

ENDOCRINE POLICY FORUM

Endocrine Policy Forum Frequently Asked Questions about Endocrine Disruptors

General Background on Endocrine Disruption

Why all the talk about endocrine disruptors?

In response to public concern that certain environmental chemicals may interfere with endocrine processes in humans, the U.S. Congress passed the Food Quality Protection Act and amendments to the Safe Drinking Water Act in 1996. These laws directed the US EPA to develop and implement a program to investigate the potential for substances to cause adverse health effects through endocrine pathways.

What are endocrine disruptors?

In 2002, the World Health Organization (WHO) along with the International Programme on Chemical Safety (IPCS) proposed the following definition of an endocrine disruptor (ED):

An endocrine disruptor is an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub)populations.

This internationally accepted definition of an ED has two very important pieces; first, that the substance alters the function of the hormonal system and second, by doing so causes an adverse effect (*i.e.* toxicity). The likelihood that an ED will cause harmful effects is based on its potency (how active it is) and potential for exposure (dosage, frequency, and duration). The definition is important so as not to confuse “endocrine effects” with “endocrine disruption,” with the latter term being linked to adverse effects.

Why make a distinction between endocrine effects and disruption?

A precise definition is important because the majority of the substances that may interact with the endocrine system result in effects that are harmless, or in some cases, even essential to our well-being. There are terms that are becoming popularized in media reports mislabeling many chemicals as “Endocrine Disrupting Chemicals” or “EDCs” when in fact scientific study is still underway or not supportive of such labels. From a regulatory policy and scientific perspective, it is important to focus on those substances that have a real potential to cause harm to people or the environment.

Shouldn't we be concerned about any endocrine or hormone changes?

The endocrine system naturally responds to exposures from our environment, both chemical and physical. In the case of chemical exposures, the endocrine system responds to both natural (e.g.,

food) and synthetic sources of chemicals. For example, a change in temperature, food, or daylight can affect the level of hormones circulating through our body. Most of these changes are harmless and necessary to allow our bodies to adjust to an ever changing environment as we undertake our normal daily activities.

Don't synthetic chemicals pose more of a threat than natural substances?

It is a common misunderstanding to assume a synthetic chemical is more hazardous than a natural one. At the molecular level – where chemical interactions occur – the body does not differentiate between natural and synthetic substances with respect to potential effects.

Are you suggesting we don't need to worry about substances that affect our hormones?

No, but we shouldn't misinterpret the significance of endocrine effects, either. The biological activity of any substance can be good, bad or indifferent. Hormonal activity by itself does not imply a health risk to a living organism, unless it can be shown to lead to harmful effects.

How then do we know if something is likely to be a true endocrine disruptor?

That's why a comprehensive testing approach, such as EPA's Endocrine Disruptor Screening Program (EDSP), is so important in determining the true potential of a substance to act as an endocrine disruptor. And it is also the reason why we support the EPA's weight of evidence reports, which help provide a meaningful regulatory framework to make this determination moving forward.

The US EPA Endocrine Disruptor Screening Program (EDSP)

In 1996, the Food Quality Protection Act (FQPA) and the Safe Drinking Water Act (SDWA) directed EPA to develop and implement a screening program to determine whether certain substances can have an estrogenic effect in humans. Why has it taken EPA so long to implement the EDSP?

After the laws were passed, in response to extensive public input EPA developed a comprehensive endocrine screening and testing program (the EDSP) to screen both pesticide and non-pesticide chemicals for potential estrogen, androgen and thyroid effects in humans and wildlife. EPA then initiated an extensive research and development program, composed of both basic and applied research, to develop, standardize and validate a series of specialized endocrine screens and test methods. At the time the legislation was enacted, there existed no reliable screening assays (laboratory tests) to determine endocrine activity or endocrine disruption. Congress mandated that EPA use validated tests. Validation, while scientifically and legally necessary, is an exacting and time consuming process. EPA has expended over \$100 million dollars since 1996 for both applied and basic research. These research and program funds were used by EPA to provide a better scientific foundation for evaluating potential endocrine-mediated effects and to conduct the lab studies needed to assure establishment by the Agency of scientific, validated methods.

