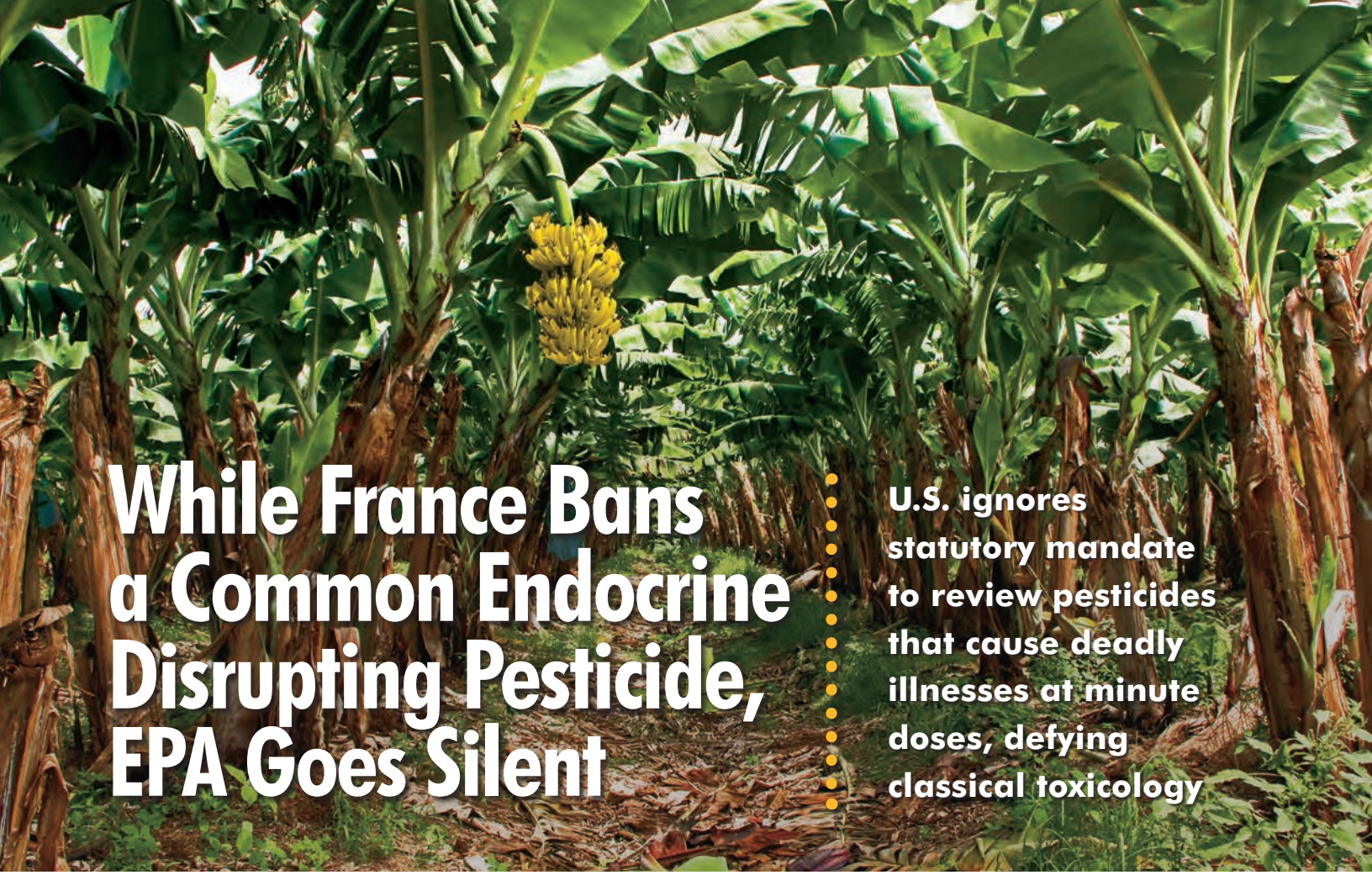


While France Bans a Common Endocrine Disrupting Pesticide, EPA Goes Silent

U.S. ignores statutory mandate to review pesticides that cause deadly illnesses at minute doses, defying classical toxicology

