

Final

**PROCESS FOR EVALUATING & IMPLEMENTING ALTERNATIVE
APPROACHES TO TRADITIONAL *IN VIVO* ACUTE TOXICITY
STUDIES FOR FIFRA REGULATORY USE**

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I. BACKGROUND

EPA's Office of Pesticide Programs (OPP) has developed a strategic vision¹ for implementing the 2007 National Research Council (NRC) of the National Academy of Science report on Toxicity Testing in the 21st Century². 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 158³ in support of pesticide registration. In May 2011, the agency sought expert advice and input from its 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 REQUIREMENTS⁴" which describes some of the key principles in moving towards smarter testing approaches. In addition to seeking alternative testing strategies, in March 2012 the Agency also published a "Guidance for Waiving or Bridging of Mammalian Acute Toxicity Tests for Pesticides and Pesticide Products"⁵ which provides a foundation for reducing redundant or unnecessary testing and thus reducing animal use. 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

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>

⁵ <http://www2.epa.gov/sites/production/files/documents/acute-data-waiver-guidance.pdf>

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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 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, and inhalation toxicity, along with skin and eye irritation and skin sensitization (often collectively referred to as the "six pack studies"). 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*, *in silico*, or other alternative methods of determining the acute toxicity of pesticides and pesticide inerts for use in OPP's regulatory decision making.

These components include:

- 1. Evaluation**
- 2. Proposal & Public Comment**
- 3. Implementation**

OPP expects the alternative 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

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methods (for example, methods that are documented to be reliable and transferable from one laboratory to another). For *in vitro* methods without a guideline, OPP recommends following OECD Guidance Document 211 for describing non-guideline *in vitro* test methods⁶. Methods still in development or poorly characterized with respect to performance require further research and evaluation that is 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 of An Alternative Method

The purpose of the evaluation phase is to determine whether an alternative method(s) could be used for OPP 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.*, International Cooperation on Alternative Test Methods, ICATM, or its member countries; ASTM International⁷) 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;

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[http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=ENV/JM/MONO\(2014\)35&doclanguage=en](http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=ENV/JM/MONO(2014)35&doclanguage=en)

⁷ http://www.astm.org/ABOUT/full_overview.html

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- 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)⁸ process or integrated testing strategy;
- 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 aggregate results could be reported without disclosure of confidential business information (CBI), or data could be compiled from the open scientific literature.

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

⁸ **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](http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=ENV/JM/MONO(2014)19&doclanguage=en)

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from the alternative method to classify products for acute toxicity labeling (Categories I – IV)⁹. Note that there is not a specific threshold volume of data deemed sufficient for an analysis. Whether enough data is available to make a decision regarding suitability for regulatory purpose is a factor of multiple considerations such as how well the data set represents the pesticide chemical domain and the variability of the data set. Throughout the course of an evaluation, the agency will engage diverse stakeholders including states, non-government organizations (NGOs), international partners and other federal agencies. The agency will seek peer review of the evaluation where appropriate. In general, during the evaluation phase, the Agency does not intend to rely on compiled data to make regulatory decisions.

When EPA determines that an alternative method appears suitable for determining a pesticide's acute toxicity category for FIFRA regulatory purposes, EPA intends to publish it for public review and comment (e.g., as a draft waiver guidance or draft alternative testing guideline). The Agency anticipates that such a determination would come in the form of an EPA publication of a draft policy document for public comment on the proposed approach and the appropriateness of the alternative method for assessing one or more types of acute toxicity, including the establishment of a correlation between the alternative method's results and an acute toxic effect similar to those measured by current guidelines. The draft policy document would also discuss any limitations or additional data needs the agency may have. If the Agency identifies *in vivo* data needs that cannot be fulfilled with the alternative method, those exceptions will be identified in the policy document for that particular method (e.g., *in vivo* oral acute toxicity data on active ingredients may be needed to support ecological risk assessments even if *in vitro* oral acute toxicity alternative methods are accepted for formulations).

EPA anticipates that the draft policy would also include the Agency's expectations and timeframes for reporting under section 6(a)(2) of FIFRA adverse effects information specific to the alternative method.

⁹ <http://www2.epa.gov/pesticide-registration/label-review-manual>

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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 or method development 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. Proposal & Public Comment

During this phase, 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, federal and international regulators on use of the alternative method.

C. Implementation

After addressing any potential issues identified through public comments, EPA intends to issue a final policy regarding the alternative approach. Subsequently, data generated from the accepted alternative approach may be submitted to fulfill the requirement of its standard *in vivo* counterpart, as provided in 40 CFR 158.70 and 158.80. 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

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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 from 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.¹⁰ Through its evaluation process, the agency will determine whether the

¹⁰ 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.

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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.