Does inclusion on EPA's List 1 mean all of those chemicals are endocrine disruptors?

No, the selection criteria for the 67 chemicals on List 1 for Tier 1 screening in EPA's EDSP was not based on the potential to cause endocrine effects, but instead was based on the potential

exposure to the chemical in at least three of the four designated pathways (food, water, residential, and occupational). The fact that the chemicals on List 1 are pesticide chemicals simply reflects the Congressional mandate that EPA screen pesticide chemicals. Congress also provided EPA the discretion, under the SDWA, to require endocrine screening of certain non-pesticide chemicals. EPA has exercised its authority to include non-pesticide chemicals on its List 2.

Does inclusion on EPA’s List 2 mean these chemicals are endocrine disruptors?

EPA’s revised List 2 includes 109 chemicals for Tier 1 screening. Similar to List 1, candidates on List 2 were selected not because of their potential to interfere with the endocrine systems of humans or other species, but because of their possible presence in public drinking water and/or, in the case of pesticides, their registration review status within EPA.

I recognize the names of some of the chemicals on EPA’s EDSP List 1 and List 2. Does that mean these chemicals are endocrine disruptors? Should I be concerned?

No, you should not be concerned. The listing of any substance on List 1 or List 2 was not based on any potential to cause effects on the endocrine system of humans or other species. As EPA states on its [website](#), “[t]he public should not presume the listing of a chemical or substance indicates it interferes with the endocrine systems of humans or other species simply because it has been listed for screening under the EDSP. EPA believes that these chemicals or substances should be candidates, at least for screening purposes, under EDSP based only on their pesticide registration status and/or because such substances may occur in sources of drinking water to which a substantial population may be exposed.”

How do we test chemicals to determine whether they are endocrine disruptors?

Considerable information concerning the potential of a substance to interact with the endocrine system is currently available from standard toxicity studies conducted as part of product safety testing. In addition, the US EPA has developed a two-tier screening and testing approach aimed at identifying the ability of chemicals to interact with the endocrine systems of mammals, birds, fish, and frogs, and to determine whether a substance could cause harm to humans or the environment. Only those substances that are identified as having potential endocrine activity in the first tier will be advanced for further testing in the second tier and would undergo dose-response evaluations for endocrine disruption prior to assessing risk.

What’s involved in Tier 1 screening?

Tier 1 is a battery of screening assays used to identify chemicals that can *potentially interact* with the endocrine system. Because they are designed to be highly sensitive, Tier 1 screens may generate “false positive” results and, therefore, need to be interpreted together to determine if the substance has the potential to interact with the endocrine system. To conduct a full battery of Tier 1 screens on a single compound can take more than two years and exceed one million dollars in cost.

Do effects observed in Tier 1 screens indicate a substance is an endocrine disruptor?

Screening tests are useful indicators of a substance’s potential to interact with the endocrine system, but they do not predict a substance’s ability to cause harm to a living organism. These latter effects can only be determined in higher tiered animal studies.

What's involved in Tier 2 testing?

Tier 2 testing is a higher level of study that involves evaluations of several different animal species and uses more concentrations of the substance than was evaluated in Tier 1. Using more concentrations in the test design allows for a better characterization of the dose-response relationship in Tier 2. The Tier 2 tests include measurements that are focused on general toxicity responses and also measurements that are more specific to endocrine activity. The Tier 2 tests are longer in duration and cover multiple life-stages and some of these tests monitor the test species through multiple generations. The intent of these tests is to evaluate potential harmful effects in whole animals and establish dose-response relationships that will be used to assess risk to humans and the environment.

What is EPA doing to increase its ability to evaluate further substances in the EDSP?

