Washington Watch

The Endocrine Disruptor Screening Program: Where Are We?

US EPA issues its final list of chemicals for the first group of substances to be screened

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On April 15, 2009, the U.S. Environmental Protection Agency (EPA) issued its final list of chemicals in the first group of substances that will be screened under the Endocrine Disruptor Screening Program (EDSP).[1] Development of this list caps a long, thoughtful, and arduous administrative process that spans over a decade.

This "Washington Watch" column briefly reviews the development of the program, with emphasis on key elements of the current EDSP. The discussion also highlights the implications of the program for industry stakeholders.

Concerns About Potential Endocrine Disruptors

According to researchers, regulators, and other interested parties, a loosely defined class of substances referred to generally as "endocrine disruptors" are believed to interfere with the body's endocrine system. Exposure to these substances under some circumstances is believed to result in adverse developmental, reproductive, neurological, and immune effects in both humans and wildlife.

Over the years, researchers have pointed to a growing list of anomalous health effects (including the feminization of certain male wild fish and male reproductive disorders in humans) that are believed to be attributable to endocrine disruptor substances.

Based on concern about the potential effects of exposure to endocrine disruptor substances, Congress included provisions in the Food Quality Protection Act of 1996 and the Safe Drinking Water Act Amendments of 1996 requiring EPA to identify, characterize, and regulate endocrine disrupting chemicals, as appropriate.

EDSTAC and Its Recommendations

To achieve this formidable Congressional goal, EPA first had to develop an appropriate conceptual approach for identifying and validating endocrine disrupting chemicals. As an initial step, the Agency established the Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC) in 1996.

EDSTAC, which consisted of representatives from diverse stakeholder groups, was charged with providing advice and recommendations to EPA regarding a strategy for determining whether chemical substances may have an effect on humans similar to effects produced by naturally occurring hormones.

EDSTAC began its deliberations in October 1996 and completed them in July 1998. The committee issued a final report on its findings on August 3, 1998.[2] In its report, EDSTAC urged EPA to address endocrine effects; examine biological processes involving estrogen, androgen, and thyroid hormones; and include in its review pesticide chemicals, commercial chemicals, and environmental contaminants.

0501.078 / 8 / 00054806.DOCThis is a reprint of an article published in *Environmental Quality Management*, Autumn 2009. Copyright 2009 Wiley Periodicals, Inc.

Creation of the EDSP

In response to the EDSTAC recommendations, EPA initiated the Endocrine Disruptor Screening Program in 1998. In its *Federal Register* notice announcing the EDSP's formation, the Agency stated its intent to screen pesticide chemicals and environmental contaminants for their potential to affect the endocrine systems of humans and wildlife.[3]

The EDSP would identify potential endocrine disruptor substances by using validated methods to screen and test chemicals believed to pose endocrine disruptor effects. The objective was to assess -- and ultimately manage -- the risks posed.

At the time the EDSP was initiated, EPA noted that some 87,000 chemicals were believed to be in commerce. The Agency readily acknowledged that the scientific data and information it had on most of these chemicals was not sufficient to permit a defensible evaluation of their endocrine-associated risks.

EPA accordingly developed a two-tier screening and testing program. Under Tier 1, the Agency would identify chemicals that have the potential to interact with the endocrine system. Tier 1 screening was to rely on short-term assays that could detect potential chemical interactions with the endocrine system. Under Tier 2, EPA would use longer-term assays to identify the specific impact caused by each endocrine disruptor and establish a dose at which the effect is believed to occur.

EDMVS Formation

To assist in developing the EDSP, EPA chartered the Endocrine Disruptor Methods Validation Subcommittee (EDMVS) as part of the National Advisory Council for Environmental Policy and Technology, in accordance with the Federal Advisory Committee Act.[4]

The purpose of the EDMVS, which was created in 2001, was to provide advice and comment on both the new and ongoing studies that were necessary to validate EDSP assays. Additionally, the EDMVS was intended to provide a forum for a "diverse group of individuals representing a broad range of interests and backgrounds . . . to consult with and make recommendations to the Agency on matters relating to the validation and external scientific peer review of endocrine disruptor screening and testing methods."

Not surprisingly, the concept of validating EDSP assays was -- and continues to be -- controversial.

