Draft For Public Comments

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PROCESS FOR ESTABLISHING & IMPLEMENTING ALTERNATIVE APPROACHES TO TRADITIONAL *IN VIVO* ACUTE TOXICITY STUDIES

12/15/2014

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I. BACKGROUND

EPA's Office of Pesticide Programs (OPP) has developed a strategic vision[1] for implementing the 2007 NRC report on Toxicity Testing in the 21st Century[2]. This strategic vision has multiple components involving a combination of computational and predictive modeling approaches, *in vitro* techniques, and limited, targeted *in vivo* testing, to supplement or replace the existing toxicity tests required in 40 C.F.R. part 158[3] (40CFR158) in support of pesticide registration. In May 2011, the agency sought expert advice and input from its the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) Scientific Advisory Panel (SAP) on OPP's vision and scientific issues associated with adopting integrated approaches to testing and assessment (IATA) and strategies for using new computational and molecular tools. The Panel concurred that OPP's strategic vision clearly articulated a sound scientific basis for utilizing the NRC's recommendations regarding "21st Century Toxicity Testing" in a manner that makes the risk assessment process more efficient and informative. And, the Panel commented that utilizing data from rapidly and inexpensively performed *in silico* and *in vitro* technologies appears to be the most logical way to address the need to improve efficiency.

As part of the implementation of the strategic vision, OPP developed a document called "GUIDING PRINCIPLES for DATA REQUIREMENTS[4]" which describes some of the key principles in moving towards smarter testing approaches. In 2013, OPP's policy on the "Use of An Alternative Testing Framework for Classification of Eye Irritation Potential of EPA Pesticide Products" was another early step toward this vision. As science is rapidly advancing and new technologies are emerging, including some alternatives assays with Organization for Economic Co-operation and Development (OECD) guidelines, there is increasing potential for the use of alternative methods in regulatory risk assessment. OPP plans to continue to expand its acceptance of alternative methods for acute toxicity testing. The agency's goals for alternative testing approaches include: assessing a broader range and potentially more human-relevant

[1] http://www.epa.gov/pesticides/science/testing-assessment.html#pesticide
[2] http://dels.nas.edu/resources/static-assets/materials-based-on-reports/reports-in-brief/Toxicity_Testing_final.pdf
[3] http://www.ecfr.gov/cgi-bin/text-idx?tpl=/ecfrbrowse/Title40/40cfr158_main_02.tpl
[4] http://www.epa.gov/pesticides/regulating/data-require-guide-principle.pdf

adverse effects, faster and less expensive data generation and review, and reducing use of laboratory animals in regulatory testing.

This document describes a transparent, stepwise process for evaluating and implementing alternative methods of testing for acute oral, dermal, inhalation toxicity, along with skin and eye irritation and skin sensitization (often referred to as the "six pack studies")[5]. Included in this document is a discussion of the three major phases of this process, and the implications for reporting information under section 6(a)(2) of FIFRA. Having such a process and a clear articulation of the related reporting requirements addresses a challenge that has previously been associated with adopting alternative methods. Successfully putting this process into place will require an open dialogue with stakeholders, other regulatory organizations, and the scientific community.

II. STEPWISE PROCESS FOR EVALUATING & IMPLEMENTING ALTERNATIVE METHODS

The following text describes the major components of a transparent, stepwise process for evaluating and implementing *in vitro* or other alternative methods in OPP's regulatory decision making with respect to acute toxicity tests. These components include:

1. **Evaluation**
2. **Transition**
3. **Implementation**

OPP expects the alterative methodologies considered appropriate for this stepwise process to be well established by the scientific community with respect to reproducibility and domain of applicability; these methods may or may not have OECD guidelines. This process is focused on the utility of methods for regulatory application and is thus designed for well-established methods (for example, methods that have been ring-tested). Methods still in development or poorly characterized with respect to performance require further research and evaluation that is

[5] This document does not apply to *in vitro* or alternative methods used for other purposes such as quantitative structure activity relationships, mechanistic or pharmacokinetic data used to support mode of action, adverse outcome pathways, or pharmacokinetic models.

out of the scope of this process. The process does not prescribe a specific timeframe for each stage as the analysis required at each stage may differ among various methods.

A. Evaluation Phase of Alternative Method(s)

The purpose of the evaluation phase is to determine whether an alternative method(s) could be used for regulatory purposes. The first step in the process is to identify an alternative method or system (array) of methods that have the potential to be used in place of a traditional acute toxicity test. Organizations or coalitions of stakeholders interested in pursuing an evaluation of an alternative method for regulatory applicability are welcome to contact OPP for a consultation. Alternatively, EPA may identify promising alternatives.