On June 18, EPA [announced](#) a plan to introduce an alternative high throughput screening (HTS) approach to screen chemicals for their ability to interact with the endocrine system. The HTS assays will replace some of the current Tier 1 battery tests and provide greater reliability. The HTS system has already been evaluated on more than 1800 chemicals. EPA has been actively coordinating with other government agencies, industry and environmental groups in the development of these methods. Implementing this new methodology will accelerate the pace of screening, decrease costs, and reduce the need for animal testing.

There have been complaints that industry frequently asks to delay the program. What is industry's issue with the EDSP?

Industry supports EPA's efforts to test chemicals for potential endocrine effects and to manage endocrine-related risks. Indeed, the chemical industry takes the issue of endocrine disruption very seriously and has no desire to delay EPA's program. We support and contribute to the transparent peer-review EPA has established for vetting new science policy and the research efforts to develop and improve the EDSP. Sometimes these efforts are time-consuming, but the science is improved by multi-stakeholder participation. Industry's goal is to have an EDSP that can generate meaningful results that will inform EPA's risk management (i.e., regulatory) decisions.

EPA's Release of the List 1 Weight of Evidence (WoE) Evaluations

Could you describe exactly what has been recently released by EPA in regards to the List 1 chemicals?

EPA recently released its *Tier 1 Weight-of-Evidence* evaluation reports for each of the supported "List 1" chemicals, as part of its long-standing Endocrine Disruptor Screening Program to screen certain chemicals subject to the Food Quality Protection Act (FQPA) and the Safe Drinking Water Act (SDWA) for potential interactions with the endocrine system.

What does "Weight of Evidence" mean?

EPA refers to a weight of evidence approach as the process for characterizing the extent to which the available data support a hypothesis that an agent causes a particular effect (USEPA 1999; 2002a; 2005). Because of the normal variability inherent in complex biological systems resulting in variability in assay results, a single test may not reveal the true potential of a substance to

cause endocrine effects. To overcome this challenge, researchers use multiple studies to assess if cause-and-effect relationships can be established within an assay and the Tier 1 battery. Weight of evidence decisions do not involve a simple tally of positive and negative studies, but rely on professional judgment to integrate all of the results to form a meaningful conclusion.

What is a Weight of Evidence report?

A WoE report is a narrative or characterization that typically accompanies the detailed analysis of the individual studies and the analysis of multiple lines of evidence. The EDSP WoE report is intended to be transparent and allow the reader to clearly understand the reasoning behind the conclusions as to whether there is sufficient evidence to indicate that a substance has the potential to interact with one or more components of the endocrine system and if Tier 2 testing is needed.

What are the possible Weight of Evidence outcomes?

Based on EPA's weight of evidence guidance, the Agency may conclude that the available information does not suggest any potential for endocrine activity and no further testing is needed, or it may determine there are still uncertainties and a targeted study is needed to identify whether there is a potential for activity. EPA may also conclude that there is the potential for interaction with a hormone pathway and that specific Tier 2 studies are needed. The weight of evidence report explains the basis of the conclusions that are reached by EPA.

How does an individual Tier 1 assay relate to the overall Weight of Evidence?

Generally, a single assay cannot determine whether a substance can interact with the endocrine system. The Tier 1 battery was developed understanding the strengths and weakness of each individual assay. The 11 Tier 1 assays have been combined in a manner such that "limitations of one assay are complemented by the strengths of another" (EDSTAC, 1998). Each Tier 1 assay provides information for the weight of evidence but the outcome of each individual assay cannot be considered in isolation. Thus, in order to determine if a test substance has the **potential** to interact with hormone systems, a WoE evaluation of all Tier 1 assay results in combination with findings reported in other toxicity studies (referred to as Other Scientifically Relevant Information or OSRI) is performed.

What's the practical significance of EPA's reports regarding the use of the pesticides discussed in those reports?

It is critical that regulatory decisions impacting the use of important crop protection products are based on a comprehensive risk assessment process that helps preserve our food supply without jeopardizing the health of people, wildlife or the environment. The Tier 1 Weight of Evidence reports may identify substances of potential concern that will undergo further evaluation to arrive at risk based decisions on whether reductions in exposure to humans or wildlife are necessary.

