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VIA WWW.REGULATIONS.GOV

Mr. Don Bergfelt
Office of Science Coordination and Policy (7203M)
U.S. Environmental Protection Agency
1200 Pennsylvania Avenue, N.W.
Washington, DC 20460-0001

RE: Endocrine Disruptor Screening Program (EDSP); Announcing the Availability of a Draft for Weight-of-Evidence Guidance Document: Evaluating Results of EDSP Tier 1 Screening to Identify Candidate Chemicals for Tier 2 Testing; EPA-HQ-OPPT-2010-0877.

Dear Mr. Bergfelt:

The Chemical Producers & Distributors Association (“CPDA”) appreciates this opportunity to comment on the above-referenced draft weight-of-evidence guidance document (“Guidance Document”). CPDA is the primary advocate on federal legislative and regulatory issues for generic pesticide registrants, adjuvant and inert ingredient manufacturers, and product formulators and distributors.

The U.S. Environmental Protection Agency (“EPA” or “Agency”) is required to screen certain chemicals for their potential to interact with the human endocrine system¹ and has implemented this Congressional mandate through the Endocrine Disruptor Screening Program (“EDSP”).² EPA has developed this draft Guidance Document in response to a House Appropriations Committee report directing the Agency to develop criteria to evaluate Tier 1 screening results and determine the need for further testing.³ In addition, the Office of Management and Budget (“OMB”) has directed EPA to maximize the practical utility (i.e., benefits) of the Tier 1 information collection by “ensuring sufficient opportunity for public comment and peer review of the EPA tools to be developed to guide agency decisions on whether a chemical must proceed to Tier 2, including the Weight of the Evidence Approach and Standard Evaluation Procedures.”⁴

CPDA strongly supports the use of the weight-of-evidence approach for evaluating both the Tier 1 assay results and other scientifically relevant information (“OSRI”). However, for the reasons set forth below, CPDA believes the Guidance Document does not comply with the directives of the Committee report or OMB and provides only minimal useful guidance for evaluating Tier 1 screening results or OSRI for use in the EDSP.

Evaluating Tier 1 Screening Results

EPA states in the first sentence of the Guidance Document that “the purpose of this document is to set forth some of the general principles, criteria, and considerations EPA generally believes to be relevant to using a weight-of-evidence approach to evaluate data....” Although EPA describes a weight-of-evidence evaluation as “a process where potentially relevant studies are judged in a professional manner for quality,” and the Guidance Document as providing “a transparent scientific approach for broadly evaluating Tier 1 screening data,” the Agency fails to provide essential details and scientific references⁵ to support its purported

¹ FFDCA §408(p).

² The current screening effort includes the estrogen, androgen, and thyroid hormone pathways of the human endocrine system.

³ House Appropriations Committee for Interior and Environment FY 2010 Report 111-180 for HR 2996.

⁴ *Tier 1 Screening of Certain Chemicals under the Endocrine Disruptor Screening Program (EDSP)*; Terms of Clearance for the Agency’s Information Collection Request (OMB Control No. 2010-0176); October 2, 2009.

⁵ EPA references only five (possibly seven) EPA documents and ignores the considerable public literature on this topic.

“transparent” approach. Instead, the seven-page Guidance Document contains almost four pages of summary background information about the EDSP, and only about two pages that address the weight-of-evidence approach the Agency will use to evaluate tens of millions of dollars worth of data for the Tier 1 screening alone. It provides essentially no guidance on how to actually conduct a weight-of-evidence evaluation of endocrine system-related data, and is not suitable for guiding data evaluations “in a professional manner for quality.”

There are eleven Tier 1 screening assays that will require significant expertise and detailed guidance to ensure that individual assays and the entire battery of eleven assays are properly evaluated individually and as a group to make weight-of-evidence decisions about the need for Tier 2 testing. The screening program is a complex undertaking that must be based on solid scientific information and decision-making throughout. EPA correctly notes that a weight-of-evidence evaluation “is not a process that simply involves tallying the number of positive and negative results within and among studies,” and that the process must ensure that “[c]ritical assessment of an entire body of available data is taken into account for consistency, coherence, and biological plausibility.” However, the Guidance Document provides only the general context for a qualitative, subjective analysis rather than the specific detailed decisions that must be made in a quantitative, objective weight-of-evidence analysis. The Agency does provide several categories of data evaluation criteria (e.g., “nature of the effect(s) seen,” “potency of the responses,” and “dose- and time-dependent changes”) that are used to evaluate toxicological data and adverse effects. However, the determination and analysis of adverse effects are not the purpose of Tier 1 screening, which is only to assess the potential of a chemical to interact with the endocrine system. EPA’s guidance for conducting weight-of-evidence determinations for Tier 1 screening data must be detailed and focused solely on the purpose of the screening program.

CPDA urges EPA to revise the Guidance Document so that it provides users with the detail needed to determine why each specific Tier 1 assay result can be relied upon (quality-reliability determination) and how that assay should be integrated with the other assays to inform an assessment of a chemical’s potential to interact with the endocrine system (i.e., whether it should undergo Tier 2 testing). The Agency should also:

- Develop multiple examples of how each different type of assay result should be evaluated and include explanations about which assays and which endpoints have the greatest weights for determining each potential hormonal activity within the Tier 1 battery.
- Develop a detailed scheme for weighting each specific result in each assay based on the known range of possible responses for an endpoint using relevant known positive and negative control chemicals.
- Explain how a response pattern for a chemical can be integrated across all Tier 1 assays to derive an overall weight-of-evidence determination of the potential for the chemical to interact with each hormonal pathway covered by the Tier 1 assays.