EPA's December 2002 Proposal

Based on the work of the EDMVS, on December 30, 2002 EPA requested public comment on the approach it planned to use for selecting the first group of chemicals to be screened under the EDSP.[5] Using recommendations from the Science Advisory Board/Scientific Advisory Panel (SAP), the Agency proposed to select and screen chemicals drawn from lists of pesticide active ingredients and high production volume chemicals that had some pesticidal inert uses (HPV/inert chemicals). "High production volume" chemicals are defined as those that are manufactured or imported into the U.S. in amounts equal to or greater than 1 million pounds per year.

EPA stated that it planned to submit the data obtained from the screening process to an independent external panel of experts. The Agency would request an evaluation of

whether the program could be improved or optimized and, if so, how.

EPA proposed using several data sets to identify pesticide active ingredients for screening in the first application of the Tier 1 battery. These data focused on human exposure by various pathways, including exposure via consuming food or drinking water containing pesticide residues. The Agency would also consider the consequences resulting from residential use of pesticide products and occupational exposure to pesticide-treated surfaces.

For each of these pathways, EPA identified existing data that it believed would yield active ingredients likely to be among those having either relatively more widespread or higher levels of human exposure than would be expected from other active ingredients. The Agency proposed to give higher priority for inclusion on the initial list to chemicals that were likely to result in human exposure via multiple pathways, with the highest priority being given to substances having exposure through all four pathways, followed by those having exposure via three pathways, and so forth.

EPA proposed a generally similar approach for identifying HPV/inert chemicals to be included in the initial list for the Tier 1 battery. For HPV/inerts, the Agency focused on several indicators of the potential for human exposure, including production volume, specific pathways of exposure, and presence in human tissues.

EPA first reviewed existing databases to identify substances that are both pesticide inerts and HPV chemicals. This step sought to ensure that initial Tier 1 screening of pesticide inerts would focus on chemicals that involve a higher potential for human exposure because they are produced or imported in large amounts.

The Agency next reviewed existing data to identify HPV/inert chemicals that have been found to be present in human tissue, ecological tissues that have human food uses (e.g., fish tissues), drinking water, and/or indoor air. Under this approach, an HPV/inert chemical appearing in monitoring data from one or more of these media would be a higher priority for testing than an HPV/inert chemical that does not appear in monitoring data from any of the media.

Conceptual Approach to Chemical Selection

The next major step in developing the EDSP occurred a few years later, in September 2005, when EPA published its conceptual approach for selecting the first group of chemicals to be screened under the program.[6]

According to the published notice, the Agency would select 50 to 100 chemicals based on their relatively high potential for human exposure. EPA specified that it did not intend "to select substances it considers to be a low priority for early screening under the EDSP because they are anticipated to have low potential to cause endocrine disruption." The Agency also planned to exclude chemicals that were being used as "positive controls" for validating the EDSP screening assays.

The Agency's 2005 announcement was generally consistent with the proposed approach described in its December 2002 *Federal Register* notice.

Draft List of Chemicals for Tier 1 Screening

In June 2007, EPA described its priority-setting approach for choosing candidate chemicals.[7] The Agency also announced a draft list of 73 initial pesticide active ingredients and HPV/inerts to be considered for Tier 1 screening.[8]

EPA produced the draft list using the approach described in its September 2005 *Federal Register* notice. The list included chemicals that the Agency believed should be tested first, based upon each substance's exposure potential.

In creating the draft list, EPA analyzed data on exposure pathways for pesticide active ingredients and HPV/inert chemicals. Because there were a large number of chemicals on the candidate lists, EPA decided to establish priorities for selecting chemicals for initial screening. The Agency gave priority in the selection process to chemicals that appeared most often in the exposure pathway databases.

Tier 1 Screening Tests

The Tier 1 screening tests use a variety of endocrine test methods. These include estrogen and androgen receptor binding assays, steroidogenesis assays, aromatase assay, uterotrophic assay, Hershberger assay, pubertal assays, and fish reproductive screening.[9]

Final List of Tier 1 Screening Chemicals

In April 2009, EPA published its final list of the first group of chemicals that will be screened under the EDSP.[10] According to the published notice, the list includes chemicals that the Agency, "in its discretion, has decided should be tested first, based upon exposure potential."

