

## TOXIC AND HAZARDOUS SUBSTANCES LITIGATION

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## Pesticide Chemicals and Endocrine Disruptor Allegations: An Update on the Environmental Protection Agency's Endocrine Disruptor Screening Program

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In April 2007, we discussed the Environmental Protection Agency's ("EPA's") Endocrine Disruptor Screening Program ("EDSP").<sup>1</sup> Endocrine Disruptors ("EDs") are those chemicals that allegedly interfere with and disrupt the normal signaling processes of the endogenous hormones at cell receptors. For example, an ED chemical, at low doses, supposedly can act as estrogen, androgen, or thyroid ("E, A, or T") and cause harmful human health effects. Pesticide chemicals, *i.e.*, chemical ingredients or components of pesticides, have emerged as the guinea pigs for EDSP as the program moves forward.<sup>2</sup> We now briefly examine EDSP's procedures and possible effects.<sup>3</sup>

### **EDSP Background**

Recently, EPA published an action notice that formally established the availability of the EDSP Tier 1 battery of assays ("assays") and protocols for conducting the assays.<sup>4</sup> EPA has selected an initial list of 67 pesticide chemicals<sup>5</sup> that manufacturers and industry users will have to examine.<sup>6</sup> The list of

chemicals has been selected on the basis of "exposure potential only." Therefore, according to EPA, "it should not be construed or characterized as a list of known or likely endocrine disruptors."<sup>7</sup>

Within EDSP, EPA has created a two-tier testing system to locate possible endocrine disrupting chemicals. Tier 1 testing protocols are designed to determine the potential of each substance to interact with E, A, or T. After receiving the results from the 67 chemicals chosen, EPA will determine the interaction with the E, A, or T systems based on the "weight of the evidence."<sup>8</sup>

Chemicals found to have a potential interaction with E, A, or T systems will proceed to Tier 2 testing.<sup>9</sup> Tier 2 testing will be designed to locate any specific adverse ED effects and distinguish between the effects on either the E, A, or T hormonal systems. However, EPA is careful to note that just because a substance passes through Tier 1 to Tier 2 does *not* mean that the substance is an ED.<sup>10</sup>

We previously stated that defense of alleged EDs lays not only in science, but also in public opinion and public fear.<sup>11</sup> Although the EDSP assays will not determine whether a pesticide chemical – or any other future

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<sup>1</sup> Berger, B. & Junk, M., *Endocrine Disruptors: The Potential Cloud of Manufacturer Toxic Tort Liability*, Defense Counsel J., 106-118 (April 2007).

<sup>2</sup> Most, but not all, of the chemicals are active ingredients as opposed to inert ingredients.

<sup>3</sup> In 1996, EDSP arose under statutory authorization found in 21 U.S.C. § 346a(p)(3), (5). Commonly known as the Federal Food, Drug and Cosmetic Act ("FFDCA") section 408(p)(3), the Congress directed EPA to "develop a screening program" to determine which substances may be EDs. 21 U.S.C. § 346a(p).

<sup>4</sup> Endocrine Disruptor Screening Program ("EDSP"), 74 Fed. Reg. 54,416, 54,416 (Oct. 21, 2009) (notice).

<sup>5</sup> Final List to be Screened Under the Federal Food, Drug, and Cosmetic Act ("Final List"), 74 Fed. Reg. 17,579, 17,583-585 (Apr. 15, 2009) (notice).

<sup>6</sup> The first 19 of the 67 chemicals to be tested are: 2,4-D, Acephate, Atrazine, Benfluralin, Chlorpyrifos, Chlorthal-Dimethyl (DCPA), Diazinon, Dimethoate, Disulfoton, Ethoprop, Fenbutatin oxide, Malathion, Methamidophos, Methidathion, Methyl parathion,

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Norflurazon, Phosmet, Propargite, and Tetrachlorvinphos/Gardona. See <http://www.epa.gov/endo/pubs/regaspects/testorders.htm> (last visited Nov. 12, 2009).

<sup>7</sup> <http://www.epa.gov/scipoly/oscp/endo/pubs/prioritysetting/finallist.html> (last visited Nov. 12, 2009).

<sup>8</sup> EDSP, 74 Fed. Reg. at 54,416.

<sup>9</sup> EPA is in the process of developing and validating Tier 2 tests.

<http://www.epa.gov/endo/pubs/assayvalidation/status.htm> (last visited Nov. 12, 2009).

