Evaluation of Pesticide Mixture Interaction (Synergy)
PPDC Meeting, May 3, 2017, Session 4d

The long-standing ecological risk assessment approach for pesticides to support FIFRA regulatory decisions has been based on a toxicological evaluation of single active ingredients. EPA's position that regulatory decisions and risk mitigation efforts focused on the effects and therefore risks of individual pesticides has been appropriate because:

1. Toxicological interactions between active ingredients that produce significantly greater toxicity than expected is a rare occurrence,
2. Available environmental monitoring information (e.g. U.S. Geological Survey's ambient water monitoring) indicates that, in a predominant number of cases across the country, the potential toxic risk of contaminants is dominated by one to a few chemicals, and
3. By focusing risk-based decisions using the chronic no effects thresholds and extreme low probability acute thresholds for individual pesticide active ingredients, EPA would avoid much of the concern for a potential of biologically significant mixtures effects (e.g. the combined effect of exposure to two pesticides, both at no effect levels, is reasonably a no effect).

The National Research Council, in its review of Office of Pesticide Program's risk assessment methods for endangered species effects determinations, supported the general opinion that synergistic interactions between pesticides are rare (NRC 2013[1]). The Council suggested that the Agency consider pesticide active ingredient interactions when the best available scientific evidence supports the quantitative evaluation.

Since 2015, the Agency has discovered a number of cases where pesticide producers have been granted patents by the U.S. Patent and Trade Office (USPTO) for claims that selected mixtures of pesticides produce toxicological effects in excess of expected additive effects (i.e., claims of synergistic interactions). These claims are made primarily for effects seen in pest species (i.e., enhanced herbicidal, fungicidal, or insecticidal effects). However, under the Agency's risk assessment approach using effects testing of surrogate plants and animals to represent flora and fauna in the field, it is appropriate to consider the USPTO data with pest species to determine if the observations are applicable to the Agency's pesticide ecological risk assessments. EPA has chosen to explore the development of a process to review and, if necessary, account for these pesticide interaction claims in ecological risk assessments. For the available patent data, EPA is addressing the suggestion by the National Research Council[1], that pesticide interactions be considered to the extent supported by scientific evidence.

EPA has elected to begin the pesticide interaction evaluation with the USPTO patents for a number of reasons:

1. There are a large number of United States patents with claims of interactions;
2. The supporting data are readily available and efficiently accessed;

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[1] National Research Council. 2013. *Assessing Risks to Endangered and Threatened Species from Pesticides.* Washington, DC: The National Academies Press. doi:https://doi.org/10.17226/18344.

3. Pesticide producers have direct access to much of the data and underlying information;
4. The USPTO has established which data sets, in their evaluation process, support interaction claims;
5. The extent of mixtures, conditions of testing, effects observed and organisms evaluated can be readily determined in the majority of patent claims; and
6. Many of the taxa tested and the effects reported are applicable to the ecological risk assessment process.

The goal of the evaluation process for patent claims of pesticide interaction is to determine:

1. If the available evidence would impact the risk conclusions and risk mitigation decisions for a given pesticide, and if "yes"
2. The methods the Agency may use to qualitatively or quantitatively incorporate this information into the regulatory decision.

To support this effort, EPA has developed a process for rapidly searching and screening USPTO data for interaction claims. The process is applicable to new chemicals proposed for registration as well as pesticide registrations for proposed application to genetically modified crops. It assigns the searching and sorting responsibilities to the pesticide producer as part of the submission package. The process:

1. Outlines the suggested patent search use of available databases and a set of useful search terms;
2. Describes a series of criteria used to screen patents for the relevance to the EPA ecological risk assessment;
3. Presents a series of criteria for reporting data to EPA from patents meeting the relevance criteria above; and
4. Lists a set of information fields for the data reported to EPA. (EPA anticipates development of a reporting template in the future)

EPA reviews and evaluates the reported information to determine:

1. If the available evidence would impact the risk conclusions and risk mitigation decisions for the pesticide registration; and
2. The qualitative or quantitative process for incorporating the information in the supporting risk assessment.

To date, EPA has completed, or is nearing completion, eight cases of patent searches and associated data evaluation. The majority of patents discovered during the patent search did not contain relevant information. The reasons for exclusion from further consideration included:

1. Key words were identified in the text but no specific claims of interactions were actually made;
2. No effects test data were presented to support the patent claims;
3. Tests supporting the patent were not conducted using the active ingredients under regulatory consideration;
4. Tests supporting the patent involved organisms for which EPA does not conduct ecological risk assessments (e.g., fungi); or

5. Tests supporting the patent involved effects information not relevant to the effects considered in the ecological risk assessment (e.g., leaf damage from phytophagous insects).

In two registration cases, available patent information was being used to evaluate pesticide interaction for specific proposed formulations comprised of multiple active ingredients. The patents in these two cases were relevant to the ecological risk assessment (tested taxa and endpoints were relevant) and the tests involved mixtures of the pesticides directly applicable to proposed registration of a mixture product. In both cases, the EPA and the pesticide producer determined that the most direct and efficient way to address the observed effects was testing of the end-product formulations using existing guideline effects studies and then directly use the effects information from those studies in the ecological risk assessment.

In all the other cases, the submitted patent data has been insufficient to demonstrate a need for further consideration of interactions in the ecological risk assessment because:

1. The data did not support a statistical evaluation of any observed effects;
2. The data from mixtures were statistically indistinct from the expected variability of individually tested pesticides; and/or
3. The effects interactions of mixtures, when qualitatively or quantitatively considered, would not be expected to alter existing ecological risk conclusions or risk mitigation efforts.

EPA will continue to evaluate specific cases of patent claims. It is expected that the current process will evolve as the Agency gains more experience with the data sets, their limitations, and the value of the reviewed information in the context of regulatory decision making.