France's Agency for Food, Environmental and Occupational Health and Safety, ANSES, announced in May a ban on the sale of epoxiconazole, a triazole fungicide commonly used on crops such as bananas, coffee, grains, and beetroot. The ban means that all epoxiconazole products must be removed from commerce within 12 months. The agency indicated that it regards epoxiconazole as a danger to human health, as a likely carcinogen that also affects reproductive function through its endocrine disrupting impacts—risks that are well established. Such threats to human health and to critical ecological and biological systems posed by the use of toxic chemicals are the reasons Beyond Pesticides insists that in the U.S. a far more precautionary approach is needed to the management of pests, whether fungi or insects or plant diseases—there are safer alternative practices and products available.

THE CONCERN ABOUT ENDOCRINE DISRUPTORS

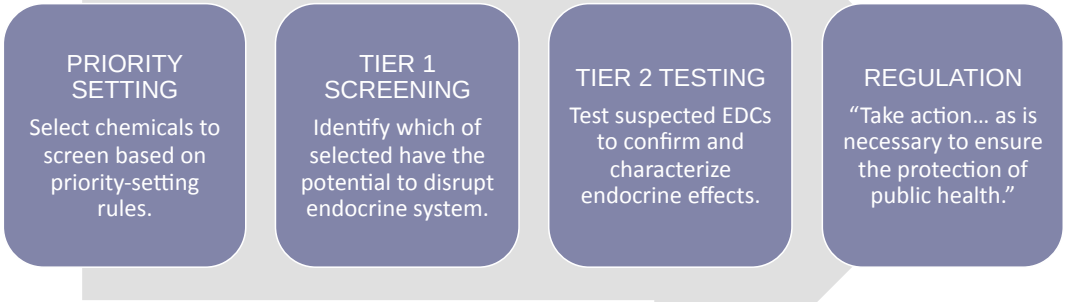
Endocrine disruptors are chemicals that can, even at low exposure levels, disrupt normal hormonal (endocrine) function. Such endocrine disrupting compounds (EDC) include many pesticides, exposures to which have been linked to infertility and other reproductive disorders, diabetes, cardiovascular disease, obesity, and early puberty, as well as attention deficit hyperactivity disorder (ADHD), Parkinson's, Alzheimer's, and childhood and adult cancers. The U.S. Environmental Protection Agency (EPA) and its Endocrine Disruptor Screening Program (EDSP) began, then virtually stopped, its review and regulation of endocrine disrupting pesticides, despite a mandate in the 1996 *Food Quality Protection Act* (FQPA) to develop a screening program within two years and then begin regulating.

Epoxiconazole is not registered for agricultural use in the U.S., but EPA, which is responsible for registering (i.e., allowing the use of) pesticides, has established a pesticide tolerance for it in the commonly imported crops coffee and bananas. (An EPA tolerance is the maximum amount of a pesticide residue EPA decides may be allowed to remain in or on a food.) In addition to epoxiconazole, there are a host of other triazole fungicides for which EPA has established tolerances (e.g., cyproconazole, fenbuconazole, flutriafol, metconazole, myclobutanil, propiconazole, tebuconazole, and tetraconazole), and many are registered for use in the U.S.

ANSES managing director Caroline Semaille noted that ANSES focused on epoxiconazole because of its ubiquity in French agriculture, but that the agency will examine other pesticide compounds in the context of the European Union guidelines. Ms. Semaille also commented, "A guide published in June 2018 at the European level set scientific criteria to say whether an active substance is an endocrine disruptor. On the basis of the new guide, we can establish and confirm that [epoxiconazole] is an endocrine disruptor."

FIGURE 1

Endocrine Disruptor Screening Program (EDSP) Stages



Tier 2 testing and regulatory action has never been completed by the U.S. Environmental Protection Agency.