<sup>10</sup> *Id.*

<sup>11</sup> Berger, B. & Junk, M., *Endocrine Disruptors: The Potential Cloud of Manufacturer Toxic Tort Liability*, Defense Counsel J., 112 (April 2007).

chemical group – actually works as an ED in human beings, public fears may nonetheless be inflamed as to chemicals that pass from Tier 1 to Tier 2. Manufacturers and industrial users of pesticide chemicals that are passed through to Tier 2 testing must prepare for potential litigation, even if public concerns lack an adequate scientific basis.

### The Assays

EPA “developed, standardized, and validated” a select battery of assays.<sup>12</sup> The assays are to serve “as gross screening devices”<sup>13</sup> to whittle down chemicals to those more likely to potentially act as EDs.<sup>14</sup> EDSP used a five-step assay validation process designed to “establish relevance and reliability.”<sup>15</sup> EDSP relevance means “the ability of an assay or endpoints within an assay to detect chemicals with the potential to interact with one or more of the E, A, or T hormonal systems, whereas reliability is the reproducibility of those results within and between or among laboratories.”<sup>16</sup> The 11 assays are meant to function as a unit “so that the limitations of one assay are offset by the strengths of another.”<sup>17</sup>

EPA adopted the five-step validation procedure from the Interagency Coordinating Committee for the Validation of Alternative

Methods (“ICCVAM”).<sup>18</sup> The first step is test development, where EPA prepared a Detailed Review Paper to explain the purpose, context, and “scientific basis upon which the assay’s protocol, endpoints, and relevance rest.”<sup>19</sup> Second, prevalidation involves refining, optimizing, and initially assessing the transferability and performance of the protocols.<sup>20</sup> Inter-laboratory validation follows, which includes conducting studies in independent laboratories to determine variability and check performance criteria.<sup>21</sup> Finally, peer review and regulatory acceptance conclude the five-step process.<sup>22</sup>

In order to acquire more data on each of the 67 pesticide chemicals chosen, EDSP requires manufactures and industrial users to perform their own assays. EPA has published a Sample Order which illustrates this process.<sup>23</sup> The Order lists the chemical to be tested and “requires” registrants of the pesticides containing the chemical “to submit certain data or otherwise respond” to EPA.<sup>24</sup> The Order further warns that EPA may issue a later Order requiring additional testing under EDSP’s Tier 2 testing.<sup>25</sup> The Tier 1 battery,

<sup>12</sup> EDSP, 74 Fed. Reg. at 54,416.

<sup>13</sup> Berger, B. & Junk, M., *Endocrine Disruptors: The Potential Cloud of Manufacturer Toxic Tort Liability*, Defense Counsel J., 116 (April 2007).

<sup>14</sup> EDSP, 74 Fed. Reg. 54,416-417.

<sup>15</sup> *Id.* at 54,417.

<sup>16</sup> *Id.*

<sup>17</sup> Validation of Screening & Testing Assay Protocols Proposed for EDSP (“VSTAPP”), DRAFT version 5.4, Environmental Protection Agency, 1-21, 6 (July 16, 2007) (available at [http://www.epa.gov/endo/pubs/edsp\\_validation\\_paper\\_v%205.4.pdf](http://www.epa.gov/endo/pubs/edsp_validation_paper_v%205.4.pdf) (last visited Nov. 12, 2009)).

<sup>18</sup> Available at

[http://iccvam.niehs.nih.gov/docs/about\\_docs/validate.pdf](http://iccvam.niehs.nih.gov/docs/about_docs/validate.pdf) (last visited Nov. 12, 2009). EPA also recognizes the future obstacles of this process with Tier 2 testing because ICCVAM was designed for *in vitro* assays.

See VSTAPP at 3.

<sup>19</sup> VSTAPP at 3.

<sup>20</sup> *Id.*

<sup>21</sup> *Id.*

<sup>22</sup> *Id.* at 4.

<sup>23</sup> Sample Order for Pesticide Registrants, 1-16 (“Sample Order”) (available at

[http://www.epa.gov/endo/pubs/sample\\_EDSP\\_Order\\_PAIs.pdf](http://www.epa.gov/endo/pubs/sample_EDSP_Order_PAIs.pdf) (last visited Nov. 12, 2009)). EPA has also published a Sample Order for Inert Ingredients (available at [http://www.epa.gov/endo/pubs/sample\\_EDSP\\_Order\\_Inerts.pdf](http://www.epa.gov/endo/pubs/sample_EDSP_Order_Inerts.pdf) (last visited Nov. 12, 2009)).

<sup>24</sup> *Id.* at 1.