Tier 1 Test Orders for List 1 were issued in 2009 and most data was submitted by the end of 2012. Why has it taken EPA so long to complete this stage of the program for List 1?

First, EPA needed time to review the substantial volume of "other scientifically relevant information" submitted by test order recipients to satisfy selected screening assays. Then, there was significant time and resources invested by industry in generating new data, along with delays resulting from the limited laboratory capacity for conducting many of the Tier 1 assays

and corresponding time extension requests. Finally, the Agency has been conducting a scientifically rigorous review of all of the data available for each substance, focusing on the performance of each assay and the performance of the combined Tier 1 battery, as it developed its WoE assessments. The review of the initial List 1 chemicals has imposed significant burdens on test order recipients and the Agency, but it was necessary to ensure scientifically robust and transparent assessments.

EPA's Decisions

What did EPA conclude in the Weight of Evidence reports for the 52 List 1 chemicals?

Of the 52 chemicals evaluated from List 1 of the EDSP, there was no evidence for potential interaction with any of the endocrine pathways for 20 chemicals. Fourteen chemicals showed potential interaction with one or more pathways; however, EPA decided that there was already sufficient information available to conclude that they do not pose a risk. Of the remaining 18 chemicals, all 18 showed potential interaction with the thyroid pathway, 17 of them with the androgen pathway, and 14 also potentially interacted with the estrogen pathway. In reaching its WoE conclusions, the Agency compared the dose of a chemical required to elicit a response in the EDSP Tier 1 assays to the dose level currently used by the Agency to evaluate risks of adverse effects from chemical exposure. The comparison allowed the Agency to determine whether further testing could alter its risk assessment conclusions for each chemical. This helps to ensure consistency of the process and enables EPA to make informed decisions regarding the need for further analysis of the List 1 chemicals.

Why is further testing not required for some substances that induced effects in one or more of the Tier 1 assays?

Weight of evidence decisions are not a simple tally of positive and negative results from the screens, but rely on professional scientific judgment to integrate all of the results to form a meaningful conclusion. The Tier 1 battery was purposely designed to make it more likely to produce *false positive* results instead of *false negative* results. Using a weight of evidence approach ensures the results of a single assay cannot be misconstrued or considered in isolation from other assays in the full battery of tests.

How can we be sure EPA did a thorough job in its Weight of Evidence (WoE) evaluations since so few List 1 chemicals need higher tier data?

EPA's WoE evaluations concern the pesticide chemicals which comprised List 1. For many years, regulatory requirements for pesticides have required extensive data demonstrating a lack of risk for adverse effects on reproduction, development, behavior, and other outcomes that could possibly be due to an endocrine effect, so it is not surprising that the results of Tier 1 have not raised new concerns about pesticides. It's important to remember that EPA did not select List 1 chemicals because it thought those chemicals might have endocrine activity. Rather, Congress in the Food Quality Protection Act of 1996 required EPA to screen pesticide chemicals. Then certain pesticides were included in List 1 because they are used commonly and they could be found in at least three of four designated exposure pathways (food, water, residential, and occupational). EPA has substantial toxicology data for these chemicals which allows the Agency to verify the results of Tier 1.

How can we trust EPA's conclusions when the Tier 1 battery contains only 11 screening assays?

EPA's Weight of Evidence evaluations included results of all Tier 1 assays in addition to existing regulatory safety testing data and relevant peer-reviewed literature results. The majority of substances selected by EPA for List 1 are pesticides and these substances have been evaluated, as required by EPA for pesticide registration, in a broad array of safety studies that include evaluation of the endocrine system. The results of these studies assist in validating the results of the Tier 1 screening program.

How do we know that List 1 pesticides identified as having the potential for endocrine activity are safe (of low concern) and can remain on the market while more data are being developed?