TRIAZOLE FUNGICIDES KNOWN TO DISRUPT THE ENDOCRINE SYSTEM

The triazoles are part of a class of demethylation inhibitors (DMI). This, of course, is not new to EPA. In fact, a U.S. Geological Survey report, *Toxicity, Sublethal Effects, and Potential Modes of Action of Select Fungicides on Freshwater Fish and Invertebrates,* cited the scientific literature in its report in 2012 (updated 2014) that finds endocrine disrupting effects associated with the DMI class of fungicides. The report states: "Imidazoles, triazoles, and the pyrimidine fungicide fenarimol belong to the cytochrome P450-de-methylase inhibiting (DMI) class of fungicides, but disrupt other CYP450s, such as aromatase (CYP19) in both mammals and fish, indicating endocrine disruptive action is associated with DMI fungicides (Ankley and others, 2005). . . ."[1]

WHAT DOES THE LAW REQUIRE?

FQPA mandates that EPA (working with Department of Health and Human Services and the Food and Drug Administration) evaluate pesticides for their endocrine disrupting properties. In the authorities, standards, and tolerance section of the law, FQPA states, "In establishing, modifying, leaving in effect, or revoking a tolerance or exemption for a pesticide chemical residue, the Administrator shall consider, among other relevant factors—such information as the Administrator may require on whether the pesticide chemical may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen or other endocrine effects."[2] More broadly, the law calls for EPA's program to conduct screening of pesticides and "any other substance that may have an effect cumulative to an effect of a pesticide chemical if . . . a substantial population may be exposed to such substance." If such effects are found, the law states, "[T]he Administrator shall, as appropriate, take action under such statutory authority . . . as is necessary to ensure the protection of public health."

Despite the FQPA mandate, EPA missed the statutory deadline to develop a screening program by 1998 and complete implementation of a plan by August 1999. In its 1999 progress report, EPA said, "[T]he Endocrine Disruptors Screening and Testing Advisory Committee (EDSTAC) was formed to help us develop a process for determining which chemicals might potentially disrupt the hormone (endocrine) systems of humans and wildlife. EDSTAC reached consensus on recommendations in August 1998 and those recommendations, considered in combination with public comments, are helping EPA develop a final endocrine disruptor effects screening program."