<sup>25</sup> *Id.* at 3.

as described in the Order, contains 11 assays that the registrant must complete.

EPA has prepared a step-by-step laboratory protocol for each assay. Respondents must follow these 11 protocols or be in violation of EPA's Order.<sup>26</sup> Respondents are given a maximum of 24 months from the issuance of the order to submit data to EPA, and EPA requires interim status reports.<sup>27</sup> The following sections describe two of the 11 assays to provide examples of the kind of testing that EPA will rely upon.

### Amphibian Metamorphosis Assay

Respondents will have to complete the Amphibian Metamorphosis Assay ("AMA") as one of the 11 assays.<sup>28</sup> AMA involves the use of tadpoles to determine if chemicals affect the hypothalamic-pituitary-thyroid ("HPT") axis during metamorphosis, resulting in developmental effects.<sup>29</sup> The AMA serves as a "generalized vertebrate model" and provides evidence showing only the thyroid processes *may* be affected by the alleged chemical.<sup>30</sup> Thus, AMA does not confirm endocrine disruption.<sup>31</sup> In addition, AMA is the only assay in the battery that targets thyroid activity in animals "undergoing morphological development."<sup>32</sup> During

postembryonic development, T allegedly affects almost every tissue in an animal's body, and scientists created AMA to exploit T's role in metamorphosis.<sup>33</sup>

AMA protocol involves exposing *Xenopus laevis* tadpoles to at least three aqueous concentrations of a given chemical "and a dilution water control for 21 days."<sup>34</sup> AMA has three main endpoints: daily mortality, morphological conditions, and histology. Although peer reviewers found AMA relevant and appropriate, several limitations exist.<sup>35</sup> Some chemicals cannot be tested in aquatic systems, the sensitivity of the assay is not fully characterized, and non-thyroid toxicities may affect the results.<sup>36</sup>

The Organization of Economic Cooperation and Development ("OECD") suggests AMA is relevant to effects on the human T system because both amphibians and humans are vertebrates.<sup>37</sup> OECD claims that evolution has not noticeably altered the T systems in vertebrates, "and the underlying cellular and molecular pathways that control these processes are similar, if not identical."<sup>38</sup> Amphibians, and especially anurans like frogs, are a good "general model" from which to extrapolate T disruption.<sup>39</sup> However, compounds that disrupt T function and

<sup>26</sup> *Id.* at 5.

<sup>27</sup> *Id.* at 7.

<sup>28</sup> *Id.* at 3.

<sup>29</sup> *Id.*

<sup>30</sup> Appendix A1 – Amphibian Metamorphosis, Environmental Protection Agency ("App'x A1"), 36-38, 36 (available at [http://www.epa.gov/endo/pubs/ama\\_fs.pdf](http://www.epa.gov/endo/pubs/ama_fs.pdf) (last visited Nov. 12, 2009)).

<sup>31</sup> *Id.*

<sup>32</sup> Validation of the Amphibian Metamorphosis Assay as a Screen for Thyroid-Active Chemicals: Integrated Summary Report ("AMISR"), Organization of Economic Cooperation & Development, 1-95, 11 (Oct. 16, 2007) (available at

[http://www.epa.gov/endo/pubs/ama\\_isr.pdf](http://www.epa.gov/endo/pubs/ama_isr.pdf) (last visited Nov. 12, 2009)).

<sup>33</sup> *Id.*

<sup>34</sup> App'x A1 at 36.

<sup>35</sup> *Id.* at 38.

<sup>36</sup> *Id.*

<sup>37</sup> Detailed Review Paper on Amphibian Metamorphosis Assay for the Detection of Thyroid Active Substances ("DRP"), JT00172273, Organization for Economic Cooperation & Development, 1-106, 19 ¶5 (Oct. 22, 2004) (available at

[http://www.epa.gov/scipoly/oscp/endo/pubs/edmvac/occd\\_amphibian\\_drp.pdf](http://www.epa.gov/scipoly/oscp/endo/pubs/edmvac/occd_amphibian_drp.pdf) (last visited Nov. 12, 2009)).

<sup>38</sup> AMISR at 11.

<sup>39</sup> DRP at 19 ¶5.

regulation in tissues and in peripheral mechanisms differ from those in humans, *e.g.*, “[a]mphibian transthyretins (TTRs) . . . are T3 binding proteins, whereas mammalian TTRs are T4 binding proteins . . . thus . . . compounds that disrupt binding of T[] to TTR may differ between amphibians and mammals.”<sup>40</sup>

Although AMA may be appropriate to function as a gross screening assay, human extrapolation is unlikely. Under EPA’s Tier 1 guidelines, however, AMA need only show a potential for endocrine disruption to pass a chemical to Tier 2 testing.

