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USEPA, OPPTS  
Office of Pesticide Programs  
Biopesticides and Pollution Prevention

Submitted via the Federal eRulemaking Portal

## **RESPONSE TO DOCKET NUMBER EPA-HQ-OPP-2008-0835**

The Environmental Protection Agency has requested comments relative to the data required to register plant-incorporated protectants (PIPs) in conjunction with the FIFRA Scientific Advisory Panel Meeting on this subject. The following comments, specific to the EPA position paper and charge questions to the Panel, are submitted on behalf of the Biosafety Institute for Genetically Modified Agricultural Products (BIGMAP) at Iowa State University. BIGMAP is dedicated to providing an objective voice for assessing and communicating risks for sound public policy and regulatory decision-making as it pertains to the products of agricultural biotechnology. The goals of BIGMAP are to support expert analysis of risk/benefit assessments and mitigation alternatives, to encourage science-based public debate regarding genetically modified agricultural products, and to communicate the results of these activities to key regulatory and public policy stakeholders.

***We encourage the development of regulatory guidance that adheres to principles of risk assessment.***

Key to any data requirement is use of appropriate problem formulation that identifies and prioritizes on a case-by-case basis relevant exposure pathways and adverse consequences arising from exposure. Addressing scientific issues relevant to registration of any given PIP should not be driven by a data requirement in the first instance; but rather should encourage sound problem formulation which identifies relevant concerns and uncertainties and leads to an analytical plan consistent with the needs of decision-making. As a general observation we encourage guidance which is sufficiently flexible to accommodate problem formulation as a critical first step. A general concern we have is that Guidelines Documents in development by EPA may be overly prescriptive in terms of data to be generated and therefore fail to allow well-formulated risk hypotheses to determine the relevant data for sound risk assessment.

***Charge question B.1.*** Short sequence searches for allergenic epitopes to date have not proven useful as a statistically or biologically meaningful approach to addressing allergenicity risk. The use of short-peptide matches have not been validated as a tool for prediction of allergenicity and should not be used. The high frequency of false positives generated by short-segment searches misdirects the weight-of-evidence analysis for allergenicity risk. We encourage a sensible approach to allergenicity risk assessment (e.g., Goodman et al. 2008 *Nat Biotech* 26:73-81)

which is initiated by consideration of gene source and bioinformatics searches keyed to >35% matches over 80 amino acids in comparison to known allergen sequences.

**Charge question C.1.** The methodology for synergistic effects (OPPTS 890.3800) may be too restrictive for all relevant cases. The guidance should be sufficiently flexible to allow for alternative experimental approaches. The guidelines, for instance, may need to account for the degree to which the activities of the PIPs are similar. And guidelines may additionally need to account for instances when multiple (that is more than two) PIPs are considered.

**Charge question C.2.** The lack of an approach based on sound principles of environmental risk assessment appears to be a fundamental limitation in the EPA's position on soil microbial community effects. Even though EPA's position paper does a good job of encapsulating the crux of issues regarding soil microbial community effects of PIPs, there needs to be recognition of a tiered approach to studies and assessments to address risks of PIPs to the soil ecosystem. Therefore, while we support the establishment of the guideline study as worst case confirmation of reasonable certainty of no harm to the soil microbial community, we are concerned that there has been no attempt to elaborate an overall paradigm for assessment of risks of PIPs to the soil ecosystem. For instance, how does the proposed soil microbial community toxicity test (OPPTS 890.3850) relate to laboratory studies of soil persistence and field studies of accumulation which have been traditionally required for PIP registrations (or as a condition of registration)? Does this test replace or augment such studies? Is there a logical, stepwise process envisioned for the evaluation of effects to the soil ecosystem (that is, a tiered process)? And are there established endpoints of concern for findings of the soil microbial community toxicity test? How does the design rationale for this test align with the exposure of a given PIP to the environment in terms of the anticipated pathway, intensity, and duration of exposure?

It is important, however, to recognize the guideline describes a the test system and protocol which are highly contrived and cannot represent the natural soil microbial community (due to the way soils are treated and dosed as well as difficulties inherent in sampling, storage and preparation of the test soils). This is not problematic in as much as the test is intended as a first tier screen or confirmatory study. As a screening level test, we view the focus on functional endpoints with emphasis on CO<sub>2</sub> efflux rate and the NO<sub>3</sub> and NH<sub>3</sub> as appropriate. Neither the guidance nor the position paper provide information as to how the results for the soil microbial community study are to be interpreted.

The methodology is rich in certain ancillary details (i.e., cleaning and sterilization of glassware) while at the same time providing limited detail on critical aspects of experimental design and conduct. Test soil selection is arbitrary outside of very gross characteristics (surface soil, pH 4 to 8, < 70% sand, etc.). Since the study as outlined is highly artificial, it may be preferable to specify a specific (and perhaps artificial) soil to afford greater comparability across cases.