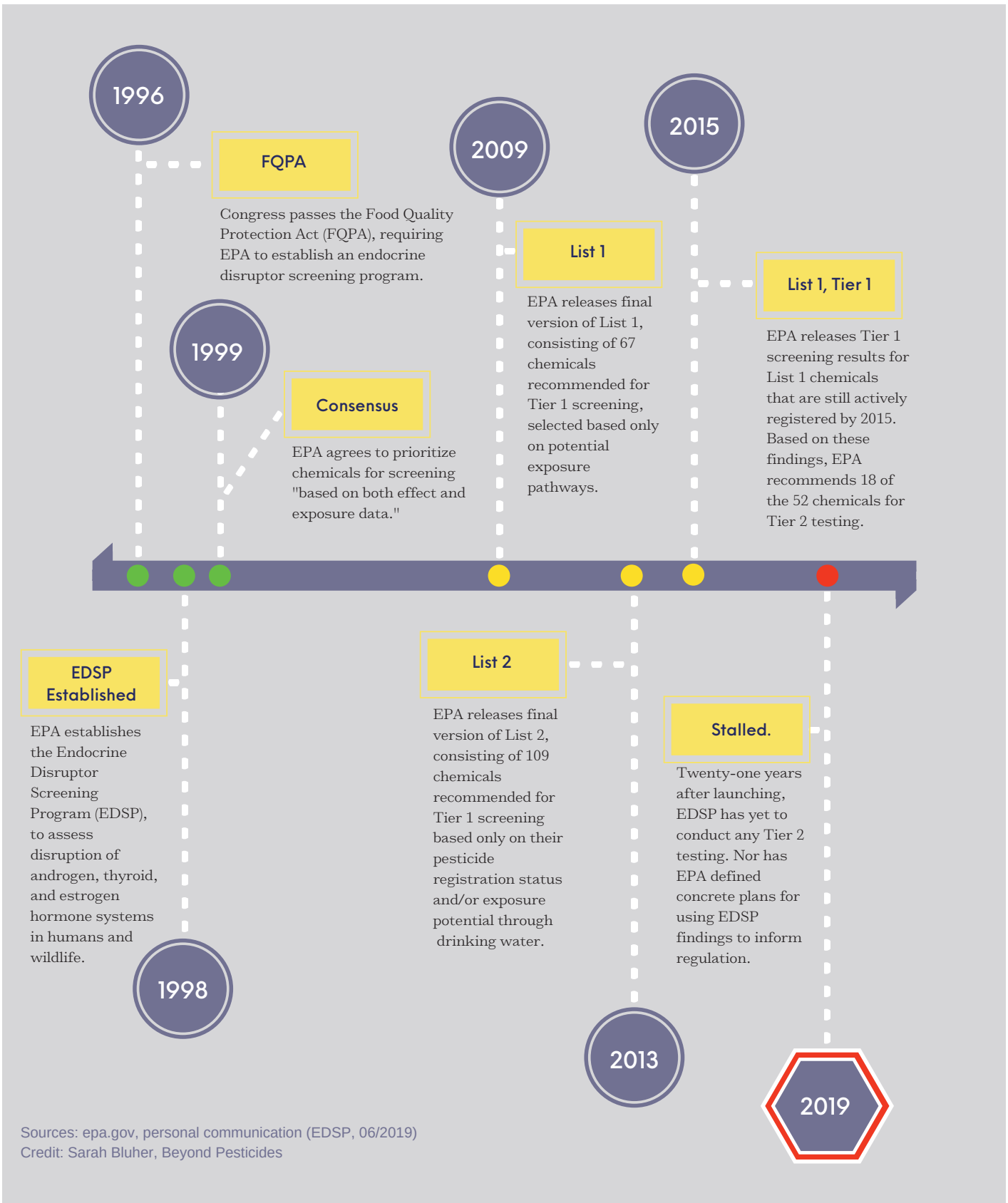
HOW DOES EPA SCREEN AND TEST CHEMICALS?

The screening and testing protocol established by EPA, with input from EDSTAC, begins with priority setting. Of the more than 87,000 pesticide chemicals that could possibly be screened, EDSP attempts to select subsets for screening based on certain priority-setting rules. Early on in the program's development, EPA's EDSTAC recommended a process of priority-setting for selecting chemicals to be screened, "based on *both effect and exposure* data following guidance in NRC [National Research Council/National Academy of Sciences] and EPA risk assessment literature."[3] A 1999 EPA advisory committee report states, "The greatest weight should be given to chemicals for which we have data that indicates actual human or environmental exposure and effects." Yet, when EPA made its selections for screening, titled List 1 and List 2, only registration status and exposure data were considered as prioritization factors. Lists 1 and 2 were both defined without using any available information on actual endocrine disrupting effects.

The Tier 1 Screening Battery is "designed to detect a substance's *potential* for causing disruption in one or more of the three hormone systems . . . estrogen, androgen, and thyroid."