Fish Short-term Reproduction Assay

EPA has also selected the Fish Short-term Reproduction Assay (“FSRA”) as one of the 11 assays in the Tier 1 battery. FSRA exposes mature fathead minnows to chemicals to determine if any interference with the hypothalamic-pituitary-gonadal (“HPG”) axis affects reproduction.<sup>41</sup> Like AMA, any results are merely “indicative” of possible endocrine disruption,<sup>42</sup> and “the assay is not intended to quantify or confirm endocrine disruption . . . .”<sup>43</sup>

In FSRA, at least three concentrations of a chemical are to be tested.<sup>44</sup> The assay’s key

endpoints include: fecundity, fertilization success, gonadal histopathology, appearance and secondary sex characteristics, and biochemical measures.<sup>45</sup> FSRA targets contaminants that might disturb any portion of “a complex environmental and endocrine signaling network” that “controls gametogenesis . . . [and] induces changes in external morphology (secondary sex characteristics) and behavior that result in spawning.”<sup>46</sup>

Some researchers contend that FSRA has the potential to apply to humans because the HPG axis has been relatively unchanged by evolution across vertebrates,<sup>47</sup> and thus FSRA can possibly locate EDs in other vertebrates.<sup>48</sup> However, major biological differences in reproduction exist between minnows and humans. For instance, contrary to human reproduction, minnows lay eggs and spawn about every three days.<sup>49</sup> FSRA therefore serves as only an “effective generalized” model to identify “chemicals that affect specific components of the vertebrate HPG axis.”<sup>50</sup>

**EDSP Effects on the Future of Pesticide Chemicals**

Going forward, the assays have the potential to negatively affect pesticide chemical manufacturers and industrial users. Upon completion of the assays, public awareness

<sup>40</sup> AMISR at 91.

<sup>41</sup> Appendix A6 – Fish Short-term Reproduction (“App’x A6”), Environmental Protection Agency, 46-48, 46 (available at [http://www.epa.gov/endo/pubs/fish\\_fs.pdf](http://www.epa.gov/endo/pubs/fish_fs.pdf) (last visited Nov. 12, 2009)).

<sup>42</sup> *Id.* at 47.

<sup>43</sup> Validation of the Fish Short-Term Reproduction Assay: Integrated Summary Report (“FISR”), Environmental Protection Agency Endocrine Disruptor Screening Program, 1-102, 11 (Dec. 15, 2007) (available at [http://www.epa.gov/endo/pubs/fish\\_assay\\_isr.pdf](http://www.epa.gov/endo/pubs/fish_assay_isr.pdf) (last visited Nov. 12, 2009)).

<sup>44</sup> App’x A6 at 46.

<sup>45</sup> *Id.*

<sup>46</sup> FISR at 11.

<sup>47</sup> Gerald T. Ankley & Rodney D. Johnson, *Small Fish Models for Identifying & Assessing the Effects of Endocrine-disrupting Chemicals*, 45 *ILAR J.* 4, 469-483, 469 (2004)(available at [http://www.epa.gov/scipoly/oscp/endo/pubs/edmvac/ankley\\_review.pdf](http://www.epa.gov/scipoly/oscp/endo/pubs/edmvac/ankley_review.pdf) (last visited Nov. 12, 2009)).

<sup>48</sup> *Id.* (“[M]uch of the basic molecular machinery involved in initiation of toxic responses is highly conserved across vertebrate species.”).

<sup>49</sup> *Id.* at 470, 475.

<sup>50</sup> *Id.* at 480.

groups may begin zealous campaigns to rid all products of a given chemical.

We have seen groups act similarly in the past. For instance, after the publication of *Our Stolen Future* in 1996, the authors created a website that tracks ED developments.<sup>51</sup> Lately, the site has focused on Bisphenol-A and phthalate, but an emphasis on pesticides may emerge if EDSP findings fall within the realm of “the cutting edge of science related to endocrine disruption.”<sup>52</sup>

