Accounting for Pesticidal Mixture Interaction in Ecological Risk Assessment in the USEPA Office of Pesticide Programs

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Issue

- There is a body of United States patent information that makes claims of effects interactions for mixtures of pesticidal active ingredients
- The Agency has begun a case-by-case evaluation to determine if the available information provides evidence that current ecological risk assessments need to quantitatively account for these observations
- The process that is developing must be
  - Scientifically credible
  - Efficient
  - Transparent
  - Mindful of the existing pesticide risk picture

Current Focus of the Process

- Granted United States Patents
  - There are a large volume of U.S. patents (granted, pending, and applications) with claims regarding combined effects
  - The U.S. Patent and Trade Office (USPTO) has completed their evaluation of supporting data regarding claims of interaction: increases the efficiency of evaluation
  - Claims are readily searchable using a number of Internet-based tools
  - The data supporting the patents and underlying documents are accessible through the USPTO

Mixture Process: By who and how are patents currently searched?

- Presently, the process for searching US patent information applies to new chemical registrations
- New chemicals are initially prohibited in a tank mixture with other pesticides
- A search of U.S. Patents is conducted by the registrant, and the initial prohibition of a tank mixture is modified to include only those mixtures for which available information passes through a series of criteria for relevancy and data reporting to EPA
- EPA evaluates the submitted results, and the prohibition list gets futher modified as that evaluation is completed

By who and how are patents currently searched? (Cont.)

- EPA has developed a provisional search strategy for registrants:
  - Recommended databases
  - Recommended key words for the searches
  - Other data sources or key words are not excluded
- Registrants conduct the search and develop a summary report of the discovered patents as they relate to select criteria
- Registrants provide EPA with patent-supporting data that meet reporting criteria

What are the relevancy criteria?

- Designed to reduce the volume of evaluation work
- Focus on those patents with data potentially **relevant** to the pesticide ecological risk assessment process.
  - Patent contains actual measurement data for effects
  - Data pertain to the pesticide active ingredient subject to the regulatory decision in a mixture with other active ingredients registered in the United States
  - Measured effects are on a taxonomic group for which EPA assesses risk
  - Effects are reported as direct measures of effects to the taxon

What's EPA's focus on relevant patents?

- Mixture effects data that can be used to determine if and how the ecological risk assessment is to be modified
- EPA focuses the risk assessment at the labeled application rate of a pesticide and lower exposures due to run-off, drift, and other off-site transport processes
- Patent data are often generated using application rates well in excess of labeled field rates
- Criteria are focused on data that can allow EPA, if need be, to relate patent conditions to conditions assessed in the ecological risk assessment

What are the reporting criteria?

- Reporting criteria for relevant patents include data meeting the following:
  - The patent claims toxicity in excess of additivity in three or more treatments at and above the (proposed) labeled field application rate;
  - There are two or more treatments where the patent claims toxicity in excess of additivity in one, or more treatments at/above the (current or proposed) labeled field application rate, but at least one treatment in the progression did not show synergy;
  - The patent claims toxicity in excess of additivity in one or more treatments at or below the (current or proposed) labeled field application

What information should be reported?

- EPA has found the following information fields to be important to the evaluation of the patent data:
  - General design of the experiment
  - Identity of active ingredients
  - Application method/rates/dose progressions evaluated, including any blank control or other test solution controls
  - Observation data reported for each treatment/control and each date (days after treatment) of observation for the individual and combined active ingredient effects
  - Description of the mathematical method employed to establish baseline combined expected toxicity/efficacy for the patent
  - Statistical methods used to identify significant departures from expected combined toxicity/efficacy
  - Relevant labeled field rates of all active ingredient components tested

What does EPA do with reported information?

- EPA does not evaluate the USPTO decision on claims made in a particular patent
- EPA evaluates the reporting data to determine if the observations reported must be qualitatively or quantitatively incorporated into an ecological risk assessment supporting a FIFRA regulatory decision.
- EPA will applymany of the evaluation criteria for non-guideline effects studies that are used to determine quality of data:
  - Controlled experiments
  - Well-defined test materials
  - Risk assessment appropriate exposures
  - Dose response
  - Replication
  - Statistical significance
  - Relationship of effects measurements to measurement endpoints in ecological risk assessment

How will EPA consider the weight of evidence?

- For data where EPA feels the observations are of appropriate technical rigor to support potential quantitative application, EPA will consider:
    - The magnitude of effects beyond predicted additivity
    - Trends in observations across treatment levels (if any)
    - Other lines of evidence associated with mechanisms of action that could inform interaction assumptions (EPA welcomes registrant input)
    - Background information on the frequency of observations of effects interactions in data sets extending beyond the patent reporting (EPA welcomes summary information from registrant)
    - Existing ecological risk assessment findings
- Can the data be reliably extrapolated to field exposures and below?
- Would quantitation of excess toxicity alter risk assessment conclusions or risk mitigation measures?

What has EPA learned so far?

- Nine cases are now complete or are nearing completion
  - Majority of patents captured by the searches for selected interaction terms **do not include data relevant to an ecological risk assessment**
  - Of the relevant patents, EPA has found that most do not indicate a need for quantitative consideration in the ecological risk assessment
    - Data reported was devoid of replicates (no way to distinguish random events)
    - Many reported mixture response observations beyond assumed additivity:
      - Were not statistically significant relative to expected additive response, or
      - Were within the expected endpoint variability expected for the test with the single dominant active ingredient
    - The extent of excursion from assumed additivity was very small or would have no impact on the existing conclusions and mitigations associated with the ecological risk assessment.

What has EPA learned so far?

- In two cases involving patents with herbicidal claims of interactions, additional toxicological work was conducted.
  - Case one involved a formulation of two actives, and the EPA and registrant felt that existing policies for herbicidal testing of a representative “typical end use product” would provide rapid and direct endpoints for risk assessment.
  - In Case two, the registrant reached the same conclusion even before meeting with the Agency
  - In both cases, the use of endpoints from guideline type studies using the proposed mixtures provided direct and unambiguous endpoints for use in the ecological risk assessment.
- While some formulation product test data exists, testing all mixtures with additional guideline-type studies is not ultimately an efficient process for all possible mixture situations.

This Process is Evolving

- Each case has afforded the Agency with a perspective on the utility of available patent data
- Reporting criteria, search strategies, and evaluation techniques are changing in response to the growing experience with patent information
- EPA would welcome additional input for stakeholders on
  - Efficient methods for data evaluation
  - Other lines of evidence
    - Overviews of best available scientific information on mechanism of action based expectations for interactions
    - Background frequency of interaction observations in broader data sets.