FIGURE 2

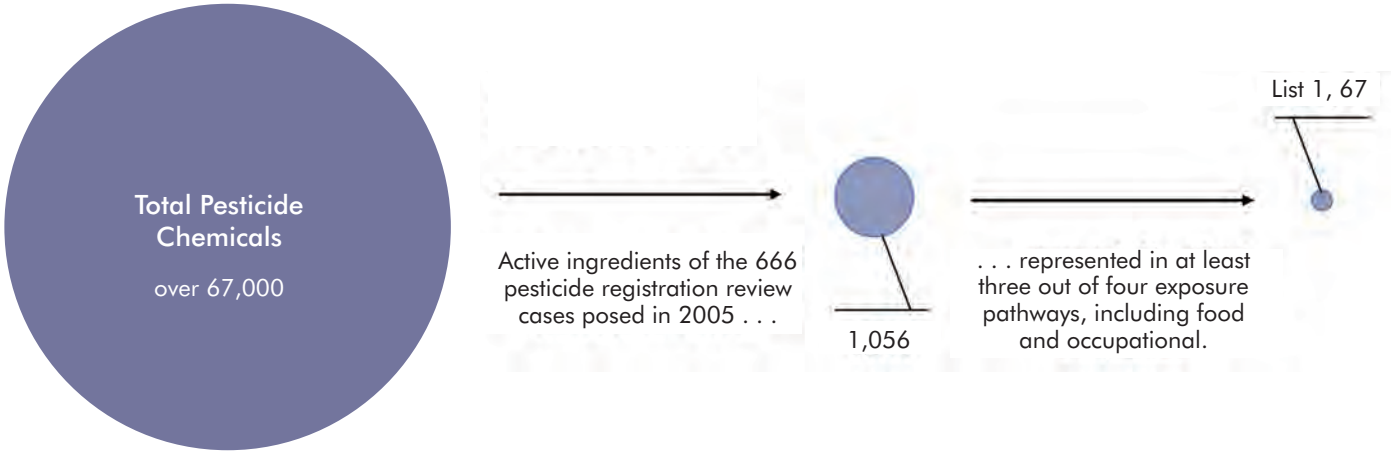
Endocrine Disruptor Screening Program (EDSP): From Start to Stalled, 1996–2019



Sources: epa.gov, personal communication (EDSP, 06/2019)
Credit: Sarah Bluher, Beyond Pesticides

FIGURE 3

How Did EPA Choose the Chemicals to Screen?



As emphasized by EPA, Tier 1 Screening is not sufficient to implicate a chemical as an endocrine disrupting chemical (EDC). In other words, Tier 1 findings do not hold much weight on their own. Rather, they are a tool for defining which chemicals must undergo Tier 2 testing.

Tier 2 testing is intended to confirm and characterize endocrine effects, establishing dose-response relationships and other metrics typically used in conducting EPA risk assessments. EPA holds that only Tier 2, and not Tier 1 testing, can "provide definitive proof of a substance's ability to interact adversely with these hormone systems in the intact organism." Therefore, Tier 2 testing is the only stage that can influence regulatory decision making.

WILL THE RESULTS BE USED TO REGULATE?

Since its formation 21 years ago, EDSP has generated two lists of chemicals to screen, conducted Tier 1 screening for the first of those lists, and recommended 18 of the 52 screened chemicals for Tier 2 testing.[4] As of June, 2019, EDSP has not begun Tier 2 testing—not even the first step, making data call-ins—for any of the 18 List 1 chemicals that screened positive for potential endocrine disrupting effects in 2015. Nor has the program begun to move forward with any screening for List 2 chemicals.[5] There are no plans as yet to expand on the small subset of chemicals selected for screening in Lists 1 and 2.

When EDSP generated Lists 1 and 2, narrowing down from over 87,000 options to just a few hundred chemicals, only registration status and exposure data were considered as prioritization factors. In other words, EPA eliminated thousands of chemicals from undergoing even the first round of screening, without considering whether or not those chemicals were already shown at the time to cause endocrine disruption. And, in fact, many of the chemicals excluded from consideration *did* have known or suspected endocrine disrupting effects, as openly acknowledged in EPA's 2013 public notice on the release of List 2, which offers no reasoning for their exclusion:

> "EPA also received comments stating that the Agency should have included some chemicals (e.g., triclosan, alkylphenols and alkylphenol polyethoxylates, bisphenol A, musk fragrances, and pharmaceutical estrogens) with known or suspected endocrine disrupting effects on the second list. When compiling the second EDSP list, EPA focused on priority drinking water contaminants and pesticides previously identified by EPA."

EPA has yet to establish firm plans for how any of the testing results, if completed, will be used to inform regulatory decisions, including pesticide registration reviews.[6] The view from 2019 looks not much different from 1998. EPA is sitting on the only process it has built for endocrine disruptor regulation, which is, at best, a weak regulatory tool.