The objectives of the evaluation are to determine the reliability of the alternative method, evaluate the method in the context of regulatory use, and identify uncertainties. Some considerations during the evaluation phase are:

1) the degree to which the method has been vetted by an international validation process (*e.g.*, ASTM International[6]) and/or the availability of an OECD guideline;
2) whether the method is appropriate for single chemicals, mixtures, or both;
3) the types of chemicals which can be used with the method *i.e.*, the domain of applicability;
4) whether the method can be used alone as a replacement for an *in vivo* study or the method must be used in combination with others as part of an integrated approach on testing and assessment (IATA)[7] process;

[6] http://www.astm.org/ABOUT/full_overview.html

[7] **IATA (Integrated Approach to Testing and Assessment)**: Integrate existing knowledge based on classes of chemicals with the results of biochemical and cellular assays, computational predictive methods, exposure studies, and other sources of information to identify requirements for targeted testing or develop assessment conclusions. In some cases, the application of IATA could lead to the refinement, reduction, and/or replacement of selected conventional tests (e.g., animal toxicity tests). IATA also has the potential to further enhance the understanding of mode/mechanism of action including the consideration of relevant adverse outcome pathways (AOPs) that provide biological linkages between molecular initiating events to adverse outcomes in individual organisms and populations that are the bases for human health and ecological risk assessments (NAFTA, 2012). Extracted from http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=ENV/JM/MONO(2014)19&doclanguage=en

5) additional strengths and uncertainties associated with the assay such as feasibility, sensitivity and specificity, ease of interpretation, costs, *etc*.; and,
6) whether information derived from the assay(s) is suitable for labeling and regulatory decisions (including whether the method(s) provide information relevant to risk assessment in addition to information for labeling decisions).

Once a proposed alternative method(s) is accepted as a suitable candidate, the evaluation process would consist of a number of steps. First, existing data generated using the alternative method(s) will be collated and organized (for example in a spreadsheet or database). The data could be previously generated or generated explicitly for the purpose of informing an evaluation of regulatory applicability. This data compilation could be accomplished in various ways. For example, a coalition of interested companies could work with a neutral party to collect and aggregate data so that confidential business information (CBI) would be concealed.

Once the data are compiled, OPP anticipates performing an analysis, through which OPP and interested stakeholders would cooperatively evaluate the utility of these data in the context of regulatory decision making under FIFRA (*e.g.*, approval of uses, application methods, labeling requirements for signal words and personal protective equipment). Part of this analysis will include comparison with existing data generated through EPA's approved test methods (*i.e.*, consistent with existing test guidance). This analysis would consider how EPA would use data from the alternative method to classify products for acute toxicity labeling (Categories I – IV)[8]. Throughout the course of an evaluation, the agency will engage diverse stakeholders including states, non-government organizations (NGOs) and other federal agencies. The agency will seek peer review of the evaluation when necessary.

OPP's goal for the evaluation phase is to end with a determination that an alternative method(s) is suitable for regulatory purposes. Such a determination would come in the form of an EPA publication of a draft policy document (e.g., waiver guidance) for public comment on the proposed approach method and the appropriateness of the alternative method for a stated

[8] http://www2.epa.gov/pesticide-registration/label-review-manual

regulatory purpose, including the establishment of a correlation between method results and a toxic effect similar to those measured by current guidelines. The draft policy document would also discuss any requirements the agency may have with respect to needing *in vivo* data. For example, depending on the method(s) proposed, a certain amount of *in vivo* oral acute toxicity data may be necessary to support ecological risk assessments. At this point, with the publication of the draft policy, the agency will provide notice of its expectation and timeframes for reporting under section 6(a)(2) of FIFRA.

In some cases, the method(s) may be found not useful for regulatory purposes. Sometimes, areas for additional method development that have the potential to make the method more useful for regulatory purposes may be identified. For example, some alternative assays are developed for use with a single chemical; because acute toxicity testing is conducted on both single technical ingredients and formulations (*i.e.,* mixtures), additional testing may be necessary to evaluate the applicability of a particular method for mixtures (*i.e.,* formulations). In other cases, the agency may recommend modifications to the test methods or the overall alternative approach.