Specific to pesticide chemicals, lawsuits involving EDSP have already been filed. Several years ago, individual plaintiffs along with organizations such as People for the Ethical Treatment of Animals brought suit challenging the alleged failure of the EPA to implement EDSP.<sup>53</sup> Plaintiffs alleged “that because the EPA has not implemented the [EDSP], the EPA has not restricted pesticide manufacturers and food producers from using dangerous pesticides which have endocrine-like effects.”<sup>54</sup> But plaintiffs’ claim ultimately failed because they lacked evidence that individual plaintiffs had suffered any injury in fact, *i.e.*, all plaintiffs lacked standing.<sup>55</sup>

With the launch of the assays, however, will plaintiffs soon have sufficient evidence to show an “injury in fact” sufficient

to create a case or controversy?<sup>56</sup> By February 2012, EPA will have compiled data from the assays. At that time or shortly thereafter, EPA will usher some of the 67 pesticide chemicals to Tier 2 ED testing. Although EPA has stated that merely entering Tier 2 testing does not mean a chemical is an ED, plaintiffs may not wait for the completion of Tier 2 programs.

Watchdog groups already monitor EDSP’s progress and will no doubt follow the assays’ results. *Beyond Pesticides* “works with allies in protecting public health and the environment to lead the transition to a world free of toxic pesticides.”<sup>57</sup> The group has closely followed EPA’s launch of the assays.<sup>58</sup> After the completion of the Tier 1 battery, *Beyond Pesticides* and similar groups may sway public opinion, and “the fear of liability may create intense pressure for companies using such chemicals to find alternatives quickly.”<sup>59</sup> *Beyond Pesticides*, *e.g.*, has recently reported that “bug bomb” foggers,<sup>60</sup> a product used as an in-home insecticide, may have killed a 10-month old boy.<sup>61</sup> According to *Beyond Pesticides*, “every death and injury caused by foggers must be attributed to [] the failure of EPA’s

<sup>51</sup> <http://www.ourstolenfuture.org> (“This website tracks the most recent [ED] developments.”) (last visited Nov. 12, 2009).

<sup>52</sup> <http://www.ourstolenfuture.org/Basics/about.htm> (last visited Nov. 12, 2009).

<sup>53</sup> *Physicians Committee for Responsible Med. v. U.S. Environ. Protection Agency*, No. C 05-04093 CRB, 2006 WL 3000657, \*3-4 (N.D. Cal. Oct. 20, 2006) (granting defendant’s motion for summary judgment because plaintiffs lacked standing), *aff’d*, 292 F. App’x 543 (9th Cir. 2008).

<sup>54</sup> *Id.* at \*4.

<sup>55</sup> *Id.* at \*4-7 (noting evidence was insufficient to show pesticides substantially likely to harm plaintiffs).

<sup>56</sup> See generally *Friends of the Earth v. Laidlaw*, 528 U.S. 167, 180-81 (2000).

<sup>57</sup> <http://www.beyondpesticides.org/about/mission.htm> (last visited Nov. 12, 2009).

<sup>58</sup> <http://www.beyondpesticides.org/dailynewsblog/?p=2577> (linking to news article discussing EPA’s Tier 1 battery of assays) (last visited Nov. 12, 2009).

<sup>59</sup> Berger, B. & Junk, M., *Endocrine Disruptors: The Potential Cloud of Manufacturer Toxic Tort Liability*, Defense Counsel J., 112 (April 2007).

<sup>60</sup> Foggers contain the chemicals pyrethrins, permethrin, and methoprene. See <http://www.epa.gov/kidshometour/products/fogger.htm> (last visited Nov. 12, 2009). Permethrin is one of the 67 chemicals in the Tier 1 battery of assays. See Final List, 74 Fed. Reg. at 17,584.

<sup>61</sup> <http://www.beyondpesticides.org/dailynewsblog/?p=2652> (last visited Nov. 12, 2009).

regulatory system to take an unnecessary and ineffective product off the market.”<sup>62</sup>

While much is yet unknown, EPA plans to issue Orders, like the Sample discussed above, within the next few months.<sup>63</sup> Thus, by February 2012, steps will have been taken to characterize chemicals as ED’s at a very basic level that may have no relevance whatsoever to human beings. Or, the Tier 1 results may be used by plaintiffs’ counsel in an effort to substantiate claims like those made by *Beyond Pesticides*. We will continue to follow developments.

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<sup>62</sup> *Id.*

<sup>63</sup> Press release, Environmental Protection Agency (EPA), EPA Orders Chemical Testing for Hormone Effects (Oct. 29, 2009) (available at <http://yosemite.epa.gov/opa/admpress.nsf/a543211f64e4d1998525735900404442/d60590e519ce3c2e8525765e0053f331!OpenDocument> (last visited Nov. 12, 2009)).



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