Other Scientifically Relevant Information

EPA briefly discusses OSRI in section 3.2 of the Guidance Document and references a prior guidance document that describes the Agency's approach to considering OSRI in the EDSP.⁶ However, the referenced two-page document provides only a general discussion about OSRI and its relationship to Tier 1 test orders, noting that “[d]ecisions about whether the OSRI satisfies part or all of the Tier 1 Order will be based on the weight of evidence from all relevant information available.” As with the Guidance Document, EPA chose not to provide a standardized and detailed approach for using weight of evidence analysis for OSRI.

From the beginning of the EDSP, EPA has emphasized that the purpose of the Tier 1 screening effort is to identify chemicals that have the potential to interact with the endocrine system in order to appropriately subject them to EDSP Tier 2 testing to assess hazard and develop dose-response information. However, the Agency's apparent reluctance to accept non-Tier 1 data or OSRI implies that the Agency prefers that all chemicals selected for EDSP Tier 1 screening undergo the full battery of Tier 1 assays. This is evidenced by the Agency's having

⁶ EPA, *Approach for Considering Other Scientifically Relevant Information (OSRI) under the Endocrine Disruptor Screening Program* (March 26, 2009).

allowed to date only very limited waivers from Tier 1 screening based on OSRI. Analysis of EPA's recent OSRI decisions⁷ demonstrates that:

- OSRI *in vitro* studies have been accepted only when the OSRI study protocol strongly matches a Tier 1 assay protocol.
- OSRI *in vivo* studies that indicate a chemical has no potential to interact with the endocrine system will likely not be accepted, regardless of the quality and quantity of the studies.
- A few OSRI *in vivo* studies with positive results have been accepted in lieu of conducting an assay or assays despite their poor quality and/or divergence from Tier 1 protocols.

Thus, it appears that positive results in either an *in vivo* OSRI study or a Tier 1 assay will likely result in a “potential to interact” finding and therefore move to Tier 2 testing without demonstrable weight-of-evidence analysis. The decision by test order recipients to research, compile, evaluate, and submit OSRI and/or conduct the Tier 1 assays based on a transparent weight-of-evidence approach cannot be made.

Weight-of-Evidence Approach

CPDA is disappointed in EPA's lack of referral in this draft guidance to any non-EPA literature on weight-of-evidence approaches or to approaches using both quantitative and/or qualitative methods. CPDA believes that a weight-of-evidence approach employing the most credible scientific data, regardless of its origin, should be used in making decisions on the potential for a chemical to interact with the endocrine system. EPA has been participating in the Organization for Economic Co-operation and Development's (“OECD”) efforts on evaluating the potential impacts of endocrine disrupting chemicals, yet the Agency does not reference the approach to weight-of-evidence analysis this organization is developing. The OECD documents a process⁸ that includes evaluating:

⁷ *Tier 1 EDSP: Other Scientifically Relevant Information*. Barbara Neal. ISRTP 2010 Endocrine Workshop (December 13, 2010).

⁸ Environment Directorate, Joint Meeting of the Chemicals Committee and the Working Party on Chemicals, Pesticides and Biotechnology. ENV/JM/MONO(2010)3.

1. *What endpoint has been measured and the relevance of that endpoint to the effects of potential endocrine disruption mechanisms.*
2. *The repeatability, reliability and quality of a particular study and its protocol, together with the extent of peer review.*
3. *The significance (or 'weight') of the data based on the assessments under 1 and 2 above.*
4. *Whether there is sufficient coherence of the data to draw conclusions (balance of the 'weight of evidence').*
5. *What further evidence is required, including a prioritized action identification step leading to risk assessment in accordance with the existing, or any future coherent chemicals regulatory framework.*

Although the Agency's draft Guidance Document contains general principles for making such decisions, it lacks any meaningful specific information on how to actually make those decisions. Without that concrete decision-making guidance, EPA staff and contractors and data submitters will be unable to make consistent, proper and timely decisions regarding Tier 1 assays and OSRI.⁹ Therefore, we recommend that EPA significantly revise the draft Guidance Document to include the detailed guidance needed for making transparent and scientifically defensible decisions.

Conclusion

Any guidance document lacking the details and functionality needed to provide "a transparent scientific approach" will only foster deviation from the Agency's laudable principles of assessing studies "in a professional manner for quality" and using "[c]ritical assessment of an entire body of available data" when making OSRI or Tier 1 assay decisions related to a chemical's potential to interact with the endocrine system. Therefore, CPDA recommends the Agency develop and publish for public comment and peer review, weight-of-evidence guidance that is specific to the evaluation of potential endocrine disruptors. The guidance approach should

⁹ EPA has acknowledged that OSRI science reviews are "challenges" due to "the diversity of approaches to OSRI, as well as the volume and number of responses and short time frame (90 days)." Karen Whitby, OPP; PPDC meeting presentation (December 2010).

be based on quantitative and objective criteria, for which the data being generated through the Tier 1 assays and/or offered through existing OSRI can be reliably, repeatedly, and consistently evaluated. EPA's OSRI and Tier 1 assay data decisions, based on application of the final weight-of-evidence approach, should be transmitted to the public in a timely manner with comprehensive explanation of all findings.