Comments to US EPA, Office of Pesticide Programs on the Draft Pesticide Cumulative Risk Assessment: Framework for Screening Analysis (EPA-HQ-OPP-2015-0422)

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Focus within the Framework: Proposed framework screening analysis approach for chemical mixtures (pesticide active and inert ingredients, likely chemicals occurring with pesticides in foods and water contamination)

There are numerous health and scientific issues of public health concern raised by the US EPA Office of Pesticide programs' proposed cumulative risk assessment framework.[1] Our comments focus on the evaluation of hazard and risk resulting from exposure to multiple toxic chemicals. Risk assessment of mixtures has long been recognized as a challenging issue, with regulatory guidance provided on this by US EPA in past decades. Recent scientific evidence published in peer reviewed studies provides far greater scientific insight and argues for numerous strategies to improve public health protections. However, these scientific advances are not reflected in OPP's draft framework.

OPP demonstrates their proposed approach on the pesticides abamectin and emamectin. It is relevant that there is a proposal to expand abamectin's use on widely grown and consumed foods including soybeans and sweet corn, on lactating dairy cattle and the Caneberry subgroup 13-07A, and on golf course turf, a common source of water pollution.

Exposure to multiple toxic chemicals, which may be referred to as "cumulative exposures" in some contexts, imposes a greater health burden than exposure to a single chemical (Carpenter et al, 2002). For this reason all US agencies that address chemical hazards require consideration of the impact of mixtures as distinct from exposure to a single chemical (e.g., EPA, ATSDR-CDC, NIOSH, OSHA). In 2009, the National Academy of Sciences argued for greater emphasis on this issue (NAS, 2009). The current Director of the National Center for Environmental Assessment at US EPA, Dr. Kenneth Olden,also argued the importance of mixtures evaluation in the article "Chemical mixtures research: significance and future perspectives" (Suk et al, 2001).

There is no question that when qualitatively evaluating potential health hazards or when estimating risk or presumptive "safe" levels, the presence of multiple toxic chemicals requires additional evaluation and protective strategies. Most agricultural pesticides are applied with so-called "inert ingredients" that are often toxic. Most crops are treated with more than one pesticide. Consequently, agricultural workers, their communities, food handlers and consumers of foods

[1] For example, see comments on the proposed framework from Dr. Jennifer Sass of NRDC 9/28/2015.

treated with pesticides and/or grown in soil treated with pesticides containing residues are inevitably exposed to mixtures of toxic chemicals.

This is of heightened concern when the chemicals are capable of causing developmental harm and/or are genotoxic. This imposes greater concern for individual harm and broad societal harm in the case of pesticides. An international consensus statement developed by scientists, pediatricians, and others at a conference on development stated that: "Fetal life and early infancy are periods of remarkable susceptibility to environmental hazards. Toxic exposures to chemical pollutants during these windows of increased susceptibility can cause disease and disability in children and across the entire span of human life." (Grandjean et al, 2007).

When pesticides are involved that will impact the food supply of people of all ages, including pregnant women and newborns, it is imperative that the best current science and appropriately protective approaches be taken (WHO, 2004). It is clear that environmental exposures, including food, are of substantial concern in the US (WHO, 2006) and that the burden of disease and disability can be reduced through greater protections from exposure to environmental hazards (WHO, 2007).

Although there is currently no universally agree-upon approach to mixtures (Sarigiannis and Hansen, 2010), dose addition is often used, whether via a hazard-quotient approach or similar approaches (US EPA, 2000; SCHER, SCENIHR, SCCS, 2012). Unfortunately, OPP's proposed methodology doesn't even address this very simplistic and limited option. We now have considerable evidence demonstrating that chemical mixtures can cause harm:

1) that goes far beyond simple additivity (i.e., causing synergistic effects),

2) where common mechanisms of toxicity are not necessary for additive or synergistic effects, and

3) that can cause damaging health effects that that were not even anticipated based on studies of the individual chemicals.

In a study by Rider et al (2010) that evaluated adverse reproductive effects, the authors concluded: "In summary, our results indicate that compounds that act by disparate mechanisms of toxicity to disrupt the dynamic interactions among the interconnected signaling pathways in differentiating tissues produce cumulative dose-additive effects, regardless of the mechanism or mode of action of the individual mixture component." (Underscored for emphasis)

This finding clearly requires that agencies charged with public protection go beyond the 1996 Food Quality Protection Act requirements that agencies consider the cumulative risk of chemicals that act via a common mechanism of toxicity. While understanding mechanisms and modes of action- commonly touted litmus tests for additive impacts - may be useful, it is only one of many considerations.