The final list of initial chemicals for screening is shown in **Exhibit 1**. EPA deleted six chemicals that were included in the 2007 draft list. According to the April 2009 notice, the Agency removed two of the chemicals, azinphos-methyl and fenvalerate, because all uses of these pesticides have ended or will end before Tier 2 data can be generated in 2012. EPA removed four other chemicals (aldicarb, allethrin, dichlorvos, and methiocarb) based on reassessment of their uses. The reassessment confirmed that these chemicals are expected to be present in only two, instead of three, exposure pathways.

In separate notices, the Agency described other aspects of the EDSP, such as its revised policies and procedures for initial screening[11] and the final test guidelines.[12] EPA also announced that it was submitting an information collection request concerning the EDSP to the Office of Management and Budget for review.[13]

Testing Policies and Procedures

According to the notice explaining EPA's revised EDSP policies and procedures, the Agency generally intends to commence Tier 1 screening of the first group of pesticide chemicals by issuing test orders under section 408(p) of the Federal Food, Drug, and Cosmetic Act (FFDCA).

Test orders will be issued to pesticide registrants and/or to chemical companies that are identified as manufacturers or importers of the identified chemicals.[14] While it is unclear when test orders will be issued, the date could be as early as autumn 2009.

Revisions and Clarifications

EPA's revised policies and procedures include changes made in response to public comments submitted to the Agency regarding a draft version of its policies and procedures, which was published in December 2007.[15] The key changes and clarifications to the draft version include:

- modification of the response options for pesticide inert ingredients;
- establishment of a Pesticide Inert Ingredients Data Submitters and Suppliers List (PIIDSSL);
- announcement of the Agency's intent to issue "catch-up" orders for a period of 15 years after initial test orders are issued (these orders will be issued to parties who enter the market for particular chemicals after the initial test data on those chemicals have been submitted);
- clarification of the policies and statutory interpretations relating to pre-enforcement review and informal administrative review;
- clarification related to the citation or submission of other scientifically relevant information; and
- revised time and cost estimates for paperwork activities.[16]

EPA also made clear that, in order to address the more complex issues surrounding joint data development and the availability of data compensation and data protection, the Agency intends to issue some test orders jointly under FFDCA section 408(p)(5) and Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) section 3(c)(2)(B).

Test Orders: Initial Response Requirements

Each recipient of a test order will be 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 recipient can indicate that it:

- intends to generate new data;
- is submitting or citing existing data (including other scientifically relevant information);
- intends to form (or offer to form) a consortium to provide data;
- is not subject to the test order;
- intends to voluntarily cancel any pesticide registration to which the order relates;
- intends to reformulate its product or products to exclude the chemical;
- is claiming a formulator's exemption;
- 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;

- 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.[17]

According to EPA, this initial response "is intended to be used to report the recipient's commitment to act in response to the test order in one of several ways for each assay specified in the order." The recipient may indicate a different response commitment for each assay.[18]

The Agency states that test orders will include a "final submission" due date of 24 months after issuance of the order.[19]

EDSP Screening: Practical Implications and Key Issues

Implementation of the EDSP raises many issues for manufacturers, importers, and users of Tier 1 chemicals. A few key concerns are discussed below.

Responding to Tier 1 Test Orders

Recipients of any Tier 1 test order 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.

Generating new data invites uncertain results and can be very costly. If EPA requires new data (having determined that existing data are deficient), recipients of test orders will need to weigh the costs of testing against the benefits of continuing to produce the chemical that is the subject of the order. Stakeholders must keep in mind that forming testing consortia, negotiating cost-sharing agreements, developing data, and addressing and protecting data-compensation rights all take time and a great deal of attention.

If our collective history with FIFRA -- and newer experiences under the European Union's Registration, Evaluation, Authorization and Restriction of Chemicals (REACH) regulations -- tell us anything, it is that managing data rights and generating data jointly are activities that should not be undertaken lightly. They demand focus, along with significant legal and commercial expertise.

EPA's Duty to Minimize Duplicative Testing

Under FFDCA section 408(p)(5)(B), EPA is required to minimize duplicative testing. The Agency has responded to this mandate in part by promoting cost-sharing and rights to data compensation.

EPA's April 15, 2009 document on policies and procedures spells out how the Agency believes its policies promote the goal of reducing duplication in testing. One of the key policies in this respect is the option for test order recipients to cite or submit existing data in their initial responses. This option is available for any assay that EPA believes must be developed to assess whether a substance exhibits endocrine disruptor properties.

