these comments.

Sincerely,

Sarah Bluher
Science and Regulatory Manager

Terry Shistar, Ph.D.
Board of Directors

## Appendix A: Examples of Conditions for Testing Requirements that Must be Altered to Specify Whole Mixtures to Comply with FIFRA

The following is a non-comprehensive list of example conditions included in 40 C.F.R. § 158[31] (as applied to both 'Required' and 'Conditionally Required' tests) that must be altered to specify the use of whole mixtures in order to ensure adequate data requirements under FIFRA. Text in bold and italics highlight areas of concern, in which conditions depend on properties of the active ingredient, or of an unspecified substance which may be interpreted as the active ingredient. To comply with FIFRA, all such conditions that currently depend on properties of the active ingredient or any other intermediary product must be altered to depend only on properties and prior testing of the whole mixture end-use product, as commonly applied.

**Example Conditions that Fail to Specify Whole Mixture Properties**

### I. Toxicology/ Human Health (40 C.F.R § 158.500)

1. Carcinogenicity tests are required if any of the following, as determined by the Agency, are met:
    a. The use of the ***pesticide is likely to result in significant human exposure*** over a considerable portion of the human life span which is significant in terms of either frequency, ***duration, or magnitude of exposure***;
    b. The use requires a tolerance or an exemption for the requirement of a tolerance; or
    c. ***The active ingredient, metabolite, degradate, or impurity*** (a) is ***structurally related to a recognized carcinogen***, (b) ***causes mutagenic effects*** ad demonstrated in vitro or in vivo testing, or (c) ***produces a morphologic effect*** in any organ (e.g., hyperplasia, metaplasia) in subchronic studies that may lead to a neoplastic change.
2. For tests of reproduction/fertility effects and developmental neurotoxicity, an information-based approach to testing is preferred, which utilizes the best available knowledge on ***the chemical (hazard, pharmacokinetic, or mechanistic data)*** to determine whether a standard guideline study, an enhanced guideline study, or an alternative study should be conducted to assess potential hazard to the developing animal, or in some cases to support a waiver for such testing. Registrants should submit any alternative proposed testing protocols and supporting scientific rationale to the Agency prior to study initiation.
3. A 1-year non-rodent study of oral toxicity (*i.e.*, 1-year dog study) would be required if the Agency finds that a ***pesticide chemical is highly bioaccumulating and is eliminated so slowly that it does not achieve steady state*** or sufficient tissue concentrations to elicit an effect during a 90-day study. EPA would require the appropriate tier II metabolism and pharmacokinetic studies to evaluate more

[31] Note: Modified for ease of comprehension. Numbering has been changed from the original text. Some conditions have been omitted for brevity, as indicated by added text in parentheses. Emphasis added.

precisely ***bioavailability, half-life, and steady state*** to determine if a longer duration dog toxicity study is needed.

**II. Terrestrial and aquatic nontarget organisms/ Ecological Effects (40 C.F.R. § 158.630)**

4. For tests of avian oral toxicity, avian dietary toxicity, and toxicity to freshwater fish, freshwater invertebrates, estuarine and marine invertebrates, and honey bees, ***data using the technical grade active ingredient (TGAI)*** are required to support all outdoor end-use product uses including, but not limited to turf. Data are generally not required to support end-use products in the form of a gas, a highly volatile liquid, a highly reactive solid, or a highly corrosive material.
5. For greenhouse and indoor end-use products, ***data using the technical grade active ingredient (TGAI)*** are required to support manufacturing-use products to be reformulated into these same end-use products or to support end-use products when there is no registered manufacturing-use product.
6. Tests for wild mammal toxicity are required based on the results of lower tier toxicology studies, such as the ***acute and subacute testing, intended use pattern, and environmental fate characteristics*** that indicate potential exposure.
7. For avian and mammalian field tests, higher tier testing may be required for a specific use pattern when a refined risk assessment indicates a concern based on ***laboratory toxicity endpoints and refined exposure assessments***.
8. Data are generally not required for outdoor residential uses, other than turf, unless data indicate that ***pesticide residues from the proposed use(s) can potentially enter waterways.***
9. End-use product (EP) or typical end-use product (TEP) testing is required for any product which meets any of the following conditions:
    a. The end-use pesticide will be introduced directly into an aquatic environment (e.g., aquatic herbicides and mosquito larvicides) when used as directed.
    b. The ***maximum expected environmental concentration (MEEC) or the estimated environmental concentration (EEC) in the aquatic environment*** is ≥one-half the LC50 or EC50 of the TGAI when the EP is used as directed.
    c. 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.
10. Data are required on estuarine/marine species if the product meets any of the following conditions (subset of all conditions):
    a. Expected to enter this environment in significant concentrations because of its expected use or ***mobility patterns***.
    b. ***Physicochemical properties indicate bioaccumulation*** of the pesticide.
    c. The pesticide is ***persistent in water (e.g., half-life in water >4 days)***.

11. Data are required on estuarine/marine species if (among other singly-sufficient conditions) the product is ***expected to enter this environment in significant concentrations*** because of its expected use or ***mobility patterns***.
12. Data are required on freshwater species if (among other singly-sufficient conditions) the end-use product is ***expected to be transported to water*** from the intended use site, and when any of the following conditions apply:
    a. If the ***estimated environmental concentration (EEC)*** is ≥0.1 of the no-observed-effect level in the fish early-life stage or invertebrate life cycle test;
    b. If studies of other organisms indicate that the reproductive physiology of fish may be affected.
13. Data are not required on certain fish and other nontarget aquatic organisms when:
    a. The ***octanol/water partition coefficients*** of the pesticide and its major degradates are <1,000; or
    b. There are ***no potential exposures*** to fish and other nontarget aquatic organisms; or
    c. The ***hydrolytic half-life*** is <5 days at pH 5, 7 and 9.
14. Field testing for aquatic organisms is required based on the results of lower tier studies such as acute **and** ***chronic aquatic organism testing***, intended use pattern, and ***environmental fate characteristics*** that indicate significant potential exposure.
15. Whole sediment testing on acute freshwater and marine invertebrates is required if:
    a. The ***half-life of the pesticide in the sediment*** is ≤10 days in either the aerobic soil or aquatic metabolism studies and if any of the following conditions exist:
        i. The ***soil partition coefficient (Kd)*** is ≥50.
        ii. The ***log Kow*** is ≥3.
        iii. The ***Koc*** ≥1,000.
16. Sediment testing with estuarine/marine test species is required if the product is (among other potential conditions) ***expected to enter this environment*** in concentrations which the Agency believes to be significant, either by runoff or erosion, because of its expected use or ***mobility pattern****.*

## III. Nontarget plant protection (40 C.F.R. § 158.660)

17. Tests of target area phytotoxicity are required on a case-by-case basis based on the results of lower tier phytotoxicity studies, adverse incident reports, intended use pattern, and ***environmental fate characteristics*** that indicate potential exposure.