A recent study of chemical mixtures' impacts on fundamental cellular processes (e.g., oxidative stress-linked genetic changes) provides further evidence that mixture effects can go beyond simple additivity. The authors concluded that "The results highlight the need of precautionary actions on

the assessment of chemical mixtures even in cases where individual toxicants are present at seemingly harmless concentrations" (Carvahlo et al, 2014).

Rider et al and Carvahlo et al's findings (and many others) were underscored in multiple 2015 articles on the Halifax Project (Carcinogenesis, Volume 36, Supplement 1, full Table of Contents at the end of the bibliography below). This project, involving dozens of research institutions, evaluated links between "exposure to environmental chemical mixtures at individually low (but collectively potentially deleterious) doses to molecular effects on cells that may commit them to the tumourigenic phenotype" (Engstrom et al, 2015). Chemicals not previously considered carcinogenic were found to pose cancer risks in mixtures. While this project focused on cancer, there is no reason to believe that the same fundamental dynamics would not be relevant for damage to organ systems, developmental toxicity and other types of harm.

This very troubling but not entirely unexpected findings of the Halifax Project underscore the need to consider interactive effects. This project demonstrated that this is especially important when individual chemicals cause physiological changes identified as "Hallmarks of Cancer" (see Engstrom et al, 2015 for a discussion of the Hallmarks; Hanahan and Weinberg, 2011). Mechanisms by which these occurs are reported in this and other peer-reviewed studies in the special supplement (e.g., Thompson et al, 2015).

The project, funded in part by the EPA and NIEHS, underscores the need to take a health protective approach to assessing risk and determining "safe" exposure levels both to individual chemicals and mixtures. Many relevant mechanistic studies can be conducted quickly and cost effectively, providing essential understanding of a chemical or mixtures potential for harm. Yet reliance on such information is not addressed in OPP's proposed approach.

We recognize that the nearly infinite number of mixtures cannot feasibly be evaluated using traditional long-term studies. But it is essential that the types of information generated by the Halifax Project be incorporated into risk assessment methods and required testing regimens. As Engstrom et al (2015) state:

> "... it is now known that many of the hallmark mechanisms of cancer can be independently enabled by individual chemicals and that realization deserves further consideration in risk assessment. Although the identification of complete carcinogens will always be an important activity, we now also need to be seriously concerned about the ways in which exposures to combinations of disruptive, but otherwise non-carcinogenic, environmental agents are able to act in concert with one another to instigate the disease. In other words, the hallmarks of cancer framework suggests that <u>we also need to be concerned about cumulative exposures to chemicals that can disrupt the cellular machinery that is associated with any number of these hallmarks, because a multitude of exposures (each enabling a number of hallmarks) could easily instigate cancer."</u> (Underlined for emphasis)

With the emergence of substantial scientific evidence regarding the impacts of mixtures, all responsible agencies must take a more thorough scientific and protective approach, acknowledging and addressing what we already know regarding mixtures. For the sake of efficiency in the short term, public protection may require the use of multiple additional "safety factors". The use of

safety factors for poor database quality has historically been employed by EPA. It is clear that there are substantial and scientifically important gaps in the knowledge required to regulate most pesticides that will invariably impose exposure to mixtures of toxic chemicals on the public and the environment.

US EPA could also elect to with hold approval of new pesticides pending adequate testing of the full product and its likely mixtures in the environment (including food). There are clearly many other strategies to minimize human exposures, health risks and environmental contamination until more comprehensive evaluations can be completed and final determinations made as to the potential safety or risks associated with pesticide use.

It is essential that OPP require testing related to the many emerging hallmarks of not only cancer, but also birth defects, endocrine disruption, immunotoxicity and other categories of health damage. The wealth of scientific publications discussing the interaction between various adverse physiological impacts (e.g., cell signaling, enzyme disruption, inflammatory responses, free-radical production, epigenetic impacts on genetic communications) can inform ways in which test results are used in risk assessments of mixtures. We recommend that the requirement for evaluation of interactions between chemically-mediated physiological disruptions by different chemicals (often numerous for each chemical) be explicitly mentioned in the proposed framework. It is an important area of emerging toxicological science for which robust scientific resources already exist. Such evaluations have the potential for substantial benefit to public health when evaluated and utilized appropriately.

Thank you for consideration of these comments.

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