Despite the Agency's stated commitment to minimizing duplicative testing, some question whether EPA is doing as much as it could in this regard, noting in particular that that the Agency currently disallows use of the ToxCast™ predictive tool in lieu of validated assays. The ToxCast™ program was launched by EPA in 2007 "in order to develop a cost-effective approach for prioritizing the toxicity testing of large numbers of chemicals in a short period of time."[20]

While critics say that the Agency's policy on the use of ToxCast™ is inappropriate and inefficient, EPA believes that the tool is not yet sufficiently vetted to be used under the EDSP in lieu of actual testing. EPA has stated, however, that it "generally expects that the ToxCast predictive tool may also be considered on a case-by-case basis to inform the Tier I determination."

Tier 1 Screening Assays and Current State-of-the-Science

Over the years, there has been considerable controversy about whether the EDSP Tier 1 screening assays are scientifically defensible. Part of the criticism is based on FIFRA SAP comments provided in March 2008, in which the SAP stated that "several assays do not represent the current state of science, or the proposed screens do not fully address major modes of action and should be updated and extended as soon as possible."

In its response to a request to reconsider aspects of the EDSP, EPA stated that the SAP comment was merely an "acknowledgement that there is always room for improvement as science knowledge evolves." Because the state-of-the-science in this area is so new and is evolving rapidly, the controversy over the probative and scientific value of the Tier 1 screens is expected to continue.

Ensuring Reliability of the EDSP Screening Results

As noted, over the years EPA has been on the defensive regarding whether the EDSP assays are sufficiently reliable to screen for endocrine effects and confirm that particular substances present a significant risk to human health or the environment.

The Agency's SAP has endorsed the Tier 1 screening battery, and EPA interprets this endorsement as confirmation of its view that the screening tests will yield scientifically relevant and probative information. It is more likely than not, however, that conducting these assays and interpreting their results will prove challenging and controversial.

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 (SEPs).

EPA intends to provide opportunities for public comment on the SEPs. The Agency will also encourage review of the draft SEPs as part of a peer review process. The SEPs will not be publicly available in final form before EPA begins issuing test orders. According to the Agency, however, they will be available before any Tier 1-related decision is announced to the public.

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 the Agency will use to do so.

Managing the "Optics" of Screening Results

Not surprisingly, since the inception of the EDSP, industry stakeholders have been concerned about the implications of having their chemicals identified as a Tier 1 screening test substances. To its credit, EPA has consistently maintained -- and has explicitly noted in written statements -- 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 slated for screening are now (and will continue to be) 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.

Conclusion

The evolution of the EDSP has been an interesting and controversial journey. EPA's impending issuance of test orders for Tier 1 screening will mark a major milestone in the process. This step will force much hard thinking by test order recipients, who will have to decide on response and communication strategies.

Selecting the correct response option will require business savvy, technical finesse, and a clear understanding of the legal implications of each alternative. Failure to respond in a timely manner to a test order could result in serious consequences, including product suspension, administrative hearings, and fines and penalties.

In short, those who receive test orders will need to make careful decisions regarding how to respond to them. Moreover, all stakeholders who manufacture, import, process, or use any Tier 1 screening substance will have to take great care in managing communications and "optics" in this area.

Exhibit 1
Final List of Initial Chemicals for EDSP Screening

Chemical Name	CAS Number
2,4-D	94757
4,7-Methano-1H-isoindole-1,3(2H)-dione,2-(2-ethylhexyl)-3a,4,7,7a-tetrahydro-	113484
Abamectin	71751412
Acephate	30560191
Acetone	67641
Atrazine	1912249
Benfluralin	1861401
Bifenthrin	82657043
Butyl benzyl phthalate	85687
Captan	133062