EPA'S ENDOCRINE TESTING IS OUTDATED AS WELL AS INCOMPLETE

In 2009, when EPA announced that it was ready to begin testing active and inert (undisclosed) pesticide product ingredients for potential endocrine disrupting effects, prominent researcher and author Theo Colborn, PhD, assailed EPA's proposed testing protocols, saying that they were outdated, insensitive, crude, and narrowly limited, and would fail to detect many serious effects on human development.

In 2015, EPA finally released results for its Tier 1 screening of 52 pesticide chemicals (both active and inert ingredients) evaluated under EDSP—with recommended Tier 2 level testing (see box, p. 13), which involves review of endocrine disrupting effects across organisms and on non-endocrine

BOX 1

EPA Starts and Stops

In 1998, following a mandate in the *Food Quality Protection Act* (FQPA) of 1996, EPA established a program to screen and test pesticides and other widespread chemical substances for endocrine disrupting effects. Despite operating for 21 years, the Endocrine Disruptor Screening Program (EDSP), established to carry out the act, has made little progress in reviewing and regulating endocrine disrupting pesticides. As of 2019, the program has stalled entirely.

To ensure timely follow-through, EPA was given a timeline to: develop a peer-reviewed screening and testing plan with public input not later than two years after enactment (August 1998); implement screening and testing not later than three years after enactment (August 1999); and report to Congress on the findings of the screening and recommendations for additional testing and actions not later than four years after enactment (August 2000).[7]

TESTING PLAN

The testing plan was due in 1998, but that was the year that EPA established EDSP, based on recommendations of EDSTAC.

IMPLEMENT SCREENING AND TESTING (WAS DUE 1999)

Tier 1 screening results were reported in 2009 and 2013. EDSTAC recommended that priority setting for selecting chemicals be screened, "based on *both effect and exposure* data,"[8] and a 1999 EPA advisory panel report stated, "The greatest weight should be given to chemicals for which we have data that indicates actual human or environmental exposure and effects." However, EPA's screening selections, titled List 1 (2009) and List 2 (2013), considered only registration status and exposure data as prioritization factors.

RESULTS (WAS DUE 2000)

Since, according to EPA, Tier 1 Screening is not sufficient to implicate a chemical as an endocrine disrupting chemical (EDC), but acts as a tool for defining which chemicals must undergo Tier 2 testing, the second tier testing is the only stage that can influence regulatory decision making. Indeed, it is unclear when or how EPA will move forward with Tier 2 testing, and how, if at all, any Tier 2 findings will be used to inform actual regulation.

Since EPA announced it was ready to begin testing both active and inert (usually the majority of the undisclosed product ingredients that compose the solution, dust, or granule) pesticide ingredients for potential endocrine disrupting effects in 2009, the protocols EPA proposed to use have become significantly outdated, having been first recommended in 1998. In the interim, science has progressed such that it offers more sophisticated assumptions than those that informed the EPA test designs. Further, as Beyond Pesticides noted in 2009, "Each of EPA's tests and assays was designed under the surveillance of corporate lawyers who had bottom lines to protect, and assorted toxicologists who were not trained in endocrinology and developmental biology. For over a decade, EPA ignored the vast wealth of information on endocrine disruption from independent academic researchers funded by the U.S. and other governments in Europe and Asia."

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REGULATION

The final stage of the EDSP process is simultaneously the most important and least defined step: regulation. A review of endocrine disruptor screening and regulation worldwide made the following criticism of the EPA's EDSP in 2011,[9] which still holds today:

> "One of the greatest challenges of the EDSP is the current lack of clear decision strategies and processes, or in other words: what happens if a chemical is flagged as a potential EDC during Tier 1 screening? While in theory flagging a chemical during Tier 1 would trigger confirmatory Tier 2 testing, it is unclear how and when this will happen. . . . Similarly, it is unclear what the decision process for removing or limiting the use of chemicals that tested positive will be . . . there is still a great deal of uncertainty and lack of clear policies and available tools that would allow moving a chemical smoothly through the complete EDSP process."

