Washington: Safe for Humans?

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Many stakeholders question whether EPA will carefully and consistently qualify what the test results mean – and do not mean.

Hundreds of U.S. businesses have already received in the mail test orders issued by the U.S. Environmental Protection Agency (EPA) for initial endocrine screening under the Endocrine Disruptor Screening Program (EDSP). Hundreds more will receive orders later this year. How recipients respond to an EDSP test order can present challenging issues. This article explains why.

A Decade of Development

Under Section 408(p) of the Federal Food, Drug and Cosmetic Act, EPA is required to develop a screening program to determine whether substances may have hormonal effects in humans. EPA has been working on various ways to implement this mandate for more than a decade.

Based on the approach EPA finally adopted, the administration assesses the suitability of a chemical for Tier 1 "screening" based on a substance's potential for human exposure.

Once Tier 1 screening has have been generated and reviewed, chemicals needing no further testing exit the EDSP. Chemicals requiring additional testing must undergo Tier 2 tests.

Last October, EPA identified the first set of chemicals to undergo Tier 1 screening. EPA selected 67 chemicals – 58 pesticide active ingredients and nine high production volume (HPV) chemicals used as pesticide inert ingredients – for which Tier 1 endocrine screening is required. The substances were selected based purely on their potential for human exposure, and not because any is known or likely to be an endocrine disruptor. Approximately 750 test orders were sent to approximately 450 companies.

A second list of substances is required to be prepared by EPA pursuant to the 2010 Appropriations Act. EPA is expected to issue a list of at least 100 chemical substances by Oct. 30, 2010. The second list of substances will consist of pesticides from EPA's registration review schedule and chemicals found in sources of drinking water.

Test Orders

As noted, EPA created under the EDSP a two-tier testing approach. Tier 1 screening is intended to identify substances that have the potential to interact with the estrogen, androgen or thyroid hormone systems using a battery of assays. The Tier 1 screening battery includes:

- **In vitro tests:** Estrogen receptor binding – rat uterus; estrogen receptor α (hERα) transcriptional activation – human cell line (HeLa-9903) (OECD Test Guideline (TG) 455); androgen receptor binding – rat prostate; steroidogenesis – human cell line (H295R) (U.S. lead, validated in OECD program); and aromatase – human recombinant.
- **In vivo tests:** Uterotrophic (rat) (OECD TG 440); Hershberger (rat) (OECD TG 441); pubertal female (rat); pubertal male (rat); amphibian metamorphosis (frog) (OECD TG 231); and fish short-term.

In general, Tier 2 testing is to identify and establish a dose-response relationship for any adverse effects that might result from the interactions identified through the Tier 1 assays. Tier 2 tests include: mammalian two-generation rat; avian reproduction; amphibian growth/reproduction; fish life-cycle; and mysid life-cycle.

Each recipient of a Tier 1 test order is directed to provide an initial response to EPA within 90 days of issuance of the order. For purposes of making this initial response, test order recipients may select among several options. The options vary between those recipients that are pesticide registrants and those recipients that manufacture or import a pesticide inert ingredient. The recipient can indicate that it:

- Intends to generate new data;
- Is submitting or citing existing data (including other scientifically relevant information or "OSRI," that include equivalent information);
- Intends to form (or offer to form) a consortium to provide data; or
- Is not subject to the test order.
- A pesticide registrant can indicate that it: Intends to cancel any pesticide registration to which the order relates;
- Intends to reformulate its product or products to exclude the chemical; or
- Is claiming a formulator's exemption.
- A pesticide inert ingredient manufacturer can indicate that it: Has discontinued or is in the process of discontinuing manufacture or importation of the chemical;
- Does not and will not sell the chemical for use in pesticide products;
- Can demonstrate that the chemical is an endocrine disruptor and additional screening or testing under EDSP is unnecessary;
- Is requesting an exemption based on hazard-related information indicating that the chemical is not an endocrine disruptor; or
- Is offering another response, such as challenging the test order or asking EPA to reconsider some or all of the testing specified in the order if certain conditions are met.

The recipient may indicate a different response commitment for each assay. Test orders have a final due date of 24 months from issuance of the order.

Practical Implications/Key Issues

Receipt of a test order raises issues. First, recipients must decide early on how best to respond. Recipients will have to choose among the response options noted above, and care will need to be taken to select the correct approach. Many recipients of test orders that are not pesticide active ingredients are uncertain as to what some of the options mean. For example, how does a recipient demonstrate that it does not and will not sell the chemical for use in pesticide products? Other questions have arisen, and EPA is expected to clarify certain issues in this regard.

Second, there continues to be controversy over whether the EDSP Tier 1 screening assays are scientifically defensible. Because the state-of-the-science in this area is new, the controversy over the probative and scientific value of the Tier 1 screens is expected to continue. EPA has stated that it is developing the tools it needs to interpret the screening results and ensure consistency in agency decision-making.

These tools include a weight-of-the-evidence approach and standard evaluation procedures (SEP). The lack of clarity regarding the SEPs and the fluidity of the process only heighten industry stakeholder concerns. Stakeholders are particularly concerned about how EPA plans to interpret and communicate screening results, and the process EPA will use to do so.

Third, managing the "optics" of the EDSP is a challenge. Since the inception of the EDSP, industry stakeholders have been concerned about the implications of having their chemicals identified as Tier 1 screening test substances. EPA has consistently maintained that merely screening a substance for endocrine effects does not mean, and should not be interpreted to mean, that the substance is an endocrine disruptor.

That said, however, manufacturers, importers, processors and users of chemicals identified for screening are concerned about how information on the EDSP and test results from the program are communicated to the public. Many industry stakeholders question whether EPA and other governmental bodies will carefully and consistently qualify what the test results mean – and do not mean.

EPA's ongoing issuance of test orders for Tier 1 screening is a major milestone in the EDSP. This step will force much hard thinking by order recipients, who will have to select a response and develop a communication strategy. Many hundreds of businesses will be considering their options soon when the next round of test orders are issued. Selecting the appropriate response requires business savvy, technical finesse and a clear understanding of the legal implications of each alternative.

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