B. Transition Phase

In this phase, OPP would accept data generated from the alternative method(s), which were conducted following the draft policy document, and submitted along with corresponding data from its *in vivo* method counterpart (or citation to previously submitted *in vivo* studies). This would provide the broader registrant community with the opportunity to practice conducting the method(s) and the agency additional experience in assessing the data. During the transition, the public will have the opportunity to provide comments on the draft policy document. The agency will use the public comments to revise the draft policy where appropriate. The agency is also aware of the importance of national and international harmonization and will continue to work with state and international regulators on use of the alternative method.

C. Implementation

After addressing any potential issues identified through public comments, a final science policy will be completed and released. Subsequently, data generated from the accepted alternative approach may be submitted to fulfill the requirement of its standard *in vivo* counterpart. Data generated with the method will be reportable under section 6(a)(2), if relevant, regardless of when the data were generated (see Section III below).

III. APPLICABILITY OF FIFRA 6(a)(2) REQUIREMENTS

FIFRA section 6(a)(2) provides that "*[i]f at any time after the registration of a pesticide the registrant has additional factual information regarding unreasonable adverse effects on the environment of the pesticide, he shall submit such information to the Administrator.*" This does not mean that the reported information will necessarily lead to regulatory decisions or label amendments: Information is reportable under section 6(a)(2) if it simply "*pertain[s]* or *relate[s] to unreasonable adverse effects on the environment; it does not have to indicate, establish, or prove the existence of such effects.*" 43 Fed.Reg. 37611, 37612 (Aug. 28, 1978) (emphasis in the original). EPA always considers new information submitted pursuant to section 6(a)(2) in the context of the full range of data previously submitted in support of the registration, applying a weight of the evidence approach to the multiple lines of available evidence. Likewise, OPP will review any information arising through the development of a new test method in relation to other pertinent information about the pesticide.

The process described above for evaluating and implementing alternative methods for *in vivo* acute toxicity studies includes comparing existing data previously generated by EPA's test methods with data generated using an alternative test methodology (*e.g.*, OECD Skin Irritation). Part of the focus of this comparison is simply to understand both the degree to which there is correlation between the standard *in vivo* and the alternative methods and the degree to which determinations regarding adverse effects can be made with the alternative method(s). Pesticide registrants cooperating in this evaluation would already have submitted to EPA any information required to be reported under section 6(a)(2) arising from previous testing generated using EPA's test guidelines (*i.e., in vivo* test results) for registered pesticides. As a result, the scope of the new information arising from the evaluation that could potentially be reportable under section

6(a)(2) would be limited to information arising from the alternative methods or from any new correlation established between the alternative methodologies and the methods upon which EPA currently relies.

At the beginning of the process, the results of the alternative testing methods are unlikely to be of interest to EPA, because the degree to which those results correspond to EPA's regulatory criteria is unknown.[9] Through its evaluation process, the agency will determine whether the alternative method(s) may meet OPP's regulatory needs. If the evaluation is successful in developing a reasonably reliable correlation between the different test methods, then the results of alternative test methods would be more likely to be of regulatory utility to EPA. For example, if a reasonably reliable correlation between the alternative assay and EPA's skin irritation criteria were developed, registrants who possess or know of information that, in the context of the new policy, would raise concerns about the continued registration of a product or about the appropriate terms and conditions of the registration of a product, would be required to report that information to EPA (§ 159.195(a)). This would apply to data previously developed using existing test methods (*e.g.,* the *in vivo* methods), as well as to data generated during initial research of new test methods. It would apply to all registrants *i.e.,* those who are not cooperating in the analysis, as well as cooperating registrants.

Information submitted pursuant to section 6(a)(2) will not necessarily dictate regulatory decisions or label amendments. For the case of acute toxicity studies, an *in vitro* test result corresponding to a higher hazard category than that associated with an acceptable *in vivo* test result would not necessarily require a label change nor would an *in vitro* result corresponding to a lower hazard category necessarily lead to a label change. EPA will consider reported data in the context of the full range of data previously submitted in support of the registration, applying a weight of the evidence approach.

[9] Even in the absence of a reasonably reliable correlation between the OECD methods and EPA's methods, it is possible – though unlikely – that testing under the OECD methods could produce information reportable under FIFRA section 6(a)(2). For example, if a product or class of products that routinely show low levels of toxicity in [some EPA method] were to consistently show unexpectedly high levels of toxicity under an alternative method, a reasonable person might view the divergence in results as raising questions about which method adequately reflects the true risk of the product(s). It would be important for EPA to have such information, even if there was little short-term likelihood of either a regulatory response or a scientific explanation for the divergence.