systems.) In 2015, Beyond Pesticides summarized the EPA's performance on evaluating endocrine disrupting chemicals and protecting the public from them: "Delays and criticisms from scientists have highlighted inadequacies of the overall program. After FQPA set a 1999 deadline for EPA to develop a battery of assays with which pesticide manufacturers were required to screen their products as possible endocrine disruptors, EPA repeatedly pushed back the deadline for over a decade. Moreover, critics of EDSP have said that EPA's testing protocol is outdated, failing to keep pace with the science." Adding to the critique, in 2017 Beyond Pesticides covered the ongoing inadequacy of EPA's progress on EDCs, noting that "inadequate federal testing, disproportionate industry influence, and subverted regulatory oversight threaten decades of progress on protecting people from hormone disrupting chemicals."

ENDOCRINE DISRUPTION AND RISK ASSESSMENT

A persistent critique of EPA's toxicological assumptions has to do with the "dose makes the poison" concept that underlies conventional toxicology. In fact, researchers have discovered that this concept—that the more exposure, the more extreme the impacts—is not consistently the case across exposures to chemical compounds such as pesticides. Additionally, even very low-level exposures (aka "doses") can, in some instances, cause more extreme health impacts. In this context, it is not dose as much as critical windows of vulnerability or timing of exposure that is important. As long as EPA is tied to the Tier 2 goal of establishing dose-response relationships and other metrics typically used in conducting EPA risk assessments, critics say it is unlikely to arrive at conclusions that are both scientifically supportable and useful for regulation. As stated by Jason M. Vogel, PhD, in 2005,[10] "The EDSP policy design represents revision at the margins of U.S. chemical regulatory policy, not a radical revision. EDSP employs the same basic strategy used to regulate carcinogenic pesticides or toxic industrial chemicals—scientifically proving harm prior to regulating a chemical. Two important aspects of this strategy include an epistemological assumption that science has the capacity to 'prove' harm under the relevant scientific *and* legal standards, and an ethical position that prioritizes profit over human health by placing the burden of proof on public and environmental health advocates."

CONCLUSION

Clearly, Europe is moving more expeditiously on the matter of pesticide hazards than is the U.S. EPA needs to expedite the protection of human and ecological health from the threats of toxic pesticides, including the triazoles and other compounds, which are implicated in multiple adverse effect outcomes. *For more information on the effects of pesticides on human health, including endocrine disruption, see Beyond Pesticides' Pesticide Induced Diseases Database.*

Contributors to this article include Debra Simes, Terry Shistar, PhD, and Sarah Bluher.

ENDNOTES

1 Elskus, A. *Toxicity, Sublethal Effects, and Potential Modes of Action of Select Fungicides on Freshwater Fish and Invertebrates.* USGS. Open-File Report 2012–1213 Version 1.1, November 2014.

2 Pub. L. No. 104-170, 110 Stat. 1489 (1996). Title IV. Amendments to the Federal Food, Drug, and Cosmetic Act. §405(a)(2)(D)(viii)

3 EPA. Review of the EPA's Proposed Environmental Endocrine Disruptor Screening Program by a Joint Subcommittee of the Science Advisory Board and Scientific Advisory Panel.

4 https://www.epa.gov/endocrine-disruption/endocrine-disruptor-screening-program-edsp-tier-1-assessments

5 Personal communication.

6 Personal communication.

7 §405(p)(1), (2), and (7).

8 EPA. Review of the EPA's Proposed Environmental Endocrine Disruptor Screening Program by a Joint Subcommittee of the Science Advisory Board and Scientific Advisory Panel.

9 Hecker, M. and Hollert, H., 2011. Endocrine disruptor screening: regulatory perspectives and needs. *Environmental Sciences Europe,* 23(1), p.15.

10 Vogel, J.M., 2005. Perils of paradigm: Complexity, policy design, and the Endocrine Disruptor Screening Program. *Environmental Health,* 4(1), p.2.