Chemical Name	CAS Number
Carbamothioic acid, dipropyl-, S-ethyl ester	759944
Carbaryl	63252
Carbofuran	1563662
Chlorothalonil	1897456
Chlorpyrifos	2921882
Cyfluthrin	68359375
Cypermethrin	52315078
DCPA (or chlorthal-dimethyl)	1861321
Diazinon	333415
Dibutyl phthalate	84742
Dichlobenil	1194656
Dicofol	115322
Diethyl phthalate	84662
Dimethoate	60515
Dimethyl phthalate	131113
Di-sec-octyl phthalate	117817
Disulfoton	298044
Endosulfan	115297
Esfenvalerate	66230044
Ethoprop	13194484
Fenbutatin oxide	13356086
Flutolanil	66332965
Folpet	133073
Gardona (cis-isomer)	22248799
Glyphosate	1071836
Imidacloprid	138261413
Iprodione	36734197
Isophorone	78591
Linuron	330552
Malathion	121755
Metalaxyl	57837191
Methamidophos	10265926
Methidathion	950378
Methomyl	16752775
Methyl ethyl ketone	78933
Methyl parathion	298000
Metolachlor	51218452

Chemical Name	CAS Number
Metribuzin	21087649
Myclobutanil	88671890
Norflurazon	27314132
o-Phenylphenol	90437
Oxamyl	23135220
Permethrin	52645531
Phosmet	732116
Piperonyl butoxide	51036
Propachlor	1918167
Propargite	2312358
Propiconazole	60207901
Propyzamide	23950585
Pyridine, 2-(1-methyl-2-(4-phenoxyphenoxy)ethoxy)-	95737681
Quintozene	82688
Resmethrin	10453868
Simazine	122349
Tebuconazole	107534963
Toluene	108883
Triadimefon	43121433
Trifluralin	1582098

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Notes

[1] Final List of Initial Pesticide Active Ingredients and Pesticide Inert Ingredients to be Screened Under the Federal Food, Drug, and Cosmetic Act, 74 Fed. Reg. 17579 (April 15, 2009). More information is available at **http://www.epa.gov/scipoly/oscpendo/pubs/prioritysetting/index.htm**.

[2] See Endocrine Disruptor Screening and Testing Advisory Committee Final Report (August 1998). Available online at **http://www.epa.gov/endo/pubs/edspoverview/finalrpt.htm**.

[3] Endocrine Disruptor Screening Program; Proposed Statement of Policy. 63 Fed. Reg. 71542 (December 28, 1998).

[4] Endocrine Disruptor Screening Program; Establishment of an Endocrine Disruptor Methods Validation Subcommittee under the National Advisory Council for Environmental Policy and Technology; Request for Nominations for Membership. 66 Fed. Reg. 23022 (May 7, 2001).

[5] Endocrine Disruptor Screening Program, Proposed Chemical Selection Approach for Initial Round of Screening; Request for Comment. 67 Fed. Reg. 79611 (December 30, 2002).

[6] Endocrine Disruptor Screening Program; Chemical Selection Approach for Initial Round of Screening. 70 Fed. Reg. 56449 (September 27, 2005).

[7] Draft List of Initial Pesticide Active Ingredients and Pesticide Inerts to be Considered for Screening under the Federal Food, Drug, and Cosmetic Act. 72 Fed. Reg. 33486 (June 18, 2007).

[8] For additional discussion of the draft list, see Bergeson, L.L. (2007, winter). Washington watch: Building the endocrine disruptor screening program: EPA makes progress. Environmental Quality Management, 17(2), 71-80.

[9] For more information, see the EDSP Assay Status Table at **http://www.epa.gov/endo/pubs/assayvalidation/status.htm**.

[10] 74 Fed. Reg. at 17579.

[11] Endocrine Disruptor Screening Program; Policies and Procedures for Initial Screening. 74 Fed. Reg. 17560 (April 15, 2009).

[12] Final Test Guidelines; Notice of Availability of Several Revised Test Guidelines. 74 Fed. Reg. 17479 (April 15, 2009).

[13] Agency Information Collection Activities; Submission To OMB for Review and Approval; Comment Request; Tier 1 Screening of Certain Chemicals Under the Endocrine Disruptor Screening Program (EDSP). 74 Fed. Reg. 17477 (April 15, 2009).

[14] 74 Fed. Reg. at 17562.

[15] Endocrine Disruptor Screening Program (EDSP); Draft Policies and Procedures for Initial

Screening; Request for Comment. 72 Fed. Reg. 70842 (December 13, 2007).

[16] 74 Fed. Reg. at 17564-65.

[17] Ibid. at 17571-73.

[18] Ibid. at 17571.

[19] Ibid. at 17574.

[20] See the ToxCast™ Program web site at **http://www.epa.gov/ncct/toxcast/**.