The guidance for test soil preparation specifies amending (an air dry?) soil with (an unspecified amount of) alfalfa, dosing, and adjusting to -10 kPa water potential. The result will be a rapid microbial burst favoring a non-representative community of microbiota. If the alfalfa load is too high the system may become rapidly anaerobic. To a certain extent this is unavoidable in laboratory environmental fate studies, however, subtleties in test material sampling, preparation and test conduct can help to moderate the effect. For instance, there is the opportunity to describe (i) time between field sampling and study initiation; (ii) soil storage conditions (moisture and

temperature) prior to study initiation; and (iii) soil pre-equilibration with the ground alfalfa at test moisture (10 kPa) for a period prior to dosing in order to reduce variability and achieve a more biologically meaningful result. In addition, environmental fate studies generally control for O<sub>2</sub> and CO<sub>2</sub> status, since the static systems described in the guideline often become oxygen-limited and CO<sub>2</sub> may rise to toxic levels.

In summary,

1. As a worst case confirmatory study OPPTS 890.3850 may have value; it however is not particularly useful to environmental risk assessment.
2. There is neither an established threshold for concern for the effects measurement in this study nor is there consideration of how the finding may relate to the pathway, duration, and intensity of environmental exposure.
3. EPA needs to elaborate a broad paradigm for the overall assessment of the soil ecosystem which uses risk assessment principles to determine the risk hypotheses to be addressed for a given PIP. This paradigm should establish how studies ostensibly designed to evaluate environmental exposure (persistence and accumulation studies) relate to a study focused on a possible consequence of exposure (the soil microbial community toxicity test).

**Charge question D.1.** The approach taken for the evaluation of environmental impacts of gene flow between sexually compatible plants (OPPTS 890.4300) should be captured in language consistent with sound principles of environmental risk assessment. This is especially important with respect to formulation of a problem and resulting assessment that account for the case-specific attributes of the PIP plant considered, its receiving environment, and its management. The approach used must balance the potential for gene flow and introgression (exposure) with the consequences that arise from the exposure. The risk assessment process has particular strength when applied in a stepwise manner, proceeding from conservatively cast projections to more realistic studies and further assessment as warranted by the degree of concern or uncertainty for the case under consideration. The guideline lists significant highly detailed information some of which may not be available in the literature. Instead of a specific data requirement for generation and/or synthesis of this comprehensive set of information, the Agency and developers should proceed in a stepwise manner and consider for a given case the information relevant to decision-making. This can be done within the formal process of environmental risk assessment using problem formulation as the first step for determining the nature of concerns and uncertainties which need be addressed.

For instance, if for a given case we know (or are willing to assume) gene flow occurs, does refinement of gene flow frequencies improve decision-making? In certain cases it may and in others it may not; problem formulation should be used to determine whether for the purposes of risk assessment refinement in gene flow frequencies is a critical data element.

A first instance of risk assessment can conservatively formulate the problem by the *a priori* assumption that gene flow and introgression occur between a particular GE plant and a sexually compatible wild relative (SCWR). The focus becomes consequences for the exposure which is assumed to occur and can be couched in three general questions: Do the PIP plant-wild hybrids out-compete SCWR (leading to localized extinctions of wild populations)? Are there PIP plant - wild hybrids that cannot be managed (leading to problems for weed control)? Is there alternation in natural populations (either the SCWR or target/non-target organisms associated with the

SCWR)? When worst-case considerations indicate a probable consequence, there is a need to reformulate the problem to determine if the concern remains under more realistic conditions. Problem reformulation at this point could for instance determine the need to creation and test plant-wild hybrids. Conversely, a finding of minimal consequence in a worst-case scenario would allow for a reasonably and conservatively stated finding of no likely harm under realistic conditions of environmental release. Such an approach conserves resources for data generation and review and allows for the environmental risk assessment to be focused on relevant concerns and uncertainties.

**Conclusion.** The Agency is bringing forward a series of Guidance Documents focused on PIP data requirements. While such guidance serves is a useful resource for developers and reviewers, there is a need for flexibility in the application of the guidance for the case-by-case consideration of PIP risks. Recognition and use of a risk assessment paradigm which is driven by problem formulation can avoid the generation of information which does not usefully inform the needs of decision-making. Problem formulation identifies concerns arising from exposure, poses relevant risk hypotheses, and outlines an analytical plan for the environmental risk assessment. These elements usefully inform determination as to what data will most meaningfully address the needs of regulatory decision-making; and avoids a check-box approach to data generation which may not address appropriate concerns or uncertainties.

Respectfully Submitted,



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