Before registering a pesticide, EPA must first ensure that the pesticide, when used according to label directions, can be used with a reasonable certainty of no harm to human health and without posing unreasonable risks to the environment. To make such determinations, EPA requires more than 100 different scientific studies and tests. As part of the WoE, EPA examined the existing data and considered whether the results from the Tier 1 screens along with other available information are consistent with the chemical's current risk assessment. If EPA had any concern given its understanding of the potential for hormone pathway interaction, it would have taken appropriate actions with the registrant(s) to mitigate any unacceptable risk.

Other than through the EDSP, does EPA currently evaluate pesticides for endocrine-related endpoints?

A pesticide undergoes extensive testing prior to registration, accumulating a diverse database that allows EPA to integrate all of the research in order to evaluate its human and environmental safety. Additionally, all pesticides must undergo a re-registration review every 15 years to ensure that tests are conducted according to the latest scientific standards. Current pesticide testing includes evaluation of numerous endocrine endpoints and sensitive life stages, thus EPA has been evaluating potential endocrine impacts as part of its normal registration process.

I have a customer/trade association member/farmer friend who is afraid to use any pesticide that EPA had determined needs more data because he hears there are food companies who are going to blacklist any List 1 endocrine active compounds. What can we do?

Please ask him/her to provide us more details and we will work to clarify the situation and try to resolve any concerns.

European vs. EPA's Endocrine Disruptor Regulatory Process

What impact could EPA's decisions on Tier 1 assays have in Europe?

The EPA has made it clear from the beginning of the EDSP that the Tier 1 assays are only meant to identify chemicals with the potential to interact with the endocrine system. There should be no reason for the EU to take any actions based on EPA's Tier 1 decisions.

What are the differences between European and U.S. regulators on endocrine disruption?

Although both regions work to harmonize the tools they use to reach regulatory decisions, the key difference lies in the regulatory decision-making policies and approaches. EPA uses a risk-based model, while European regulators currently intend to use a hazard-based approach. Modern risk assessment relies on hazard (toxicity) and exposure to assess a product's potential to cause adverse effects. By focusing on only one measure (hazard), in our view European regulators will not appropriately characterize a product's potential to cause harm. In any event, Tier 1 provides only an indication of a potential for an endocrine interaction and cannot be the sole consideration for conducting risk assessments. Likewise, Tier 1 data do not determine endocrine hazard and are not adequate to inform a hazard-based approach. While a risk-based approach is more scientifically supportable, neither approach can be undertaken until Tier 2 – type data are available.

Could you explain the difference between hazard and risk?

Risk is the combination of hazard and exposure. *Hazard*, or toxicity, represents the innate potential of a substance to cause harm (i.e., an adverse effect). *Exposure* provides context to the risk equation by assessing the likelihood that an organism will be exposed to a sufficient dose to result in harm. For example, the chemical sodium fluoride can be toxic to humans, but we use it extensively in toothpaste to protect our teeth because the dose is well below any level that could cause harm. Incorporating exposure is an essential element of risk assessment and adds balance to regulatory decision-making. Regulating based only on hazard may lead to unnecessary action to ban or limit useful and necessary chemicals, which, in turn, may lead to unnecessary and unintended consequences for human health, the environment, and/or the economy.

What does a hazard-based approach mean in terms of regulating endocrine disruptors?

If regulators were to apply an arbitrary cut-off restriction to products based only on simple screening assays, many of them would be listed as endocrine disruptors, when they are not.

Is it not more prudent for EPA to take a precautionary (hazard-based) approach when it comes to regulating chemicals?

Significant precautions are already considered during the EPA risk-based evaluation process and regulatory decisions always lean toward protecting human health and the environment. An overreliance on precaution can inhibit innovation and prevent useful new technologies from entering the marketplace or, in the case of pesticides, eliminate valuable tools for farmers without actually reducing risk.

Are there other possible downsides to the EU's precautionary approach?

The Obama administration has argued that regulating products on the basis of hazard alone, could impact U.S. exports to Europe by \$5 billion annually. Moreover, relying on precaution without considering risk creates a real potential for policy inconsistencies. For example, coffee, garlic and apples all contain naturally occurring substance that can have endocrine activity, yet no one is arguing that these exposures represent a threat to human health.